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ABSTRACTS

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05. HYPERTENSION INDUCED BY CYCLOSPORIN IN RENAL TRANSPLANT

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Introduction: Hypertension is a common side effect with the highest incidence in heart transplant recipients and the lowest incidence in renal transplant recipients. Hypertension requiring treatment was considered to be one of the main risks in cyclosporine-treated patients. The physiopathology of cyclosporine-induced hypertension has been suggested to be related to renal vasoconstriction with subsequent sodium.

Aim of the Study: The aim of our study is to evaluate the frequency of hypertension induced by cyclosporine A in renal transplant patients.

Materials and Methods: We led a retrospective study on cyclosporin A induced hypertension disease notified to nephrology unit in IBN SINA hospital between December 2001 and December 2003.

We have included in our study each transplant patient treated by cyclosporine A presenting hypertension post transplanting.

Results: We have included 20 cases in our series, aged 23 to 50 years old. Our patients was treated by triple immunosuppressive therapy (cyclosporin, corticoid and anti-proliferative).

The incidence of patients presenting hypertension post cyclosporine was 40%. Dose of cyclosporine varied from 275mg/day to 300mg/day.

Systolic pressure varied from 170mm Hg to 220mm Hg occurred on the average of 4 days.

Cyclosporin assay varied from 500 to 1000 ng/mL.

Conclusion: Hypertension is the principal cardiovascular adverse effect of cyclosporin. This may be severe and appears to be dose related, so monitoring is the main method to prevent hypertension post cyclosporine.

15. HOW TO INCREASE THE SPONTANEOUS REPORTING IN ARGENTINA?

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Argentina is a highly indebted country whose public offices are maintained with reduced budgets and personnel. Physicians work in unstable conditions earning very low salaries. The 'Generic Name Law' (2002) managed to improve the accessibility to the medicament, however, there isn't a law demanding bioequivalence studies to all the oral forms or stronger quality controls to other drugs.

The reporting rate by million inhabitants is 56.12. The lack of efficacy reporting percentage is constantly increasing (18.6% in 2003). Professionals don't report or underreport due to: lack of knowledge of the Pharmacovigilance System, fear of suffering some kind of conflict at the work place, difficulty in the reporting procedure, lack of time (workload excess), and lack of confidence in the institutions in general and in the Pharmacovigilance System in particular.

The ANMAT (Drug, Food and Medical Technology National Administration) Pharmacovigilance Department has four professionals mainly involved with the analysis of the information received and decision making. It doesn't exist any state provincial structures subsidised by the ANMAT The dissemination of the objectives and methods of Pharmacovigilance and the gathering of reporting largely depend on the human and material resources of 'peripheral effectors' (public or private structure coordinated by a well-known professional).

It becomes necessary to organise, especially in the interior of the country, a reporting procedure easy to carry out. Provincial Health Ministries or Universities haven't managed enough budget so far that allows the maintenance of Pharmacovigilance Centers with full time personnel and technological and material resources. These university Pharmacovigilance Centers could benefit with economic support from the pharmaceutical industry for the payment of salaries and of technological and material infrastructure necessary (PC Internet, furniture, free calls phone) to increase the gathering of reporting. This economic support doesn't mean an important expenditure for the pharmaceutical industry but it does for the public structures. The pharmaceutical industry has evident interests in the topic and the scientific and confidential treatment of data must be stated in the contract. Until international financial or health organisations finance the functioning of these Centers, the support of a sector of the pharmaceutical industry producing quality medicaments would be an immediate alternative to improve the Pharmacovigilance in the country and favour the increase of reporting.

20. LACK OF EFFICACY IN ANAESTHETICS

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Anaesthesia is a critical medical procedure, based on the action of immediate effect drugs. Due to their route of administration (parenteral, inhalation), these drugs are not apt to be submitted to Bioequivalence tests.

In Córdoba, Argentina, in 1997 30 Yellow Cards (YC) from Public Hospitals reported lack of efficacy (LE) in drugs used in anaesthesia (thiopental, bupivacaine, fentanyl citrate, succinylcholine). Chemical tests of samples of 6 caches showed a higher or lower drug concentration than the rate established by USPXXIII. Analysed samples of nine caches did not show quality failure chemically demonstrable, in spite of the LE reported. Caches that showed quality failure were withdrawn.

From 2001 to 2004, in 121 Yellows Cards reported in Córdoba, Argentina, 28 (26.2%) reported LE in anaesthetics. This percentage is underestimated; some YC reported FE in 'several' or 'all' the treated patients. Drugs reported are non-branded marks of local anaesthetics (bupivacaine, lidocaine), muscle relaxants (pancuronium), benzodiazepines (midazolam), analgesics (phentanyl citrate), and anaesthetics (ketamine). Seven patients were children (three reports of

pancuronio, four reports of midazolam); eight YC reported LE of bupivacaine in birth, with fetal suffering. All YC reporting LE anaesthetics drugs used in surgery came from Public Hospitals; odontologists reported LE in lidocaine. Except two cases (lidocaine, bupivacaine), YC were not accompanied by the samples to be analysed.

Lack of efficacy in anaesthetics not only can provoke serious and even fatal consequences but also can represent an increase of the direct and associated costs. Higher and better quality controls must be implemented in these drugs' manufacturing process. The controls should analyse if the product contains the drug concentration demanded by the international norms. Excipients, chirality or other potentially involved factors must also be analysed in order to guarantee the therapeutic efficacy.

The reporting to the Pharmacovigilance system must be encouraged and the gathering and sending of samples for their analysis must be facilitated. The dissemination and reinforcement of the Pharmacovigilance system are vital to increase the reporting and to make possible the decision making in the ANMAT (National Administration of Drugs, Food and Medical Technology).

25. MEDICATION ERRORS IN ANAESTHESIA

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Medication errors contribute significantly to patient morbidity and mortality and increase costs to healthcare systems. Anaesthesiologists, Clinical Pharmacologists and Argentinean National Regulatory Agency (ANMAT) developed programs to avoid them.

The purpose of this study was to summarise the way in which healthcare professionals could reduce medication errors and consequent morbidity or mortality due to anaesthetic drugs.

An observational study was performed based on the most common anaesthesiologist claims for medication errors system encountered in Argentinean Public Hospitals. These claims were reported to AAARBA Buenos Aires Association of Anaesthesiology Analgesia and Reanimation and to the Hospital de Clínicas (Córdoba National University).

One of the contributing causes to medication errors was the misidentification of drug ampoules or vials of anaesthetic drugs.

To combat this problem a new National Regulation for the labelling of anaesthetic drugs was recently approved by the ANMAT. The main changes to the new labelling regulation were: changes in the critical information panel in order to avoid overcrowded labels; different colour bands on labels according to clinical pharmacology classification of anaesthetic drugs so each pharmacological group has their own colour identification band and the introduction of bar codes to make sure that the right drug, in the right dose and route of administration is given to the correct patient. These labelling changes can make the difference between patient life and death.

30. PHARMACODYNAMIC AND PHARMACOKINETIC INSIGHTS IN HEADACHE PATIENTS WITH DRUG OVERUSE

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A substantial proportion of headache patients overuse acute medications. Overuse has been considered to be responsible, in many cases, for the development or maintenance of a chronic daily headache (CDH). The objectives of this lecture are to evaluate recent experimental and clinical data on the pathophysiology of this syndrome. The biochemical basis of CDH are not known, but the 5-HT system seems to be involved. Indeed, chronic overuse of acetaminophen induces alterations of this system both at the level of CNS and platelets, in some animal models. Similarly, some abnormalities in 5-HT levels and in 5-HT receptors have been found in patients with CDH.

Since triptans are the most effective anti-migraine drugs used and show agonist action mainly at 5-HT(1B/1D/1F) receptors, their effect after chronic use and/or after overuse deserves particular attention. In a recent study,[1] the effects of protracted triptan treatment have been evaluated in rats on 5-HT1 receptor mRNA expression and function in tissues related to migraine pathophysiology. Despite a reduction in 5-HT(1B/1D/1F) receptor mRNA, no significant effect was detected in two functional assays. Therefore, the significance of 5-HT receptor expression in migraine pathophysiology as well as pharmacokinetic implications need further analysis. In another recent study,[2] the outcomes of analgesic overuse have been evaluated by comparing a group of patients who discontinued medication overuse to a group who continued the overuse. After 1 year of follow-up there was a decrease in the frequency of headache of 73.7% in group 1 (successfully detoxified) and only 17.2% in group 2. Similarly, the duration of head pain was reduced by 61.2% in group 1 and 14.8% in group 2. Rigorous prescribing guidelines as well as successful detoxification are therefore needed when treating patients with drug overuse.

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40. ANALYSIS OF ADR REPORTS FOR YEAR 2003

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Introduction: In Singapore, the reporting of spontaneous adverse drug reactions (ADRs) by our healthcare professionals to the regulatory agency, Health Sciences Authority (HSA), is one of the most effective tools to monitor the safety of a marketed drug/health product. To improve the signals obtained from the local postmarketing spontaneous reports, the Pharmacovigilance (PV) Unit at HSA has stepped up its effort to promote ADR reporting amongst our healthcare professionals through road shows and publication of ADR bulletins.

Aim: This study was aimed to analyse the reporting rate and types of ADR reports received in 2003.

Method: We performed a search in the HSA ADR database to identify all reports received in 2003. The reports were analysed and the information extracted included the top 15 active ingredients suspected of causing ADR, the highest 10 occurrences of ADR as well as the listing and incidence of serious suspected ADR.

Results: From our analysis, the year-to-year number of ADR reports received from 1997 to 2003 has been increasing steadily at an average rate of 20%. For 2003, we received 1100 reports; this represented a 38% increase in the number of reports received in 2002. The public hospitals contributed the majority of the reports (60.3%) compared to only 4.2% from drug companies. Three-quarters of the reporters were doctors but reports from pharmacists were on the increase. The most common age group reported with ADR was the 30–39 age group. This formed 17% of the total patient cohort. The highest offending drugs are mainly the NSAIDs and antibiotics such as cotrimoxazole and cephalosporins. The top three reported ADR (by system-organ class) include skin disorders (46%), body as a whole (19%) and gastrointestinal disorders (7%). The number of serious ADR reported constitutes 18.8% of the total reports. Examples of serious suspected ADR received include Stevens Johnson syndrome, toxic epidermal necrolysis, renal failure, blood disorders, anaphylactic reactions and hepatic failure. There were a total of 34 reports associated with complementary therapies of which 6 were quoted as serious ADR.

Conclusion: With our promotional efforts, there is a continual increase in reporting rate for 2003 (reaching a rate of 260 reports per million population). Spontaneous ADR reporting remains an important component of the postmarketing surveillance activities in enhancing the safe use of drugs and related health products in Singapore.

45. DOES INFORMING GPS ABOUT COMMON ADRS INFLUENCE ADR REPORTING RATES?

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Introduction and Aim: Many prescribers are unsure about when to report ADRs to the MHRA, and many never complete a Yellow Card during their career. Additionally, the reporting rate of GPs in the UK has halved in the last five years. We investigated whether educating GPs about the most common serious reactions by sending them fact sheets had any influence on their subsequent reporting.

Method: We identified from our Regional Monitoring Centre database of ADRs the five most common serious reactions (using the MHRA's definition of severity), and produced concise fact sheets (about 500 words) on each, describing the reaction, risk factors, and strategies for avoidance.

In 2002 we received reports from 312 individual GPs out of 3157 GPs in the West Midlands region. We randomly selected 198 of the 2845 non-reporting GPs (Group A) and sent them a fact sheet each month for 5 months from December 2003. In a second arm of the study we sent fact sheets to a randomly selected sample of those reporters (Group B) who reported one of the relevant ADRs ('fact sheet reactions') to us to see if this influenced re-reporting rates.

Results: During the first six months of 2004 we received nine reports from eight of the Group A GPs (4%) who received the fact sheets, and 1 from a comparison random sample of 198 GPs (0.5%) [non-reporters in 2002] who did not receive the fact sheets. There were 34 reporters in Group B and 6 of these (18%) reported a further reaction subsequent to receiving a factsheet. Seventy-seven other reporters reported a 'fact sheet reaction' but did not receive a fact sheet and only ten of these (13%) have reported a subsequent reaction.

Discussion: GPs who received the fact sheets (Group A) had a higher reporting rate, compared with a group who did not receive the fact sheets [p = 0.022, Fisher's exact test]. Only about 10% of GPs will report an ADR in any given year; educating non-reporting GPs seems to raise them towards the mean reporting rate. There are insufficient data yet to determine whether fact sheets influence re-reporting rates and this arm of the study is ongoing. The fact sheets will need updating regularly, but this should be relatively easy. This is a potentially fruitful method of increasing reporting rate from GPs.

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50. CLINICAL FINDINGS OF ACETYLSALICYLIC ACID/ NONSTEROIDAL ANTI-INFLAMMATORY DRUGS-INDUCED URTICARIA.

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Introduction: Intolerance to acetylsalicylic acid (ASA) and other non-steroidal inflammatory drugs (NSAIDs) is a crucial problem in clinical practice. Urticaria represents one of major manifestations of ASA/NSAID intolerance.

Aim: To analyse epidemiological, chronological and semiological findings in patients with ASA/NSAID-induced urticaria. These cases were notified in Tunisian Pharmacovigilance National Center during 10 years.

Methods: Clinical characteristics of 48 patients with history of ASA/NSAIDs-induced urticaria were retrospectively analysed.

Results: There were 30 (62.5%) females and 18 males (37.5%); age varied from 3 to 60 years (median 26 years). Personal and/or familiar atopic history was present in 18 patients (37.5%). Urticaria was generalised in 39 patients. Itching was present in all cases, edema in 31 cases, dyspnoea in 10 cases and anaphylactic shock in two cases. Implicated drugs in inducing urticaria were ASA in 34 cases and NSAIDs in the 14 other cases. Time of urticaria onset varied from 5 minutes to 20 years after drug intake (median was 2 hours). In all cases, urticaria disappeared after drug withdrawal. Responsible drugs were previously taken with no intolerance reaction in 31 patients (64.5%). No rechallenge of suspected drugs was attempted in our patients.

Conclusion: ASA/NSAIDs-induced urticaria was frequent in young people, female and atopics. It is generalised in most cases. Threatening signs, i.e. dyspnoea accompanied frequently urticaria. Time of urticaria onset is usually short. No chronicity was noted.

55. AGREEMENT OF EXPERT JUDGMENT IN ASSESSMENT OF CAUSALITY OF ADVERSE DRUG REACTIONS

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Background: The possible causal relationship between a drug treatment and the occurrence of an adverse event can be assessed by three main approaches: algorithms, Bayesian approaches and global introspection.

Objective: We aimed to analyse the judgements by global introspection of senior experts about drug causation in a set of selected cases of Adverse Drug Reactions (ADRs).

Methods: A random sample of 150 drug-effect pairs was constituted from cases spontaneously reported in 1998 to the Bordeaux Pharmacovigilance Center and from a nation-wide incidence study conducted in 1998. For each pair, each of five senior experts assessed the probability (p) of drug causation (from 0–1) using a 100mm Visual Analogue Scale (VAS). The VAS ranged from no causal relationship on the extreme left ($p = 0$) to certain on the extreme right ($p = 1$). For analysis, these probabilities were arbitrarily divided into seven levels of causality: excluded, unlikely, doubtful, unassessable/unclassifiable, plausible, likely and certain. Agreement between five senior experts was assessed using Kappa coefficient.

Results: The overall agreement between experts was poor (Kappa = 0.20, $p < 0.0001$). The level of agreement varied according to the level of causality. The agreement was low for the unlikely, doubtful, unassessable/unclassifiable, and plausible levels (Kappa = 0.03, 0.03, –0.01, and 0.13, respectively). The agreement was better and statistically significant for VAS extremes [excluded (Kappa = 0.40), likely (Kappa = 0.32), and certain (Kappa = 0.30)].

Conclusion: Even with senior experts, it is difficult to reach an agreement in causality assessment. The agreement was lower for moderate levels of causality. The low agreement between experts especially concerns situations where strong evidence is lacking for confirming or ruling out drug causality. In a decision-making context, a step-by-step consensual approach of agreement such as the Delphi method is appropriate to optimise the independent assessment of such cases.

60. INTER-EXPERT AGREEMENT ABOUT SEVEN OPERATIONAL CRITERIA FOR CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS

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Introduction: In early warning systems [spontaneous reporting of Adverse Drug Reactions (ADRs)], causality assessment methods such as expert judgement, algorithms, and probabilistic approach are commonly used to evaluate the relationship between a drug and the occurrence of an adverse event. These methods either implicitly or explicitly use causality criteria (e.g. chronological criteria, clinical and biological criteria and notoriety).

Aim: To evaluate agreement between senior experts about the assessment of causality criteria.

Methods: A sample of 31 adverse event-drug pairs was constituted: 16 adverse event-drug pairs were randomly selected from cases spontaneously reported in 1998 to the Bordeaux Pharmacovigilance Center and 15 randomly selected from a nationwide incidence study conducted in 1998. For each adverse event-drug pair, five senior experts separately assessed seven causality criteria: (1) time to onset, (2) dechallenge, (3) rechallenge, (4) search for non-drug related causes, (5) risk(s) factor(s) for drug causation, (6) reaction at site of application or plasma concentrations of the drug known as toxic or validated test, and (7) previous information on the drug and drug's known pharmacology. To test the divergences between experts on the seven causality criteria, the Kappa index of reliability for multiple categories and multiple raters was used.

Results: The Kappa index was significant ($p < 0.01$ or $p < 0.001$) except for the item 'risk(s) factor(s)' (kappa = 0.09). However, even when the criteria are significant, the agreement remains low; the Kappa index of the causality criteria ranged from 0.12 to 0.38. Agreement between experts was good (0.64, $p < 0.001$) only for the criterion 'reaction at site of application or plasma concentration of the drug known as toxic or validated test'.

Conclusions: This study confirms that in the absence of an operational procedure, the agreement between experts is low. Such divergences should be considered when designing a causality assessment method. For example, criteria with a low level of agreement should have their weight reduced.

65. OPHTHALMOLOGICAL EVENTS IN PATIENTS TAKING RISEDRONATE: FOLLOW UP INFORMATION IN A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: The nitrogen bisphosphonate risedronate sodium is licensed in the UK for the prevention and treatment of osteoporosis and steroid induced osteoporosis in post-menopausal women and also for the treatment of Paget's disease. During a Prescription-Event Monitoring (PEM) study on risedronate, we noted 359 ophthalmological events. Recent publications in the medical press have described various cases of ophthalmological side effects in patients taking bisphosphonates.

Aim: To describe ophthalmological events assessed as possibly or probably related to risedronate in a patient cohort of this PEM study.

Methods: Between September 2000 and June 2002 an observational cohort study was performed using the technique of PEM. During this postmarketing surveillance study, follow up information was requested from General Practitioners (GPs) on selected events, including eye events. Using a modified World Health Organization (WHO) classification, events followed up were classified as either probably, possibly or unlikely related to risedronate. Those where insufficient clinical information was available were categorised as unassessable.

Results: The total study cohort comprised 13 643 patients; 2398 (18%) were males and 11 156 (82%) were females. During treatment with risedronate, 296 ophthalmological events were reported in 264 patients. The age range for patients with events assessed as possibly or probably related to risedronate was 50 years to 92 years. The time to onset in these patients varied between 7 and 152 days. The three most common ophthalmological events assessed as probably or possibly related to risedronate were: dry eye (6), sore eye (5), conjunctivitis (3). Further, we received three reports of iritis, two of keratitis and two of uveitis for which limited follow up information was obtained.

Conclusion: A range of adverse events affecting the eye were observed in this cohort. Doctors should have an increased awareness of these, as they may present after the first month of treatment and can affect the eyesight in a population at risk of fractures when falling. Analysis of safety data of other bisphosphonates is required to examine whether ophthalmic events are a class effect.

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70. SPONTANEOUS REPORTING OF ADRS ASSOCIATED WITH HERBAL MEDICINES: A CROSS-SECTIONAL SURVEY OF NATIONAL PHARMACOVIGILANCE CENTRES

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Introduction: The use of herbal medicines is a popular healthcare choice in developed and developing countries. In recent years, there have been several high-profile herbal safety concerns which have had an impact on the public health. Thus, there is an increasing awareness of the need to develop pharmacovigilance practices for herbal medicines; for example, the WHO has produced guidelines on this.[1] Pharmacovigilance of herbal medicines, however, presents several particular challenges in addition to those known in pharmacovigilance of conventional medicines.[2] Particular issues include whether national spontaneous reporting schemes for suspected adverse drug reactions (ADRs) specifically encourage reporting for herbal medicines by recognised reporter groups, and whether spontaneous reporting forms for ADRs are designed adequately to collect information on herbal medicines.

Aim: To explore and describe the current practices of national pharmacovigilance centres with regard to ADR reporting for herbal medicines.

Methods: The sampling frame for the study comprised all official and associate member countries (n = 72 and 12, respectively) of the WHO Uppsala Monitoring Centre (UMC); addresses were obtained from the UMC. A structured questionnaire in English was developed. The questionnaire was posted in March 2004 with a letter explaining the study and requesting a copy of the national spontaneous ADR reporting form and reporting guidelines. Four follow-up mailings were sent to non-responders at 4-week intervals. Data were entered into Microsoft Excel version 10 for analysis.

Results: To date, responses from 48 countries (57%) have been received. Of these, 43 (90%) accept spontaneous ADR reports for herbal medicines, and 15/47 respondents (32%) specifically encourage reporter groups to report suspected ADRs associated with herbal medicines. In response to statements regarding herbal ADR reporting, 27/46 respondents (59%) agreed/strongly agreed that their ADR reporting form needs modifying in order to effectively collect data on suspected herbal ADRs, and 30/46 (65%) disagreed/strongly disagreed that there should be a separate ADR reporting scheme for herbal medicines. Further results will be presented.

Conclusion: Current practices of national pharmacovigilance centres towards reporting ADRs associated with herbal medicines vary. Preliminary analysis of the data has also revealed issues regarding the dissemination, communication and harmonisation of the international pharmacovigilance of herbal medicines.

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75. KNOWLEDGE FINDING IN IMS DISEASE ANALYSER MEDIPLUS UK DATABASE – EFFECTIVE DATA MINING IN LONGITUDINAL PATIENT SAFETY DATA

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Introduction: Data mining has been used increasingly in recent years in spontaneous reporting systems to enhance the detection of signals. The BCPNN has been in routine use on the WHO database since 1998 and this method has proven successful in signal detection.

Aim: To apply the BCPNN data mining methodology to the entire two million record IMS Disease Analyzer Mediplus UK database:

- To gain an insight into the types of valuable information that can be captured by routine data mining of a longitudinal data set
- To show that such a method has the potential to highlight signals early.

Methods: The BCPNN is routinely used not only to highlight unexpected drug-ADR pairs for clinical review, but also to perform unsupervised pattern recognition, which adds value by finding more complex relationships and highlighting potential confounders. The BCPNN was adapted for knowledge finding on a longitudinal database, to account both for events occurring after drug use but also before. Unexpected drug-event detection, pattern recognition and other techniques were then applied to mine the IMS Disease Analyzer Mediplus UK database.

To show that the BCPNN could have been used to detect signals early in this Mediplus database, a retrospective analysis was performed by looking at how the IC value would have varied over time. The antidepressants were examined in more detail.

Results: Several examples of signals were detected; the association between terbinafine and angioedema, approved as a safety labelling

change by the FDA in January 2004, would have been highlighted for clinical review in 2001. For the main indications different antidepressants had similar effectiveness; however effectiveness decreases markedly for other indications. This, together with a risk analysis, allowed an assessment of risk effectiveness to be made.

Conclusion: Chronological ordering of adverse events and drug prescription on a patient level with detailed demographic information makes this data set a rich resource for data mining. Data mining of the IMS Mediplus data set is effective in finding new ADRs early, has the potential to find possible new indications, and allows risk effectiveness assessments to be made. It is in the nature of data mining to focus on the generation of hypotheses, and this must be considered when interpreting the output of such knowledge finding.

80. A RARE DRUG REACTION TO METHOTREXATE AFTER TREATMENT FOR ECTOPIC PREGNANCY

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Introduction: Ectopic pregnancies are commonly diagnosed and treated in physicians' offices. In the hemodynamically stable patient, therapy often includes treatment with methotrexate. Well-known adverse effects of this drug include mucositis, abdominal cramping, and malaise. We report a case of a rare drug reaction after treatment with methotrexate.

Case: A 34-year-old, gravida 2, para 0, at 7 weeks of gestation by last menstrual period was diagnosed with an ectopic pregnancy and treated with methotrexate. The patient had an anaphylactoid reaction shortly after administration of methotrexate.

Conclusion: Methotrexate is a commonly used therapy for ectopic pregnancies in the outpatient setting. Practitioners should be aware of the potential adverse reactions to methotrexate.

85. NEW ANTIDEPRESSIVE AGENTS DURING PREGNANCY AND LACTATION: DRUG CONCENTRATION SHOULD BE MONITORED AND THE LOWEST POSSIBLE DOSE ADMINISTERED

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This work presents a literature review on the treatment with new antidepressants during pregnancy and lactation, focusing on possible unwanted effects to the fetus and infant. Most data is available for the selective serotonin reuptake inhibitors, and particularly for fluoxetine. Some information exists for venlafaxine, whereas no published data was found for other new antidepressants such as reboxetine and mirtazapine. In general, treatment with new antidepressants during the first trimester in pregnancy has not been associated with an increased risk for congenital malformations. In contrast, symptoms such as irritability, respiratory distress and muscular hypotonia have been reported in new born babies after third trimester exposure. The excretion of new antidepressants in breast milk seems in most cases to be negligible. However, suspected adverse effects have been reported in a few infants. In conclusion, existing data seems to indicate that the positive effects of maternal drug treatment and of lactation to the infant generally outweigh the risks of possible pharmacological effects. Nevertheless, before a new antidepressant is prescribed to a pregnant or lactating woman, an individual risk/benefit-assessment should always be carried out.

95. ALLERGIC VASCULITIS TO BETA LACTAMS

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Introduction: Beta lactams, the widely used antibiotics, represent the most frequent drugs involved in allergic reactions. Various and heterogenous allergic clinical features have been described with beta lactamins; vasculitis is exceptionally described. We report here a case of an allergic vasculitis with amoxicillin.

Results: A 7-year-old girl, with no particular medical history, was treated by amoxicillin for upper respiratory tract infection. Four days later, she presents a pruriginous maculopapular eruption associated to oedematous lower limbs that motivate her hospitalisation.

Amoxicillin was stopped and replaced firstly with flucloxacillin, then with the combination of amoxicillin and clavulanic acid. A few days later, the child was admitted to the Intensive Care Unit of the Paediatric hospital because the cutaneous lesions worsened and evolved to necrotic purpura; a renal impairment developed. During the hospitalisation, she developed an ischemia of the right hand, sepsis and lung haemorrhage. The investigations eliminated an infectious disease and a systemic disease. The cutaneous anatomopathology exam revealed a leucocytoclastic vasculitis, thus confirming the drug-induced vasculitis hypothesis. The outcome evolved to the amputation of the right hand and the normalisation of renal function.

Discussion: The imputability of the case revealed a 'probable' relationship between the vasculitis and the amoxicillin intake regarding:

- The suggestive delay of onset
- The worsening of cutaneous lesions after the rechallenge of beta lactams
- And the specific aspect of the leucocytoclastic vasculitis

Conclusion: Drug-induced vasculitis remains a diagnosis of exclusion. After a suggested delay of under 3 weeks, a palpable purpura associated with a mild systemic attempt represents a strong argument for the diagnosis of drug induced vasculitis.

100. DRUG INDUCED CUTANEOUS REACTIONS: RETROSPECTIVE ANALYSIS OF THE CASE REPORTS

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Introduction: Drug-induced cutaneous reactions represent the most frequent reported cases in Pharmacovigilance. 10–25% of the hospitalisations are concerned with adverse cutaneous reactions (ACDR).

Although the majority of the reactions are moderate and transient, some of them could be serious.The responsibility of the drug is rarely confirmed and the diagnosis requires a cutaneous test.

Aim: To specify the prevalence and the description of the ACDR in the collecting data of the National centre.

Material and Methods: This is a retrospective study carried out in the Pharmacovigilance centre from reported cases collected between January 1994 and December 2002. We were interested in the morphological variety of the ACDR, the drug involved, and the demographic characteristics of the concerned patients.

Results: 398 ACDR were retained, which represents 8.9% of the total adverse drug reactions collected by the centre during this period. Women are more affected than men (63% versus 37 %). The mean age was 31.33 ± 18.98 years.

Twenty-two morphological varieties were identified; the most common are examthema (42.9%), pruritus (16%) and urticaria (13.95%).

Serious ACDR concerned 9.7 % of the cases; 58.8% were severe and 31.4% were moderate.

Antibiotics, NSAID, anticonvulsant drug, antifungal and analgesics represent the top five drugs implicated in the ACDR.

The outcome was favourable in 66.83% of the concerned patients. The high rate of lethality was observed with toxic epidermal necrolysis (42.85%). The causality assessment of the cases done by French method and reunions de consensus show that: 58.9% of ACDR were classified as doubtful, 33% as plausible, 7073% as probable and 0.2% as certain.

Conclusion: Adverse cutaneous drug reaction represent an important clinical entity; the collaboration between the Pharmacovigilance Centre and the dermatologists is hoped to improve the management of the concerned patients: while the dermatologist confirms the diagnosis, the clinical pharmacologist could add some advice for the patients (the avoided drug list…).

105. HAEMOCHOLECYSTIS RESULTING FROM INTERACTION BETWEEN ANTICOAGULANT ANTI-VIT K AND CELECOXIB

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Introduction: Haemorrhage represents the major risk associated with anticoagulant drugs. Various clinical features are described; it seems that hemocholecyst is an unusual complication of gallbladder lithiasis in coumarins treatment. The gender, age and renal failure are reported to be related to the incidence of bleeding. Drug interaction is more often observed with drugs interfering with platelet function which enhance the risk of bleeding. Few cases of hemorrhage have been described with the association of coumarins with celecoxib. We report here an exceptional case of hemocholecyst related to the association between coumarins and celecoxib.

Result: A 50 year old female under anticoagulant treatment was admitted in the ICU for shock as a result of hemocholecyst associated with other bleeding complications. One week before, she received antibiotics, and then celecoxib for hepatic colic. The third day of celecoxib intake, she developed acute abdominal pain and hematuria. Biological investigations showed increased INR up to 12.4. The anticoagulant was stopped and hemostatic disorders were corrected by vitamin K1. Radiological examinations revealed retroperitoneal, gallbladder and bladder bleeding. After hemodynamic stabilisation, the patient was transferred to surgery; she underwent an operation which confirmed the diagnosis of hemocholecyst.

Conclusion: Although the incidence of the interaction between anti vit K and celecoxib is very low; even so it would seem prudent to monitor INR in patients on coumarins if celecoxib is added.

110. PROLONGED ARTERIAL HYPOTENSION FOLLOWING PROPOFOL INDUCTION

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Introduction: Hypotension following propofol induction is a common described event which requires vigilant monitoring. This hypotension is usually transient and preoperative. The proposed mechanism of this hypotension is primarily a result of a decrease in systemic vascular resistance and also negative inotropic effects of propofol.

In common clinical practice, the hypotension is experienced in the period immediately following anaesthesic induction of propofol with a brief duration as a result of its short half-life.

Associated drugs such as opioid (fentanyl) may be induced in propofol serum concentration and potentialise this hypotension.

Method: We report four cases of severe postoperative hypotension due to propofol lasting more that 24 hours after the intervention. These cases have been observed in the same period with the same batch, which stressed the anaesthesiologist to ask for its analysis.

Results: Three women and one man aged from 26–67 years were concerned; they received the same anaesthesic induction regimen (propofol, sulfentanyl and vecuronium). Their previous history did not yield any predisposant cardiovascular disease. These four cases experienced a prolonged decrease in systolic blood pressure ranging from 04 mm Hg to 07mm Hg. All episodes resolved by 24 hours.

The management of this hypotension required ephedrine because there was no satisfactory response to intravenous fluids. The outcome was favourable for all the cases.

Discussion: Using the French method, the imputability of the four cases was classified as 'plausible' according to the delay of onset, the absence of post operative infection and the response to ephedrine which is recognised to treat propofol's hypotension.

115. IS THE RISK OF UPPER GASTROINTESTINAL BLEEDING INCREASED WITH NSAID USED AS ANALGESIC, IN CHILDREN: A CASE CROSSOVER STUDY

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Introduction: Many case-control studies have evaluated the risk of upper gastrointestinal bleeding (UGIB) with NSAID in adults while no study has evaluated this risk in children.

Aim of the Study: Our aim is to demonstrate that the risk of UGIB after NSAID intake is increased in children.

Methods: We conducted a case-crossover study in which each child enrolled served as his/her own control. All the children seen for UGIB and aged between 2 months and 16 years old were enrolled. Information on exposure to NSAID during the month period preceding the onset of UGIB was collected by a phone interview with the parents. The relative risk (RR) of NSAID related UGIB was estimated by comparing exposure to NSAID during a risk period preceding the onset of UGIB (D-7 to D0), with exposure during a control period from D-28 to D-21.

Results: A total of 178 children with UGIB were enrolled between January 2002 and January 2004. UGIB was due to a recent intake of NSAID 65 times (38%): ibuprofen (61%), acetylsalicylic acid (30%). The RR of UGIB due to NSAID intake was 16.5 (6.0–45.3). NSAID were always used as analgesic or antipyretic, with a low dosage.

Conclusion: UGIB due to NSAID intake represents a non-negligible part of paediatric UGIB. Despite a too short study period, which overestimated the risk of UGIB, this study showed that the risk of UGIB after NSAID intake, even at a low dosage, is increased in children.

116. 'PHOSSY JAW' REVISITED – DO BISPHOSPHONATES CAUSE 'BISPHOSSY JAWS'?

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Bisphosphonates are used in the management of metastatic disease of the bone and in osteoporosis. Recently a cohort of patients with necrotic lesions of the jaw was identified to share one common clinical feature: they all had received chronic bisphosphonate therapy. The typical presenting findings were a non-healing extraction socket or an exposed jawbone, both refractory to therapy. The biopsies showed no evidence of metastatic tissue. The pathogenesis of this osteonecrotic process is consistent with localized vascular insufficiency. Typically, compromised bone sequestrates either spontaneously or after a minor procedure (e.g. tooth extraction), and is often followed by secondary infection.

The study suggests that therapy with bisphosphonates is associated with a risk of osteonecrosis of the jaw. While in conservative causality assessment there is no proof that bisphosphonates cause the effect, there is a striking similarity with a classical occupational disease, phosphorus necrosis of the jaw, also known as 'phossy jaw'. This condition occurs when phosphorus is chronically inhaled by factory workers. The disease is hardly known any more. It was eradicated after elimination of white phosphorus in the manufacture of matches.

On the basis of the similarity with the 'phossy jaw' phenomenon we believe that a causal relationship with bisphosphonate therapy can be regarded as likely and thus necroses of the jaw can be considered ADRs to these substances. This notion is supported by the chemical structure of bisphosphonates, a P-C-P structure with the carbon atom carrying various residues. It has been argued, especially by the manufacturers of bisphosphonates, that patients showing the described ADR have risk factors for avascular necroses of the jaw on the basis of their underlying diseases: radiation, chemotherapy or concomitant medications like steroids. These authors even suggested treating necroses of the jaw with bisphosphonates.

Altogether we believe that the relationship of bisphosphonates and necroses of the jaw is causative. In the German spontaneous reporting system (common database of the Federal Institute for Drugs and Medical Devices and the Drug Commission of the German Medical Association) there are several reports of good quality. Manufacturers should be asked to include this ADR in their package leaflets and SPCs. Current data suggest that practitioners should be made alert to this not widely known ADR and thus to prevent advanced destructive lesions of the jaw in patients at risk. Communication between prescribing physicians (oncologists) and physicians treating the side effects (i.e. dentists) should be improved.

117. SEROTONIN SYNDROME INDUCED BY MIRTAZAPINE MONOTHERAPY

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Introduction: Serotonin syndrome (SS) is a potentially life-threatening disorder of excessive serotoninergic activity. SS presents as a triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction. All drugs that directly or indirectly increase central serotonin neurotransmission at postsynaptic 5-HT(1A) and 5-HT(2A) receptors can cause SS. It occurs most frequently when two serotonergic agents are given in combination, or when the dose of the serotoninergic agent is increased. There are also reports using a single agent.

Case Presentation: We present a case of a 75-year-old woman who had undergone vertebral repair for a traumatic lumbar fracture and which was started on 15mg mirtazapine for depression. After 36 hours she developed agitation, disorientation accompanied by a confusional state. On clinical examination she had nuchal rigidity and fever. Suspecting postsurgical meningoencephalitis she underwent brain CT scan which showed no abnormality. The MRI of the lumbar region showed enhancement at the site of the operation. A lumbar puncture was normal and systemic signs of inflammation where absent apart from fever. SS was suspected. Withdrawal of mirtazapine resulted in clinical resolution within 24 hours. The patient was also taking bromazepam, acetaminophen, esomeprazol, spironolactone, atenolol, cefuroxim and nadroparin, but none of these medications is known to have serotoninergic activity or to interact with mirtazapine.

Discussion: The temporal relationship to mirtazapine, the exclusion of other possible causes and the rapid improvement upon dechallenge suggest drug-induced SS. In the literature there are some reports of mirtazapine-induced SS, two with mirtazapine as monotherapy as in this case. The WHO database for adverse drug-reactions contains 25 reports of SS under mirtazapine out of a total of 4438. The underlying mechanism in this case is overstimulation of serotonin type 1A receptors in the brainstem and spinal cord.

Conclusion: It is vital that clinicians are aware of the potential for SS when serotoninergic agent are prescribed and that they recognise it and discontinue the causal agent.

120. SERIOUS SIDE EFFECTS OF BUPROPION: WHO IS AT RISK AMONG 524 000 EXPOSED PATIENTS?

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Introduction: Following the launch of bupropion for smoking cessation in September 2001, the French regulatory agency has implemented a safety monitoring programme.

Aim of the Study: To record and analyse serious adverse reactions (SARs). To identify patients potentially at risk of developing such reactions.

Methods: The monitoring programme is being conducted through the Regional Pharmacovigilance Center of Saint-Etienne. All cases were collected via spontaneous reporting to any French Regional Pharmacovigilance Center or to GlaxoSmithKline. The most frequent serious adverse effects were compared to the total exposed population on the basis of patients' characteristics (age, gender…), treatment regimen and adverse events descriptions (delay of onset, risk factors…). Descriptive statistics were performed using mean and standard deviation for continuous variables and frequency for qualitative ones.

Results: The population exposed to bupropion was evaluated as 524 000 patients, 56% men, mean age 41 years old.

Of 1383 cases reported, 372 (27%) were serious and the most frequent were seizures (n = 64), angioedema (n = 41), coronary disorders (n = 17) and suicide attempts (15).

Risk factors of convulsion, history, alcohol abuse, coadministration of drugs lowering the seizure threshold were found in 31 (48%) patients presenting convulsions. Fifty-one percent were women (mean age 37 ± 9.8 years old), who were significantly younger than men (45.1 ± 12.4 years old).

For angioedema, the sex ratio was similar to the exposed population. Among patients presenting coronary disease, men represented 82.4% yielding a sex ratio significantly different from the exposed population. Out of 17 patients, 13 presented cardiovascular risk factors in addition to smoking and 11 had a coronary lesion.

Fifteen suicide attempts were reported for nine women (60%), mean age 29.3 ± 8.1 years old, and six men, mean age 41.2 ± 6.0 years old. Risk factors were found in 66% of these patients.

Conclusions: Approximately half the cases of convulsions could be avoided by improving questioning on patient's past history. For coronary events and suicide attempts, risk factors are associated for 2/3 of patients.

Acknowledgements: Association of Pharmacovigilance Centres.

125. COPRESCRIPTION OF GASTROPROTECTIVE AGENTS AND SHIFTING BETWEEN DRUGS: IS THERE A DIFFERENCE BETWEEN TRADITIONAL NSAIDS AND COXIBS?

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Introduction: Coxibs were marketed in Italy in Summer 2000, and their use was expected to reduce the prescription of gastroprotective agents, and to increase adherence among chronic users.

Aim of the Study: To compare incident users of Coxib and traditional NSAIDs with regard to: concomitant and subsequent prescriptions of gastroprotective agents; shifting between NSAIDs (including coxibs).

Methods: Drug prescriptions issued in the NHS of the Umbria Region (840 000 inhabitants) are recorded in a monitoring system. Prescriptions of NSAIDs and of gastroprotective agents during 2002 were retrieved. Incident users were defined as subjects without prescriptions of NSAIDs during the 12 months preceding the first prescription of 2002. A prescription of gastroprotective agent was defined as concomitant if prescribed on the same day, and subsequent if prescribed during the current period of NSAID use (described according to the duration of the prescription on the basis of DDDs). Shifting between substances was investigated during the current use following the incident prescription. The comparison between Coxibs and traditional NSAIDs was carried out by substance, taking into account the effect of age, gender, previous use of gastroprotective agents (in order to identify subjects with greater risk to develop gastroduodenal lesions), and previous use of cardiovascular drugs. In the logictic regression diclofenac was considered as reference drug.

Results: During 2002 about 180 000 subjects received at least one prescription of NSAIDs (21% of the population), and 100 665 were incident users (12% of the population). Most of the incident users (87%) had received a traditional NSAID. A concomitant prescription of a gastroprotective agent was associated to 6.4% of the prescriptions of Coxibs and 8.5% of those of traditional NSAIDs. Compared with diclofenac the OR of coprescription was 0.6 (95% CI 0.5, 0.7) among first users of rofecoxib, and 0.6 (95% CI 0.5, 0.6) among first users of celecoxib. A prescription of gastroprotective agent during the current period following the incident prescription was similar for Coxibs and for other NSAIDs (in comparison with diclofenac the OR was 0.9 (95% CI 0.8, 1.0) for celecoxib and 0.9 for rofecoxib (95% CI 0.7, 1.1)). Compared with diclofenac the OR of shifting was 1.1 (95% CI 0.9, 1.2) among first users of rofecoxib, and 1.1 (95% CI 0.9, 1.3) among first users of celecoxib.

Conclusion: Coxibs, despite a greater price, show a similar risk of receiving a gastoprotective agent and of a shifting towards a different substance in comparison with diclofenac.

130. ANAPHYLACTIC REACTIONS TO OTC ANALGESICS, PARTICULARLY PROPYPHENAZONE-COMBINATIONS

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Introduction: The Netherlands Pharmacovigilance Centre Lareb received a substantial number of reports on anaphylactic reactions related to the use of 'over the counter' (OTC) drugs, especially analgesics. Although OTC analgesics are usually considered safe by the general public, severe anaphylactic reactions may occur.

Aim of the Study: To investigate if the risk of anaphylactic reactions being reported during the use of various OTC analgesics differs from the risk for these adverse drug reactions during the use of paracetamol.

Methods: Spontaneous reports by health professionals submitted to Lareb between January 1985 and July 1st 2004 were included. In a case/non-case design 'reporting odds ratios' (RORs) were calculated using logistic regression analysis. Cases were defined as reports in which 'anaphylactic reaction' or 'anaphylactoid reaction' or 'anaphylaxis' was reported. All other reports were considered as non-cases. The index group consisted of reports that mentioned paracetamol/propyphenazone/caffeine, naproxen, diclofenac, ibuprofen, acetylsalicylic acid or carbasalate calcium as the suspect medication, the reference group consisted of reports on paracetamol.

Results: A total number of 2191 reports was included in the analysis. In 120 reports (5.5%) an anaphylactic reaction (including anaphylactoid reaction and anaphylaxis) was reported. Among 110 reports on paracetamol six reports were coded as an anaphylactic reaction. Of the above mentioned analgesics only one differed statistically significant compared to paracetamol. Only on the combination paracetamol/propyphenazone/caffeine relatively more anaphylactic reactions have been reported. The ROR, adjusted for the source of the reports, was 20.3 (95% CI 5.6, 73.3).

Discussion: On all OTC analgesics available in The Netherlands, anaphylactic reactions have been reported. The results of our study suggest that the combination of paracetamol/propyphenazone/caffeine is strongly associated with an increased risk on anaphylactic reactions compared with the use of paracetamol. In the database of the WHO Collaborating Centre for International Drug Monitoring, anaphylactic reactions are also strongly associated with propyphenazone-combinations and not with paracetamol alone or caffeine alone. Consumers should be aware that all OTC analgesics are associated with a risk of provoking severe allergic reactions.

135. ANALGESICS AND HEPATO-BILIARY INJURIES: A PHARMACOEPIDEMIOLOGICAL CASE/NON-CASE STUDY

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Introduction: Analgesics are one of the most prescribed drug classes, and paracetamol is the most used. Although paracetamol hepatotoxicity is widely described at high doses, it is still described at therapeutic posology. The hepatotoxicity of other analgesics is less clearly established. As hepatotoxicity is a major cause of drug withdrawal, it has to be evaluated on a large exposed population of patients.

Aim: To estimate the hepatotoxicity of analgesics (paracetamol, dextropropoxyphene, tramadol, nefopam and opioids class III from OMS classification) using data from the French Pharmacovigilance Database between January 1997 to December 2003, with the case/non-case methodology.

Materials and Methods: For each analgesic, cases were side effects reported on the hepato-biliary tract, while non cases were all the other reports of reactions. We determined an odds ratio (OR) with a confidence interval of 95%.

Results: Among the 121 106 effects notified during the period, 11 066 (9.14 %) concerned the hepato-biliary tract. The risk of hepato-biliary injury was significantly increased with codeine (OR = 1.8, 95% CI 1.76, 2.55), paracetamol (OR = 2.88, 95% CI 1.79, 4.18), and dextropropoxyphene (OR = 4.27, 95% CI 2.53, 6.39) and the highest was with the association of dextropropoxyphene and paracetamol (DI ANTALVIC®) [OR = 4.59, 95% CI 2.74, 6.90]. The odds ratio was only of 1.04 (95% CI 0.86, 1.17) for tramadol, while it was not significantly increased with all the other analgesics (OR <1). Nefopam presented the smallest risk of hepato-biliary injury (OR = 0.45, 95% CI 0.32, 1.21). The database includes information on the gravity of reported effects (hospitalisation, death), and there were no more serious cases with paracetamol (68.9%) than with dextropropoxyphene (67.1%) or with their association (66.7%).

Conclusion: Although this database, related to a spontaneous reporting system, presents some limits, these results suggest that morphinics – except for codeine – are rather safe (OR <1), while nefopam would be the most interesting. However, the database doesn't allow us to take account patients' characteristics (risk factors, especially altered hepatic functions), posologies and drug associations. Further studies need to be performed to investigate whether analgesics are safe in patients with disturbed hepatic functions, in order to support practicians in their therapeutic choice. A prospective study has been started in our hospital.

140. ORGANISATION OF REGIONAL CENTRES OF PHARMACOVIGILANCE: THE EXAMPLE OF SICILY (ITALY)

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Background: As underlined in the new Italian Pharmacovigilance Directive, setting up of Regional Centres could implement the efficacy of National Pharmacovigilance System. Given this background, since January 1st 2003, the Sicilian Health Assessorship has been promoting a project for the re-organisation of a spontaneous reporting system in Sicily.

Aims: Information to healthcare professionals about risks and benefits of medicinal products.

Improvement of pharmacovigilance 'culture' through several initiatives, such as: provision of feed-back information to reporters, setting up of qualified Regional Pharmacovigilance Units, promotion of CME courses, etc.

Ultimate goal is to improve the number and the quality of ADR reports and to foster a rational and safe use of drugs.

Methods: The project relies on the following organisation: the Regional Pharmacovigilance Office coordinates the activity of four Units, organises courses for healthcare professionals and collaborates with other health regional offices. Three qualified Pharmacovigilance Units focus their activity on specific topics: drugs in pregnancy and phytovigilance, vaccine-vigilance and chemotherapy-related toxicity. The fourth Unit (Spontaneous Reporting Unit) is in charge of recording all ADR reports, forwarding to the relevant Unit those concerning the specific topics above described, and providing feedback information to reporters for the other ADRs. In particular, individual feedback consists of a qualified comment on ADRs de-

scribed and a detailed causality assessment. This Unit also conducts analysis of signals arising from ADR reports received.

Results: Since January 1st 2003 the number of ADR reports in Sicily showed a considerable increase. The rate of reporting healthcare professionals per 100 000 inhabitants rose from 5.4 in the year 2002 to 7 in 2003, and remains stable in the first half of 2004. This trend is even more significant, considering that in the same period, the National reporting rate had a remarkable decrease (from 12.1 to about 10). In fact, in 2002 Sicily ranked ninth in terms of number of forms received, whereas to June 2004, it ranks fourth. A similar improvement is shown in the rate of serious (39.5%) and unexpected (16%) ADRs reported, as well as in the accuracy and completeness of information provided in ADR forms filed by reporters.

Although still far from those of any efficient pharmacovigilance centre, these preliminary results show promise for the future. Longer times are required to assess the actual entity of this (we hope cultural) change.

150. AGE AND GENDER DISTRIBUTION OF CUTANEOUS DRUG REACTIONS IN FRANCE

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Cutaneous drug reactions (CDRs) are among the most frequent adverse events in patients receiving drug therapy. Several studies have suggested that a female preponderance may be observed in the number of CDRs.[1] Furthermore, CDRs seem to be age-related, with reporting rates substantially higher in the elderly and in the children. The aim of this study was to identify age and gender-related differences in the frequency of CDRs, in their clinical types and in the drugs responsible for these reactions in the French population.

Spontaneous reports of CDRs recorded by the French Pharmacovigilance System in 2002 were retrospectively analysed. We investigated age and gender specific incidence rates of CDRs, after forming several age groups. Drugs involved in the CDRs were analysed according to their imputability.

A total of 4551 reports of CDR in 413 children and 4138 adults were investigated [of which 2661 (58.5 %) were females and 1890 (41.5%) were males]. The study of these reports showed the most common age and gender to be female in the 40–49 year age group (9.6 %). The highest rate of recording in males was in the 50–59 year age group (7 %). The overall incidence of reporting rates per 100 000 female and male inhabitants/year of CDRs were respectively 8.7 and 6.5. The reporting rate progressively increased with age and the female/male ratio was 1.41. The most frequent CDR reported was urticaria. The most important causative drug was amoxicillin. Drug categories most frequently reported were anti-infectives, nonsteroidal anti-inflammatory drugs, general anaesthesia drugs and analgesics.

Conclusion: CDRs are recorded more often in adults aged between 40 and 59 years. There are more reports of CDRs among females than in males. Furthermore, our study confirms that CDRs are among the most frequent clinical manifestations reported. As the distribution of CDRs in our study goes with national data concerning drug consumption in France, we wondered about the interest of a single warning signal by CDRs.

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155. MEDICATION ERRORS IN SWITZERLAND: AN ANALYSIS OF THE SPONTANEOUS ADVERSE REACTION REPORTS RECEIVED AT THE SWISSMEDIC PHARMACOVIGILANCE CENTRE

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Introduction and Aims: Medication errors have an enormous impact on health systems worldwide. The observation that a large majority of medication errors seems to be preventable prompted us to look at the data collected at our centre with the aim of identifying strategies to reduce the frequency of such errors.

Methods: We searched our database for all reports coded as medication error and entered between January 1st 1997 and April 30th 2004. We analysed our data regarding kind of error, drug involved, seriousness, outcome and preventability. To assess the latter we reviewed each case and the corresponding product information leaflet.

Results: A total of 73 of 16 383 reports fulfilled our inclusion criteria. As our database is designed for a spontaneous reporting system and not for a systematic recording of medication errors, a substantial underreporting is inevitable. Analgesics were the most frequently involved drugs (17%), followed by antimicrobials (11%), antineoplastics (10%) and psychotropic drugs (10%). Application errors were reported in 36% of cases, wrong dosage in 33%, administration of a wrong drug in 19% and prescribing errors in 12%. A serious reaction was experienced by 63% of the patients while 22% suffered no reaction. In 74% of the cases the error was considered preventable, in 4% not preventable and in 22% of the reports preventability was unassessable.

Conclusions: The high percentage of preventable errors observed in our data set is consistent with published data. Several strategies for reducing medication errors such as computerised precriber order entry or laboratory-pharmacy linkage have been proposed. Our results suggest that the available product information is not taken into due account by healthcare professionals. A cost-effective and necessary first step would therefore consist in increasing the awareness among professionals of the necessity to consult carefully and adhere strictly to the product information when prescribing, dispensing and administering drugs.

165. CLINICAL PHARMACISTS' ROLE IN PHARMACOVIGILENCE IN A CARDIOVASCULAR WARD OF CHINA

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Introduction: Clinical pharmacy, a patient-focused pharmacy activity, is an emerging discipline in China. ADEs are common in a cardiovascular ward. However, no data are available about the prevent-

ability of ADEs in China and the impact of the clinical pharmacist on preventing ADEs remains unknown.

Aim of the Study: To assess the preventability of adverse drug events and measure the impact of the clinical pharmacist's participation in clinical practice on the prevention of ADEs.

Methods: Cohort comparing study. All the patients admitted to the cardiovascular ward, Huashan Hospital between May 2002 and March 2003 were included. Study was designed into two phases.

Phase 1: Investigating the preventability of ADEs without pharmacist's participation; *Phase 2:* Investigating the preventability of ADEs with pharmacist's participation.

Results: There were 64 identified ADEs in phase 1, of which 18 (28.1%) were preventable that were more serious than the non-preventable ADEs.The rate of preventable ADEs decreased by 33% from 4.5 per 1000 patient-days in phase 1 to 3.0 per 1000 patient-days in phase 2. In phase 2 pharmacists made 383 recommendations, of which 88.7% were accepted by the physicians.

Conclusion: ADEs are common and often preventable. More serious ADEs are more likely to be preventable. A lower rate of preventable ADEs was associated with pharmacist's participation. However, more effort should be made to improve the quality of pharmacist's participation.

170. CICLOSPORIN AND SERIOUS INTESTINAL DISORDERS

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Introduction: The World Health Organization collects summaries of case reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centers (NCs) in 76 countries. The Uppsala Monitoring Centre (UMC) holds this database and presents information derived from it, in collaboration with the UMC Review Panel. From 1984 up to April 2004, 120 reports of intestinal disorders associated with ciclosporin have been reported to the WHO ADR database, Vigibase, from eight different countries. Ciclosporin is one of the most important immunosuppressive agents, used alone or in combination with immunosuppressive drugs like steroids, azathioprine or cyclophosphamide to prevent or to treat organ rejection after kidney, liver, lung, pancreas and heart transplant. The drug information leaflet of ciclosporin lists diarrhoea, nausea/vomiting, abdominal discomfort, pancreatitis, gastritis, peptic ulcer and anorexia as gastrointestinal adverse reactions occurring in 2–3%, or greater, of transplanted patients (Prod Info Sandimmune®, 2001). However intestinal disorders, like those observed in WHO spontaneous reports, are documented in the literature only in few case reports.

Aim of the Study: To assess spontaneously reported cases on serious intestinal disorders as possible adverse reactions to ciclosporin.

Methods: A clinical review of case reports in Vigibase was performed.

Results: We assessed the WHO reports and divided them into five main groups, according to the type of disorders mentioned in the reports and coded by WHO-ART system: 39 colitis, 10 intestinal perforation, 19 peritonitis, 48 enteritis and 4 intestinal gangrenes, with globally 12 deaths. The high number of reports we assessed and the complex picture described suggest that cyclosporine can complicate the intestinal status of patients and this is insufficiently documented in literature. Considering all the case reports, we underline that ciclosporin was the only administered drug in more than one third of patients. In many cases, the disorders (colitis, pseudomembranous colitis and enteritis) seem to be related to viral or bacterial infections, probably resulting from the immunosuppressive activity of ciclosporin. As well, a disregulation of intestinal mucosa immune system could also explain, together with other risk factors, the cases with severe pathologies such as ulcerative colitis and its possible complications (intestinal perforation and peritonitis).

Conclusion: Considering that the spontaneous reporting data are proven to be useful in generating hypotheses to be confirmed by epidemiological studies, ciclosporin intestinal toxicity seems worthwhile to be signalled and monitored in the future.

175. SIGNAL DETECTION IN SPONTANEOUS REPORTING DATABASE: DATA FROM GIF, AN ITALIAN INTER-REGIONAL DATABASE

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The Italian Interregional Group on Pharmacovigilance (GIF) is made by five different regional Centres in Italy, where active groups working on pharmacovigilance have been present for many years. The GIF database includes today about 31 000 reports: in 2003 we received 3484 reports, about 55% of total Italian reports.

In May 2003 a new law on pharmacovigilance was introduced by the Italian government with new guidelines on reporting (non-serious reactions should now be reported not for all drugs but only for drugs inserted in an 'intensive monitoring' list). Furthermore reporting has been enlarged to nurses and other health operators. In 2003 a decrease of both number of reports (−20%) and number of reporters (−12%) and an increase in the percentage of serious adverse reactions (+5%) have been observed in the GIF area. These variations are much more evident in the second half of the year. No reports have been received by nurses or other health operators.

It is well known that the main goal of a spontaneous reporting system is to identify 'signals' on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Signal detection in GIF database is made every six months by quantitative analysis (Proportional Reporting Ratio) and case-by-case assessment. Signals related to the whole 2003 and to the first half of 2004 are discussed. Furthermore, we report also known serious adverse drug reactions, which can be reduced by a more rational drug use.

Presented signals include: clodronate and acute renal failure, amiodarone and renal toxicity, bisphosphonates and visual disorders, buprenorphine and weight loss, ceftriaxone and anaphylactic shock, ciprofloxacin and renal failure, NSAIDs and amenorrhoea and visual

disorders, flutamide and hepatotoxicity in women, levofloxacin and tendon rupture and dysphonia, dipyrone and vasculitis, nimesulide and renal failure and oligohydramnios, omega polienoics and epistaxis, teicoplanine and agranulocytosis, telitromycin and visual disorders, ticlopidine and serious haematological reactions.

180. GLIMEPIRIDE AND GLIBENCLAMIDE: SUMMARY OF TOXIC EPIDERMAL NECROLYSIS AND STEVENS JOHNSON SYNDROME

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Introduction: Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare and devastating diseases, often attributed to drug causes. Background incidences are estimated to be approximately 1 to 6 cases per million person-years and 0.4 to 1.2 cases per million person-years, respectively. Early withdrawal of causative drugs decreases mortality. The most common drug cause for SJS or TEN is the antibacterial sulfonamide group. Such conditions usually occur after a recent exposure (7 days for most drugs, depending on half-life), and a short duration. Sulfonylureas have also been implicated because of an assumed cross-allergenicity among sulfur-containing drugs. This assumption is not proven by available literature. The largest case-control study ever conducted (Roujeau, et al.) involved surveillance networks in four European countries, and yielded 245 cases of SJS or TEN. This study demonstrated no excess risk for the development of SJS or TEN associated with sulfonylurea therapy.

Aim: The aim of the study was to assess the potential correlation of data from a spontaneous reports database with case-control studies to verify the presence or absence of the hypothetical risk based on chemical structure alone.

Method: Postmarketing surveillance for glimepiride and glibenclamide has been performed in the Aventis Safety Database since 1998 and 1969, when these products were first marketed. A cumulative review of case reports in this database was performed using MedDRA terms, Stevens Johnson syndrome, toxic epidermal necrolysis, or oculomucocutaneous syndrome. Cases reported to Aventis from the Roujeau study were deemed unrelated to sulfonylurea therapy on the basis of the author's conclusions. Other cases in the Aventis database were examined in clinical detail, and only those agents with proven excess risk were classified as more likely causes than treatment with glimepiride or glibenclamide.

As of 6 May 2004, over two-thirds of reports of SJS or TEN received by Aventis Pharmaceuticals were reported by investigators from the Roujeau study. All other well-documented cases were regarded as unlikely related to glimepiride or glibenclamide because either there was a more likely drug cause with a compatible temporal exposure (within weeks), or there was an incompatible duration (years) of glimepiride or glibenclamide exposure prior to onset of the event.

The medical literature has not established a risk for sulfonylureas in the development of SJS or TEN to corroborate the historical suspicion. Individual case review of reports for glimepiride and glibenclamide does not suggest a safety signal.

185. MESSAGE FROM THE TOP: CHIEF PHARMACISTS VIEWS OF ADVERSE DRUG REACTIONS REPORTING

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Introduction and Aims: Hospital pharmacists were admitted to the MHRA's Yellow Card Scheme in 1997. This survey was performed to assess chief pharmacists' views on hospital ADR reporting, the pressures affecting it, and the priority it receives.

Method: A self-completion questionnaire survey was piloted on four chief pharmacists, and four principal pharmacists. An amended questionnaire was sent to the chief pharmacists of all 209 acute NHS trusts in the UK with a covering letter and pre-paid return envelope in February 2002. A tick box allowed non-respondents to indicate their reasons for not doing so. A second mailing was sent 9 weeks later.

Results: The questionnaire's response rate was 66% after the first mailing and 82% following the second mailing. Eighteen declined to participate, leaving 154 completed questionnaires (74% of questionnaires sent).

Overall, 37% of respondents operated a local ADR reporting scheme. Sixty-seven percent of respondents strongly agreed or agreed, that yellow cards from pharmacists should be reviewed by the pharmacy department before submission to the CSM. Seventy percent of respondents felt their pharmacists did not have the competency or were unsure of their pharmacists' ability to detect ADRs.

Three chief pharmacists reported complaints from medical staff (2%) about pharmacist ADR reporting; no complaints from patients were reported.

While 96% felt that ADR reporting was an essential component of a pharmacist's role, this fell to 78% strongly agreeing or agreeing with the statement 'monitoring of adverse drug reactions should be a priority for pharmacy services'.

Increased time on the wards in a clinical capacity was felt likely to increase ADR reporting rates by 86% of respondents. Seventy percent of respondents agreed that 'current recruitment and retention problems are inhibiting pharmacist ADR reporting'. Eighty-eight percent felt that increased training would benefit pharmacists.

Conclusion: A significant number of chief pharmacists have concerns about their pharmacists' involvement in ADR reporting, two thirds believing reports should be reviewed by the pharmacy department. This may be an attempt to maintain the quality of reports, or a desire to reduce the risk of local complaints. The MHRA have expressed no concerns about the quality of pharmacists' reports and this survey's finding of few complaints should allay these fears; local causality assessments may prevent reports reaching regulatory authorities. Addressing recruitment difficulties and training may improve reporting.

188. PHARMACOVIGILANCE IN PUBLIC HEALTH PROGRAMMES: DO WE NEED IT?

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The goal of the Filariasis Elimination program is to eliminate Filariasis from the Philippines by year 2010 using Mass Drug Adminis-

tration (MDA) of DEC and Albendazole to every eligible person in established endemic areas. Region V is known to be endemic to the parasite with 4 037 516 eligible for MDA in 2003. It used the existing health care system composed of three tiers of health workers (HW) to distribute the drugs. DEC was supplied by the government while Albendazole was donated. ADR reports came from local HW only when they received spontaneous reports from family members. HW visit the family to investigate the reported ADR but not to provide treatment.

Aims: To determine the prevalence of serious ADRs after the MDA.
Result: About 3,479,474 people took the drugs. 24% reported dizziness, headache, nausea, headache, fever and fatigue as the most common side effects. Noticeable among the Filipino patients were prolonged sleep duration, sleepiness and severe abdominal pain. Alarmingly, nine deaths were reported, the youngest occurring in a 4-year-old female who vomited worms prior to her death. Another 6 year old apparently well succumbed only after a few hours of drug intake. Lethargy was reported in both 2- and 8-year-old patients prior to death. Only one death was felt not related to the drugs due to encephalitis.

Discussion: Despite the uncommonness of serious ADRs (3/100 000) the report of deaths stresses the need for a more active ADR surveillance system. The effects of other parasites which can migrate aberrantly causing lung obstruction and death, the concomitant effects of malnutrition, effects on potassium of the drugs, a possible sequence effect causing harmful drug-drug or drug-disease interactions and different but more serious CNS side effects among Filipinos are issues for future study. It also showed that reports of serious ADRs may endanger both the success of the program and the lives of the health workers. Lastly, donated drugs used in public health programs should not be exempted from ADR monitoring especially when administered to large number of people of varying ages.

190. PILOT PROGRAMME ACTIVITY COSMETIC-VIGILANCE COSMETIC-SURVEILLANCE ACTIVITY: INQUIRY ABOUT COSMETICS ADVERSE REACTIONS BETWEEN QUESTIONNAIRE IN FIVE PHARMACIES OF NAPLES

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Cosmetics are largely diffuse substances topically applied to wash, to perfume, to improve the look. Cosmetic industries use about 9000 chemicals traded in 30 000 different commercial denomination.

Despite a large use of cosmetics, no high incidence of adverse reaction is reported. Therefore cosmetic adverse reactions might be underestimated, not because of the severity of event, but diagnostic inability without any medical consultation.

Skin disease are the most common cosmetic adverse reactions. They are generally not serious but widely various.

The cosmetic intolerance is increased by the presence of toxic substances involuntarily introduced in the formulation, originated by ingredients' reaction, and created by photo-induced reaction. Abuse/incorrect use or association of several products, pre-existent injuries and at last individual factors also play an important role in the appearance of cosmetic adverse reactions.

Aims: To evaluate the population cosmetic use behaviour through a questionnaire supplied by pharmacists. To assess the prevalence and the features of cosmetic adverse reactions.

Material and Methods: Pharmacies involved agreed to submit a specific questionnaire to all customers. Two weeks, 7 hours/day, of data collection were made between 10am to 1pm and 4pm to 8pm. Customers were asked about the cosmetic use behaviour and the possible onset of any adverse reaction ascribed to their use. The typology of reaction and the substance probably involved were also investigated.

The filled questionnaires were recorded in a database and data were analysed.

Results: Actually about 4000 people were interviewed in nine different pharmacies and the first 460 answers collected from one pharmacy were analysed. 88 (19.1%) customers refused to fill out the questionnaire. Females represented 78.2% of responders with 44.2 ± 15.6 mean age (no differences between gender). 99% of female and 88.9% of male customers declared cosmetic use. About half of people go to the pharmacy to take a drug and over one third to buy a cosmetic. 24.2% of cosmetic users experienced at least one adverse reaction and females the most (26.7% F; 13.9% M).

Data entry is actually in course to increase the power of the study, necessary to analyse the impact of cosmetic use and the real prevalence of cosmetic adverse reactions.

Preliminary results highlight the large use of cosmetics among pharmacy customers. The rate of people reporting adverse reactions, although preliminary, suggests that these products, often considered as completely safe, may put people at risk of adverse events and need a higher level of attention in their use.

195. DRUGS AND DEAFNESS: A PHARMACO-EPIDEMIOLOGICAL CASE/NON-CASE STUDY

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Introduction: Drug inducing deafness are not always readily detected and some of them can be the cause of irreversible auditory lesions. They should be promptly recognised in order to withdraw the suspected drug and to avoid further exposure. Many pharmacological classes are associated with deafness such as anti-infectious, vaccines, antineoplastics, and diuretics.

Aim: To assess the relationship between exposure to drugs and deafness from the French Pharmacovigilance database.

Method: We used the case/non case study methodology. Cases were deafness reports and non cases were all reports of adverse reactions other than those being studied. An odds ratio (OR) was determined with a confidence interval (CI) of 95%.

Results: Among the 171 717 adverse drug reactions recorded in the database from January 1993 to December 2003, 174 (0.1%) concerned deafness. We found that this side effect was associated especially with anti-infectious and antineoplastics. In addition to the well

known ototoxicity of aminosides, other antibiotics incriminated in deafness onset were macrolides (azithromycin OR = 10.59, 95% CI 10.55, 14.36), glycopeptides (teicoplanin OR = 7.83, 95% CI 7.71, 9.07), tetracyclines (doxycycline OR = 6.98, 95% CI 6.22, 8.88) and cephalosporins (ceftazidime OR = 6, 95% CI 5.55, 6.54). Among antimalarial agents, the highest odds ratio were for quinine (OR = 181.48, 95% CI 176.98, 219.21) and the combination pyrimethamine + sulfadoxine (OR = 31.01, 95% CI 28.07, 39.81). Some antifungals (amphotericin B OR = 4.21, 95% CI 3.94, 5.11), antiretroviral drugs (zalcitabine OR = 2.04, 95% CI 1.74, 2.54) and vaccines (MMR vaccine OR = 24.98, 95% CI 23.17, 36.05) were also associated with deafness. Fluorouracil had the second most important OR among antineoplastics after cisplatin (OR = 29.23, 95% CI 27.90, 34.22). Among diuretics, furosemide had the most important OR 4.10, 95% CI 4.07, 4.68). Moreover, the database indicates the evolution for each case, showing a recovery with (16%) or without (24%) sequel. Issue was unknown in 43.26% of the cases.

Conclusion: Although under reporting is a limit of a spontaneous reporting system, its contribution is useful to improve the knowledge about drug-induced deafness and allowed to emphasise some drugs which were poorly described in the literature.

200. SAFETY MONITORING OF A NEW PENTAVALENT VACCINE (DPT+HEPB+HIB) IN GHANA'S EXPANDED PROGRAMME ON IMMUNISATION (EPI)

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Introduction: In 2002, a new pentavalent vaccine DPT+HepB+Hib was introduced into Ghana's EPI for routine immunisation. The vaccine which is administered at 6, 10 and 14 weeks after birth permitted the introduction of new antigens – hepatitis B (HepB) and haemophilus influenzae type b (Hib) vaccines – into Ghana's EPI and was combined with and administered at the same time as the existing diphtheria, pertussis and tetanus (DPT) vaccine. While DPT has been used extensively, there was relatively little experience on the safety of DPT+HepB+Hib.

Aims: To document adverse events following immunisation with DPT+HepB+Hib during routine immunisation in four settings – a teaching hospital, two nearby polyclinics and a community immunisation centre.

Methods: Prospective observational study wherein, following Ethical Approval, and, after signed informed consent from parents/carers, infants administered DPT+HepB+Hib in line with EPI guidelines were followed up. Adverse events following immunisation (AEFI) reports were obtained from hospital folders collected at a dedicated hospital department. AEFI reports were also solicited using structured investigator-administered questionnaires during subsequent immunisation and follow-up at the immunisation centres.

Results and Discussion: 351 participants were recruited in 8 months. 260 have completed the study, 54 on-going and 37 lost to follow-up due to various reasons including geographical relocation, continuation of immunisation elsewhere and withdrawal of consent. Follow-up of defaulters included telephone calls and home visits. There were 89 attendances at the dedicated AEFI hospital department by 70 patients. The main AEFI reported by patients on follow-up was fever (38.8% of patients) within three days of vaccination whilst cough was the main cause of hospital visit (12.5%) occurring in nearly all cases after 7 days of vaccination. Only 5 cases led to hospitalisation (average 2 days) but all patients recovered without sequalae. Challenges encountered included huge time needed for initial recruitment and administration of questionnaires and following-up 'lost' patients.

Conclusion: The newly introduced pentavalent vaccine DPT+HepB+Hib in Ghana's EPI has been shown to be safe and well tolerated. The study has indicated that it is possible to carry out well-designed AEFI monitoring in resource poor settings.

Acknowledgement: Study funded by the Ghanaian-Dutch Collaboration for Health Research and Development.

205. ADVERSE EFFECTS IN HIV INFECTED PATIENTS CO-INFECTED WITH HEPATITIS C VIRUS (HCV) RECEIVING ANTIRETROVIRAL TREATMENT AND THE TREATMENT OF TUBERCULOSIS INFECTION

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Introduction: In HIV infected patients co-infected with hepatitis C virus (HCV) tuberculosis was shown in those with lymphocytes CD4 <200 cells/mm^3 and/or with lymphocytes CD4>500 cells/mm^3 and with PPD >5 mm, as well. Antiretroviral and antituberculotic treatment could interact on different ways, especially in HIV patients co-infected with hepatitis C virus (HCV) and produce adverse effects.

Aim of the Study: The aim of this study was to quantify the adverse effects of antituberculotic treatment in HIV infected patients and its relationship with HCV, highly active antiretroviral treatment (HAART) and CD4 count.

Methods: Data were obtained from patients continuously monitored at the HIV/AIDS Unit, a university teaching hospital, Belgrade, Serbia and Montenegro. The prevalence of adverse effects between groups of patients on IDN+ and IDN- regimens were compared using the chi-square test. The probability of developing each adverse effect was estimated by the Univariate logistic regression and stepwise Multivariate logistic regression.

Results: There were 338 HIV infected patients include in this study (187 HIV+HCV+ and 151 HIV+HCV–). The treatment finished in the same proportion in both groups. However, we must consider that HIV+HCV+ patients abandoned the treatment due to the adverse effects (71/187 = 37.96%) while HIV+HCV– patients abandoned it in a shorter percentage (26/151 =1 7.21%; $p < 0.001$). Amongst the adverse effects, hepatotoxicity was the most frequent in HIV+HCV+ (65% vs 38%; $p = 0.036$). Univariate and stepwise multivariate lo-

gistic regression has shown that the risk of developing hepatotoxicity is almost 6-fold greater in HIV+HCV+ group of patients (RR = 5.8; 95%CI 1.5, 22.1). We did not find an association between the appearance of adverse effects or hepatotoxicity with the antiretroviral treatment nor with CD4 values.

Conclusion: The adverse effects in the treatment of tuberculosis infection are related to HIV infection and HCV status. In HIV infected patients hepatotoxicity is related to hepatitis C virus and not to the antiretroviral treatment nor to the CD4 values.

215. LIVER TOXICITY OF LOPINAVIR/ROTONAVIR-CONTAINING REGIMENS IN HIV-INFECTED PATIENTS WITH OR WITHOUT HCV CO-INFECTION

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Introduction: Liver toxicity is a common side effect of antiretroviral therapy, particularly in subjects with hepatitis C virus (HCV). It leads to treatment discontinuation in 10–15% of patients who initiate highly active antiretroviral therapy (HAART).

Aim of the Study: The incidence of severe liver toxicity after initiation of lopinavir (LPV) + ritonavir (RTV) were assessed in all consecutive HIV infected patients.

Methods: Data were obtained from patients continuously monitored during 2003 at the HIV/AIDS Unit, a university teaching hospital, Belgrade, Serbia and Montenegro.

Results: A total of 116 HIV infected patients were analysed. Mean features: 82% men; 52% co-infected with HCV; mean age 36 years; mean CD4 count 276 cells/ml; and mean plasma HIV-RNA 73,041 cop/mL. The incidence of grade 3–4 liver toxicity (>5-fold elevation in liver enzymes) at 3 months was 1.9% and the cumulative incidence at 12 months was 4.3%. All cases occurred among patients with HCV, and all had liver enzyme elevations at baseline. Among HCV infected patients, the cumulative incidence of LPV/RTV severe liver toxicity was 10%, which was significantly greater ($p = 0.011$) than among HCV-negative individuals (0%).

Conclusions: The incidence of severe liver toxicity attributable to LPV/RTV is low, although this complication may be more frequent among HCV co-infected patients.

220. LOPINAVIR/RITONAVIR VS INDINAVIR/RITONAVIR IN HIV INFECTED PATIENTS: IMMUNO-VIROLOGICAL OUTCOME AND SIDE EFFECTS

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Introduction: A comparison between lopinavir/ritonavir (LPV/RTV) and indinavir/ritonavir (IDV/RTV) as first-line HAART is not available at the moment.

Aim of the Study: The aim of this study was to compare effectiveness and drug-related adverse events of LPV/RTV and IDV/RTV as first-line HAART.

Methods: Data were obtained from patients continuously monitored at the HIV/AIDS Unit, a university teaching hospital, Belgrade, Serbia and Montenegro. We retrospectively selected 28 patients starting with LPV/RTV and 34 starting IDV/RTV as first-line HAART. We recorded demographic characteristics, immuno-virological and metabolic parameters (triglycerides, total cholesterol) and side effects at baseline and every 3 months.

Results: In a median follow-up of 1 year in LPV/RTV group and in IDV/RTV group, a significant improvement of median immunological parameters was observed in both groups, respectively. There were no significant differences between two groups. Similar results were obtained for plasma viral load (HIV-RNA: 4.79 vs 4.88 at baseline; from month 3 median plasma viral load maintained undetectable. Triglycerides increased similarly in both groups. Patients who received IDV/RTV had a higher increase of total cholesterol at month 3 and 6 ($p = 0.04$), but this data was not confirmed at month 12. One patient receiving LPV/RTV and 9 receiving IDV/RTV stopped definitively the PI during observation. One patient receiving LPV/RTV stopped because of alopecia. Seven patients receiving IDV/RTV stopped because of nephrolithiasis, and two because of nausea and vomiting.

Conclusion: In our setting, LPV/RTV and IDV/RTV showed the same effectiveness as first-line HAART. Patients receiving IDV/RTV had a higher risk of stopping therapy because of drug-related adverse events such as nephrolithiasis, nausea and vomiting.

225. LOW-DOSE STAVUDINE: AS EFFECTIVE AS STANDARD DOSE BUT FEWER SIDE EFFECTS

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Introduction: Stavudine (d4T) is associated with peripheral neuropathy (PNP). Cohort data discuss that d4T is involved in mitochondrial toxicity. A reasonable approach to reduce toxicity could be a dose reduction of d4T, provided that antiretroviral efficacy is sustained.

Aim of the Study: Data were obtained from patients continuously monitored for incident cases of PNP at the HIV/AIDS Unit, a university teaching hospital, Belgrade, Serbia and Montenegro. This prospective analysis of an outpatient clinic cohort compares HIV-patients receiving d4T 'low dose' with 'standard dose' – regarding efficacy and adverse effects.

Methods: 168 patients were taking d4T between January 1999 and June 2003. 109 patients received standard dose (>60kg: 40mg; <60 kg: 30mg) and 59 patients low dose (>60 kg: 30mg; <60kg: 20mg).

Results: Baseline characteristics were comparable, but significantly more women (36%) received low dose d4T than men (11%). After 36 months, mean change in viral load was –1.7 log ($p < 0.001$) and mean CD4-change was +260/μL ($p < 0.001$). Overall, there were no differences between low and standard dose group in virological and immunological outcomes. Patients on low dose were significantly longer on d4T than those on standard dose (Kaplan Meier probability after one year: 84% vs 74%, after 3 years: 52% vs 41%; $p = 0.02$). 27% discontinued d4T due to side effects. PNP was significantly lower in the low dose (11%) than in the standard dose group (24%; $p < 0.01$).

Conclusions: D4T as part of HAART is effective in reducing viral load and in increasing CD4-count independent of low or standard dosage. PNP occurred more often on standard dose than on low dose. In order to reduce side effects like PNP slight underdosage of d4T may be a reasonable approach.

230. HOIGNE SYNDROME: CASE REPORTS AND MECHANISM OF PATHOGENESIS

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Introduction: Hoigne syndrome, described first in 1959, is still occurring and its differentiation by practitioners from an authentic anaphylactic shock remains unknown. We report three cases of Hoigne syndrome which were thought first to be anaphylactic shocks.

Case Reports: *First case report (in 1992)*: For acute bronchitis, a 63-year-old woman, was given bipenicilline® (benzylpenicilline procaine). One minute after the injection, she had lipothymy, foam at lips and cyanosis at limbs ends with 120/60mm Hg of blood pressure. The cyanosis quickly became generalised. The patient was reanimated without success and she died.

Second case report (in 1993): For erysipelas, a 43-year-old man had been taking twice a day bipenicilline® (benzylpenicilline procaine) for 7 days. During the 16th intramuscular injection, he had swarming, lower limbs paresthesia and ears buzz which regressed spontaneously in an hour.

Third case report (in 2004): A 37-year-old man was under chronic haemodialysis. For a foot abscess, he was given after haemodialysis combicillin® (benzylpenicilline procaine, benzylpenicilline sodique) intravenously. Immediately, he became anxious and had visual and auditive hallucinations, palpitations, a sensation of impending death and finally convulsions. All the signs regressed spontaneously in half an hour.

Discussion: The cases were validated according to the Begaud et al. method of imputability. The three cases were valued to very probable because of a very suggestive delay (less than 1 minute) and the evolution was suggestive (spontaneous regression after drug withdrawal in the 2nd and 3rd cases and fatal issue in the 1st case).

In the 1st case, the main criteria to diagnose Hoigne syndrome are cyanosis and normal haemodynamic constants. In the 2nd case, Hoigne syndrome was diagnosed because of neurological and sensory manifestations. In the 3rd case, the Hoigne syndrome was diagnosed because of clinical features (hallucination, anxiety, palpitation, sensation of impending death and convulsions). Using intravenous injection may explain the immediate reaction.

In the three cases, immuno-allergic manifestations were not observed. The mechanism of pathogenesis of Hoigne syndrome remains discussed but it is different from the anaphylactic shock and the other immuno-allergic reactions. It is mainly said to be due to application of depot procaine penicillin in cerebral circulation that causes cerebral embolism. This embolism generates focal ischemia.

Other authors suggest a direct toxicity of procaine in the central nervous system. Since Hoigne syndrome was reported with other antibiotics, none containing procaine, such as gentamycin and cefuroxime; another mechanism of pathogenesis is proposed.

235. FAILURE OF ORAL CONTRACEPTIVES DURING THE USE OF HYPERICUM-CONTAINING DRUGS

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Introduction: Herbal drugs may increase or decrease the breakdown of other medicines. Hypericum (St John's Wort) is an inducer of CYP3A4 activity.

Aim: To assess if the use of hypericum influences the effectiveness of oral contraceptives (OACs).

Methods: A review was made of the world-wide database of reports of suspected adverse drug reactions of the WHO Uppsala Monitoring Centre (UMC).

Results: So far a total of 16 case reports have been collected of unintended pregnancy in women using OACs and hypericum simultaneously; 13 women used a combination AOC and 3 a levonorgestrel-only OAC. Two additional patients using hypericum experienced failure of a post-coital emergency OAC.

Conclusion: Worldwide many women use OACs and also many women use drugs containing hypericum. With a pearl index of about 0.5 or 0.6 pregnancy is expected to occur by chance in a substantial number of women using both drugs simultaneously. Hypericum is known to cause intermenstrual bleeding in OAC users, however, and the experiences reported to the UMC suggest that the interaction between hypericum and OACs has practical relevance.

240. PHARMACISTS' ATTITUDES AND BEHAVIOUR RELATED TO REPORTING ADRS: A CASE-CONTROL STUDY IN PORTUGAL

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Introduction: Adverse drug reaction (ADR) spontaneous reporting systems are the basic components for the comprehensive post-marketing surveillance of drug-induced risks. Spontaneous reporting systems offer many advantages; however, underreporting is the main intrinsic disadvantage.

Aim: The study was conducted to identify pharmacists' attitudes and opinions associated with ADR reporting.

Methods: The current survey is a case-control study. The study population is the pharmacists who work in the geographic area of North Regional Health Administration (N-RHA) of Portugal. The 34 cases are pharmacists who reported at least one ADR to the regional drug surveillance of the north between 2000 and their envelopment in the study. The 280 controls were randomly selected among the remaining pharmacists. All were interviewed using a mail self-administered questionnaire.

Results: A total of 252 questionnaires were returned from 295 eligible pharmacists (85.4 %); of these, 31 were returned from cases (100 %) and 221 from controls (83.7 %). The following attitudes are

associated with a smaller probability of reporting: 'believe that really serious adverse drug reaction was well documented by the time a drug is marketed'; 'believe that only report an adverse drug reaction if I am sure that it is related to the use of a particular drug'; and 'believe that it is only necessary to report serious or not expected ADR'.

Conclusion: This study indicates there are some pharmacists' attitudes reporting ADR associated with underreporting. A possible way to increase the notification could be the development of education strategies for hospital and communitarian pharmacists with the objective of decreasing the underreporting. The design and aims of this intervention could be based on the pharmacists' attitudes and opinions with significance in this study.

245. PHYSICIAN REPORTING OF ADRS: A CASE-CONTROL STUDY IN PORTUGAL

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Introduction: Voluntary adverse drug reaction (ADR) reporting is fundamental to medical drug safety surveillance. Substantial underreporting exists and is the system's main limitation.

Aim: The study sought to identify knowledge and attitudes associated with ADR reporting by physicians.

Methods: Case-control study covering a population of National Health Service, medical practitioners in Northern Portugal. 88 cases comprised physicians who reported at least one ADR to the northern region drug surveillance unit from 2000 to date of enrolment in the study. The 771 controls were randomly selected from among the remaining physicians. All interviews were conducted using a self-administered mail questionnaire. Knowledge and attitudes regarding spontaneous ADR reporting were based on Inman's 'seven deadly sins'. Agreement with the questions included in the questionnaire was measured using a horizontal, continuous visual analog scale and unnumbered. Recorded answers were read in a range from zero to ten. We used logistic regression to determine the ADR reporting adjusted odds ratio (OR).

Results: A total of 397 questionnaires were received from 731 eligible practitioners (54.3%), 66 from cases (84.6%) and 331 from controls (50.7%). Physicians who worked in both hospital and ambulatory settings were more likely to report ADRs. Attitudes to ADRs were strongly associated with reporting probability. Hence, an interquartile decrease in any of the following attitudes increased the probability of reporting by: (a) 87% for complacency [the belief that really serious adverse drug reactions are well documented by the time a drug is marketed (1/IqOR = 1.87; 95% CI: 1.13, 3.10)], (b) 109% for insecurity [the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction (1/IqOR = 2.09; 95% CI: 1.27, 3.41)], (c) 143% for diffidence [the belief that one would only report an adverse drug reaction if one were sure that it was related to the use of a particular drug (1/IqOR = 2.43; 95% CI: 1.63, 3.65)], (d) 220% for indifference [the belief that the one case an individual doctor might see, could not contribute to medical knowledge (1/IqOR = 3.20; 95% CI: 1.73, 5.85)], and (e) 71% for ignorance [the belief that it is only necessary to report serious or unexpected ADRs (1/IqOR = 1.71; 95% CI: 1.02, 2.89)].

Conclusion: Study indicated that there are many physicians' attitudes associated with underreporting ADR and that there is strong association between such attitudes and reporting probability. We suggest that increase of notification may be achieved by implementing educational strategies directed to these identified factors of under-reporting.

250. PATIENT EXPERIENCE REPORTS CAN HELP IMPROVE THE QUALITY OF EPILEPSY TREATMENT

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Introduction: Many chronically ill patients have a profound interest in their disease and treatment. Observations by patient may improve our knowledge and understanding of patients' perception of their treatments. Good communication between patients, physicians and pharmacists can improve treatment adherence, effectiveness and safety, and help identify new adverse reactions or other problems.

Aim: To study the pharmacovigilance value of patient experience reports (PERs).

Methods: As a pilot, The Netherlands Epilepsy Society has added an electronic Patient Experience Reporting Form to its website, for communicating any possibly treatment-related events, positive as well as negative (*www.epilepsievereniging.nl*).

Results: In an 11-month period, 115 respondents completed a PER form. There were 48 positive experiences reported, 58 suspected side effects and four suspected interactions. The PERs concerned 'labelled' as well as 'unlabelled' adverse reactions. Many were considered to have potential pharmacovigilance value, often giving information about the kind of problems that worry patients. A finding of interest was, for instance, that in many patients several 'labelled' adverse events occurred simultaneously. Several PERs described characteristic symptoms of the 'polycystic ovaria syndrome' during the use of valproic acid, even though this syndrome is not mentioned in the data sheet. An example of a possible report of an 'unlabelled' interaction concerned a decreased effect of venlafaxine after starting carbamazepine.

Conclusion: Patient experience reports can pay a valuable contribution to the scientific evaluation of the treatment of chronic diseases. Patient associations are a natural and neutral place for collecting such reports.

255. NEUROPSYCHIATRIC ADVERSE DRUG REACTIONS IN GENERAL PRACTICE

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Introduction: Neuropsychiatric adverse drug reactions (ADRs) may be induced by agents used to treat neurological and mental disorders as well as by compounds prescribed for the treatment of diseases

affecting other organ-systems. Limited information is available on drug-induced neuropsychiatric disorders in general practice.

Aim: The present study aimed to examine the spontaneous reports of both neurological and psychiatric ADRs collected during a two year-period in PharmaSearch database, an Italian database recording reports of ADRs from general practitioners (GPs).

Methods: For the present survey, among all ADRs reported to the PharmaSearch Coordinating Centre, those involving central & peripheral nervous system disorders and psychiatric disorders were selected. Reports were classified according to the WHO criteria for causality assessment and evaluated by a team of experts including neuro-psychiatrists, pharmacologists, pharmacists and GPs.

Results: Between January 2002 and December 2003, 171 general practitioners sent a total of 1131 reports corresponding to 1892 ADRs. Of overall reports, 310 (27.4%) involved the central nervous system (CNS) resulting in 440 neuropsychiatric reactions (specifically, 241 neurological and 199 psychiatric). 40 reports were excluded because they were incomplete or contradictory and thus classified as 'unlikely' or 'unclassifiable'. Therefore, the present analysis was carried out on 270 reports with 391 neuropsychiatric reactions (213 neurological and 178 psychiatric, respectively). A total of 189 females (70.0%) and 81 males (30.0%) were involved in the 270 reports, and the age of patients with CNS effects was 60.5 ± 15.4 years. Vertigo (16.4%), confusion (10.7%) and headache (10.0%) were the reactions more commonly reported. Drugs indicated for the treatment of nervous system disorders (ATC 1 code = N) accounted for only 38.4% of neuropsychiatric reactions, while most of these reactions were related to drugs indicated for other than nervous system diseases. Non-steroidal anti-inflammatory drugs (NSAIDs), fluoroquinolones, antidepressant drugs, opioids, and proton pump inhibitors (PPIs) were the categories most frequently suspected for neuropsychiatric reactions. Of 391 neuropsychiatric reactions, 78 (19.9%) were unlabelled and 41 (10.5%) were serious.

Conclusion: The present study carried out in general practice underlines the importance of neuropsychiatric ADRs and reminds GPs to pay attention to this kind of toxicity when they prescribe pharmacological agents to their patients. Particularly, our findings emphasise the value of neuropsychiatric toxicity from drugs widely used (e.g. NSAIDs, antimicrobials and PPIs) and responsible for adverse reactions sometimes underestimated.

260. CASE REVIEW OF COX-2 SPECIFIC INHIBITORS RELATED ADRS RETRIEVED ROM THE DATABASE OF THE NATIONAL ADVERSE DRUGS REACTION REPORTING SYSTEM IN TAIWAN

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Introduction: The National ADR Reporting System in Taiwan was established in 1998. Since October 2000 and February 2001, the COX-2 specific inhibitors, i.e., celecoxib and rofecoxib, have been launched in Taiwan for patients with arthritis. The reimbursement by National Health Insurance system for these two drugs is restricted to arthritis patients with age >60 years, acute severe trauma, stroke, concomitant usage of steroid medications, gastrointestinal comorbidities, anticoagulants, or liver cirrhosis.

Aim of the Study: To review and characterise the ADR cases of celecoxib and rofecoxib spontaneously reported to the National ADR Reporting System in Taiwan during the years of 2000 and 2003.

Method: We retrospectively analysed all the celecoxib and rofecoxib ADR cases retrieved from the electronic database of the National ADR System in Taiwan. All ADR reported from clinical trials were excluded.

Results: In the past three years, celecoxib and rofecoxib were responsible for 45 ADR cases (26 and 19, respectively) from the database. They were reported by pharmacists (60.4%) and market authorisation holders (22.9%) to the National ADR system.

The average age of all cases is 67 ± 14. It is observed that 77.8% of cases were at the age older than 60 years. Gender predominance was not found (female 53.3%). Only 12 cases (26.7%) were documented to be prescribed for labelled indications (arthritis, etc.).

The most frequent adverse reactions included cutaneous disorders (22 cases, 48.9%), acute renal failure (seven cases, 15.6%), oedema (five cases, 11.1%), and gastrointestinal bleedings (four cases, 8.9%). Most of cases (88.4%) occurred during the first month therapy. There are ten serious cases (22.2%); among them one case was fatal (complicated with acute renal failure and hyperkalemia), and nine cases required at least 7 days to recovery. According to Naranjo's method, 82.2% cases were possibly and 17.8% cases were probably related to the suspected drugs.

Conclusion: Our data indicated that most cases were often with older age, multiple risk factors for the development of renal, gastrointestinal and cardiovascular disorders. Gastrointestinal toxicity cannot be eliminated by COX-2 specific inhibitors and renal toxicity is still a concern. We stress that careful monitoring for COX-2 specific inhibitors is necessary for patients with high risk factors for the ADR occurrence, especially during the first month therapy.

265. CAN COLCHICINE POTENTIATE THE ANTI-COAGULANT EFFECT OF FLUINDIONE?

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Introduction: The national pharmacovigilance system in France is based on a network of 31 regional centres. A monthly meeting is programmed to analyse surveys about drug safety and to exchange about received notifications to detect potential alert signals. In such a recent meeting, two cases of marked overanticoagulation were reported indicating a potential interaction between colchicine and the oral anticoagulant, fluindione. Two additional cases were also detected in the French pharmacovigilance database.

Aim of the Study: This report analysed the characteristics of these four cases.

Results: The four patients had a baseline international normalised ratio (INR) which was stable and in the therapeutic range under a long-term oral anticoagulant treatment by fluindione. This drug was administered for atrial fibrillation (2) or for heart valve mechanical replacement (2) for at least 1 year. The patient's INR was found to be largely increased after introduction of colchicine therapy for acute gout attack. Three patients remained asymptomatic although they had high INR levels after three days of colchicine therapy. The fourth patient developed haemorroidal bleeding at the 8th day (the INR was >18). In all these cases, no other factors for increased INR could be found, especially no other new potentially interacting drug, but colchicine had been added. The role of colchicine is supported by the temporal relationship to the abnormal ratio and the subsequent lower fluindione doses required to maintain the INR within the normal range when colchicine was continued. To the best of our knowledge, there is no report dealing with this interaction. In one paper,[1] an increased INR on warfarin was observed after the addition to the anticoagulant drug of fluvoxamine and colchicine. This interaction was solely attributed to fluvoxamine.

The mechanism for this potential interaction is unknown (role of P glycoproteins?). No analytical interference between colchicine and INR assay could be found in a small experimental study we performed.

Conclusion: In order to validate this hypothesis raised from notified cases analysed by the national pharmacovigilance network of an interaction between colchicine and fluindione, an appropriate pharmacokinetic study must be performed.

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270. RISK FACTORS FOR BLEEDING IN PATIENTS WITH ORAL ANTICOAGULANT TREATMENT (OAT) AND SUPRA-THERAPEUTIC INTERNATIONAL NORMALISED RATIO (INR) WHEN HOSPITALISED

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Introduction: Oral anticoagulant treatment is a widely used therapy. In France, it is estimated that 400 000 to 550 000 patients are treated by OAT each year. The benefit of OAT is well demonstrated in various cardiovascular disease.

Aim of the Study: Recently, attention has been particularly drawn the risk of bleeding events with these drugs. They account for the first cause of hospitalisations for adverse drug reactions.[1]The incidence of haemorrhages is clearly raised when the INR, which is the recommended indicator of OAT optimal use, is above the therapeutic zone[2](value of target INR ranging between 2 and 4.5 depending on the indications). However, in many observations, where patient's INR is raised, there is no clinical symptom of haemorrhage. This implies that other factors have to be associated so that haemorrhage occurs. This study aimed to identify these risk factors.

Methods: Patients analysed in this study are 293 patients hospitalised with an INR exceeding the indications of the Summary of Product Characteristics (SPCs) [INR > 5]. The inclusion of patients was retrospective (data from the database of the Amiens French Pharmacovigilance Center until 31/12/2003) and prospective (cohort of patients from 01/01/2004 until 17/05/2004). These patients, were separated into two groups: 116 patients with an symptomatic haemorrhage and 177 patients without bleeding event. Comparison of both groups of patients was performed with the software SPSS on the following different variables: age, gender, history (haemorrhage, injuries able to bleed, stroke, …), status of renal function, concomitant treatments, INR value, and a classically proposed score of haemorragic risk.[3]

Results: This study is a pilot study because the number of patients must be currently considered as not important enough. INR level seems to be the most important risk factor and justifies the recommended tightened and regular management of its value in patient's follow-up. Other current findings are: no influence of age but a role for the treatment duration and a recent traumatism.

Conclusion: These are interesting findings but would need to be confirmed with a prospective long-term study including a large population of patients.

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275. SURVEY ON TEENAGERS' SELF-MEDICATION

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Introduction: Self-medication means that a patient treats himself without any medical prescription and or medical advice by a doctor.

Aim of the Study: Beside the advantage of using OTC products for treating small pains, the risk of misuse of medicines is of concern (ignorance of side effects, delay in diagnosis, interaction with other drug, error in dosage..).

Methods: These risks were outlined in a study where 252 French teenagers from high-school were given a questionnaire to fill in about their behaviour of self-medication.

Results: 198 of them answered (137 girls and 61 boys) in two different schools. 98.5% used self-medication. The frequency of drug intake is weekly for 11.5% of them, monthly for 25.5% and quarterly for 32.5%. Analgesics are primarily used (quoted by 93.5% of the teenagers) but also, and at a significant level, some prescription drugs (18.4%) or drugs used outside the indications validated by the Marketing Authorisation (4.5%). Among the potentially dangerous drug classes mentioned are six times an opiate analgesic, four times an anxiolytic, twice an antidepressant, twice an ergot alkaloid derivate and once a neuroleptic. The teenagers' use of self-medication in particular because of the accessibility to the drugs (the home medi-

cine-chest is quoted by 69.7% of them and purchase in pharmacy for 64.6%) and also because they consider the OTC products as non-dangerous (8.5% think that they are without danger and 18.5% that there is never a serious side effect). The analysis of the questionnaires clearly emphasised the lack of knowledge of the risks related to the self-medication. An information meeting on self-medication was then proposed and was very favourably welcomed by the high-school pupils.

Conclusion: We think that this type of preventive approach on the good use of drugs is fully part of our missions of pharmacovigilance and should be encouraged.

280. DRUG-INDUCED HAEMORRHAGES IN COMMUNITY PRACTICE

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Introduction: Some drug-induced haemorrhages (DIH) can be preventable: few studies have been conducted in ambulatory care.

Aim of the Study: The aim is to describe DIH in community settings and to assess preventability.

Methods: All general practitioners and specialists (except psychiatrists) in Aquitaine (3 million inhabitants) were asked to participate in a prospective 3-month study. Each participating physician was asked to fill in a specific form for each haemorrhage occurring in a patient treated by anticoagulants (antivitamin K or heparins), antiplatelet agents (clopidogrel, ticlopidine), non steroidal anti-inflammatory drugs (NSAIDs) or aspirin (low or normal dose). Data collected for each patient were: sex, age, past history, current treatment, type of haemorrhage, evolution. Causality was assessed for each case (5-level score: definite, highly probable, possible, doubtful, excluded). For cases with causality considered as at least possible, preventability was assessed (3-level score: definitely or possibly preventable, preventability nonassessable, possibly or definitely unpreventable).

Results: Of 505 participating practitioners (7.8% of the total number in the region), 113 (85 general practitioners and 28 specialists) reported at least one haemorrhage case during the study period (September 15, 2003–December 14, 2003). Among specialists, ten medical or surgical specialities were represented.

A total of 168 patients with haemorrhage were included: mean age: 73.3 years (range: 5–99); sex ratio: 1.3.

Gastrointestinal haemorrhages represented 36% of cases, followed by epistaxis (24%), cutaneous haemorrhages (10%), haematuria (9%), CNS haemorrhage (7%) and various haemorrhages (14%). Anticoagulants were responsible for more than half of cases (antivitamins K: 49% and heparins: 5%), followed by aspirin (24%), NSAIDs (13%) and antiplatelet agents (9%).

Half of the cases were serious (78 hospitalisations and five deaths). Causality was assessed as definite in 13% of cases, highly probable in 30%, possible in 54%, and doubtful in 3%. Preventability was assessed as follows: definitely or possibly preventable: 33%, definitely or possibly preventable: 49%, non-assessable: 18%. Main reasons for preventable haemorrhages were: at-risk patients (older patients with complex past history), drug interactions, questionable indications for treatment, insufficient follow up, self-medication, lack of information of the patient on treatment, lack of co-ordination between doctors and/or other health professionals.

Conclusion: DIH are far from rare. Types of haemorrhage seen in ambulatory care are a little different from those seen in hospital (epistaxis: 24%, cutaneous hematomas: 10%); four of the five deaths were due to central nervous haemorrhage, the latter being digestive.

285. MISUSE OF EMERGENCY CONTRACEPTION PILL?

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Introduction: Two emergency contraception pills (ECPs) have been available in France since 1998: a combined oral contraceptive pill (0.25mg levonorgestrel, 0.05mg ethinylestradiol), available on medical prescription only, and a progestin-only pill (0.75mg levonorgestrel), also available over-the-counter, free for women under 18. Tablets should be taken as soon as possible and before 72 hours after an unprotected sexual intercourse. Emergency contraception is not recommended for repeated use.

Aim of the Study: To describe ECP use in Aquitaine, South Western France.

Methods: During 1 month, we conducted a prospective survey of emergency contraception prescription and dispensing in a random sample of 100 general practitioners and 155 community pharmacies. Pharmacists proposed an anonymous questionnaire to fill in to each woman who bought emergency contraception.

Results: During the study period, a single prescription of emergency contraception a combined contraception was included by a doctor. Twenty-seven women were given levonorgestrel in 14 pharmacies (0.9 ± 1.2 box/pharmacy/month). Mean age was 22.5 years (15–45); 37.5% were aged <18 years. Contraception methods used were condoms (50%), oral contraception (31%). Seven women (19%) had no ongoing contraception. Reasons for using ECP were: unprotected intercourse or local contraception failure (81%), oral contraception failure (19%). Forty four per cent (95CI: 18–72) of women had previously used ECP during the past 12 months.

Conclusion: From 1999 to 2002, the number of levonorgestrel boxes sold has increased fourfold in France. However, the number of voluntary abortions has not changed during the same period. There is a probable misuse of ECP by young women who have no contraception at all. Although no specific long-term effect has been described after repeated EPC use, classic oral contraception should be promoted.

290. USE OF COMPLEMENTARY OR ALTERNATIVE PRODUCTS IN CANCER PATIENTS

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Introduction: Few studies have been conducted in France to assess the use of complementary or alternative products (CAPs).

Aim of the Study: To describe the use of CAPs in hospitalised cancer patients.

Methods: A cross-sectional pilot study was conducted during one day in July, 2003 and one day in September, 2003 in a regional cancer centre. All clinical departments were included. In accordance to the medical staff of each ward, only patients able to answer some questions were eligible. For each patient having agreed to participate, a face-to face interview was conducted by means of a short questionnaire. Each patient was asked about his/her potential consumption of dietetic supplements, health-foods, plants, hormone derivatives, special diet, cannabis, etc.

Results: A total of 221 patients (sex ratio: 0.92) were hospitalised during the 2-day survey. Among them, 152 patients (69%; sex ratio: 0.95) were included: 53 (35%) used a CAP (seven used these products during the past month). Among users, mean age was 58 years (range: 29–78); there were 22 men (41.5%) and 31 women (58.5%) [sex ratio: 0.71]. Plants (53%), homeopathy (49%) and dietetic supplements (30%) were the most frequently used products. They were mostly bought in health-food shops, pharmacies, herb shops or obtained directly from the manufacturer (no patient obtained products from the Internet). A single patient used cannabis for its relaxant properties. Most users lived in rural areas; women were more prone to using them. Counselling from family and friends but also from different healers seemed to be the main determinant for use.

Conclusion: More than one third of participating patients used (or had recently used) a CAP. This level of use is usually underestimated, except when an adverse effect occurs, as patients are generally not questioned about use of alternative or complementary products. Use of CAPs should be systematically searched in every patient, especially those with chronic diseases.

295. FROM SIGNAL DETECTION TO HYPOTHESIS TESTING: FACIAL PARESIS FOLLOWING INTRANASAL FLU IMMUNISATION – EVIDENCE GAINED FROM SPONTANEOUS REPORTS, CASE-CONTROL STUDY, CONTROLLED RANDOMISED CLINICAL TRIALS

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Signal Detection: An intranasal influenza vaccine (Nasalflu) was launched in Switzerland for the influenza season 2000/2001. Approximately 3 months post-launch, the Swiss Drug Monitoring Centre SANZ received a number of spontaneous reports on idiopathic facial paresis (IPFP) in association with Nasalflu. No cases had been observed in any of the pre-licensure clinical trials. Physicians and patients may be more inclined to associate facial paresis with nasal rather than parenteral immunisation. It can be reasonably assumed that underreporting of such an adverse reaction is not as low as generally suspected. Therefore, estimations of IPFP incidences were calculated from the total number of doses sold and the number of cases reported. This revealed a mean reporting rate of 1 case per 1000 doses sold (0.1–1.6 cases per 1000). High regional differences in the reporting rate were observed. From September 2000 to December 2000 a Phase IV safety study involving 3500 subjects was performed in eight different centres in Switzerland. For the first time IPFP cases were observed in a clinical trial. High regional differences were also observed.

Hypothesis Testing: IPFP cases reported from the market and from the clinical trial reflected the natural occurrence of IPFP. As the background incidence for IPFP in Switzerland is unknown, a matched case control study covering October 2000 to April 2001 was performed to estimate the risk of IPFP following Nasalflu administration. The results showed a strong association: an odds ratio of 19 and an excess risk of 13 per 10 000 vaccinees. Nasalflu cases were highly over-represented due to intensive media coverage; because of the small number of Nasalflu controls, the exact risk associated with Nasalflu was difficult to quantify. To control for these massive biases a multicentre, randomised, open, controlled trial with over 13 000 subjects was performed in the influenza season 2001/2002. Preliminary results show that Nasalflu vaccinated subjects have a higher risk in experiencing IPFP. However, this large multicentre trial, involving seven countries worldwide, showed large regional differences, suggesting a selectively increased relative risk.

Conclusion: All epidemiological methods show that Nasalflu increases the risk of experiencing IPFP, although the strength of the association differs. The studies do not give information on why the risk is selectively increased and which patients are at risk. As long as the aetiology and the background risk of IPFP are unknown, the size of the effect of Nasalflu on its occurrence remains unclear.

300. ADVERSE UNEXPECTED EFFECT: IMPROVEMENT OF A PSORIASIS WITH BUPROPION

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Introduction: Bupropion, otherwise known as amfebutamone, is indicated as an aid to smoking cessation treatment. It is a monocyclic antidepressant structurally related to amphetamine. Zyban® (bupropion hydrochloride) is a non-nicotine aid to smoking cessation. In this indication, the recommended dose is 150 milligrams twice daily; an initial dose of 150 mg/day for the first 6 days is recommended. Doses should not exceed 300 milligrams per 24 hour.

Aim of the Study: We report the case of a woman who had an improvement of dermatologic disorders with bupropion.

Methods: A 41 year-old woman was treated by bupropion in doses of 150 mg/day during 1 month. She had no significant medical history apart from a psoriasis. During the treatment by this drug, she presented an improvement of her skin disorders. So 6 months later, as she presented a new exacerbation of her psoriasis, she tried to take her bupropion again by herself. And her skin lesions resolved. Discontinuation of bupropion again led to reappearance of her psoriasis. After each administration of this drug, her skin disorders resolved.

Results: The common side-effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Dermatological reactions are uncommon but include pruritus and urticaria. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. To our knowledge, only one study was conducted to determine whether bupropion may be useful in treating atopic dermatitis and psoriasis (Modell et al., 2002). In this pilot study, ten nondepressed patients with psoriasis presenting continuously over the previous year and not clearing with topical therapy were given oral bupropion sustained-release formulation 150mg once daily for 3 weeks, followed by 150mg twice daily for another 3 weeks. At week 6, eight of the ten patients with psoriasis showed decreases in the affected surface area over baseline. The skin disease remained unchanged in two subjects.

Bupropion's mechanism of action as an aid in smoking cessation is unknown. It is presumed that this action is mediated by a noradrenergic and/or dopaminergic mechanism (Asher et al., 1995). Altschuler et al. (2003) suggested that bupropion had an action in psoriasis by lowering the levels of the proinflammatory cytokine tumour necrosis factor-alpha.

Conclusion: This case seems to confirm that bupropion might improve skin disorders such as psoriasis.

305. FACTITIOUS HYPOGLYCAEMIA ASSOCIATED WITH SULPHONYLUREA DRUGS IN FRANCE DURING 3 YEARS

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Introduction: Factitious diseases are characterised by physical or psychologic symptoms that are voluntarily self-induced. Hypoglycaemia presents important diagnostic and therapeutic problems. Severe and repetitive hypoglycaemic episodes without treatment may be difficult to explain. Failure to identify factitious hypoglycaemia may lead to laparotomy or pancreatectomy.[1,2] Factitious hypoglycaemia is assessed as a manifestation of Munchausen's syndrome.[3]

Aim of the Study: To evaluate the rate of Munchausen's syndrome in unexplained severe hypoglycaemia, we performed a retrospective study during 3 years 2001–2003.

Methods: In patients with unexplained hypoglycaemia, we searched for the presence of an oral hypoglycaemic agent. The patients were recruited from all over France. Analyses were realised on plasmatic extracts. High Performance Liquid Chromatography (HPLC) with UV or mass spectrometry (MS) detection has been used.

Results: A total of 170 patients, with unexplained hypoglycaemia, were recruited. In 29 patients (18 women: mean age 57 ± 18 years, 11 men: mean age 60 ± 20 years), a second generation of sulfonylurea oral hypoglycaemic agent was detected. Glibenclamide was identified in 20 patients, gliclazide in six, and glimepiride in three. Plasma concentrations were usually supra-therapeutic. Maximal concentrations observed were 527 µg/L (normal concentration 25–50 µg/L), 19700 µg/L (normal concentration 250–1500 µg/L), and 550 µg/L (normal concentration 300 µg/L) for glibenclamide, gliclazide and glimepiride, respectively.

Conclusion: Several cases of factitious hypoglycaemia with hypoglycaemic drugs have been published.[1,2,4,5] Factitious hypoglycaemia is a specific type of Munchausen's syndrome.[6] In our study, this phenomenon represents 17% of patients with unexplained repetitive hypoglycaemic episodes. Factitious hypoglycaemia with sulfonylurea should be considered in the differential diagnosis of insulinoma.

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310. ADVANCES OF ADR REPORTING SYSTEM IN TAIWAN AND CASE REVIEW OF ANTIDEPRESSANTS FROM ADR DATABASE

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Adverse Drug Reaction System in Japan: Four regional reporting centres, northern, central, southern, eastern, and national reporting centre of adverse drug reactions (ADR), have been established since 1998. The regional and national centres investigate and complete reported cases as assessment reports, which are then sent to the Department of Health (DOH). In addition, the regional centres hold educational programs periodically to promote ADR reporting systems to hospitals, pharmacies, consumers, and pharmaceutical manufacturers. Over the past few years the ADR reporting system has been promoted step by step, including data assessment, re-evaluating drug safety, publishing Drug Safety Newsletter quarterly, and online reporting.

Case Study of Antidepressants: There are mainly 77 antidepressant certificates issued in Taiwan, containing ten active ingredients, namely bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine. The regulation sets 7 years of mandatory postmarketing surveillance for newly approved drugs since 1993. Currently, five of these agents (bupropion, mirtazapine, nefazodone, venlafaxine, and escitalopram) are still in the new drug surveillance period. According to the ADR reporting data from 1998 to 2004, 65 cases related to these ten antidepressants were reported and the main descriptions were agitation, tremor, insomnia, drowsiness, and sweating. In order to assure the safe use of antidepressants and prevent ADR due to abrupt discontinuation of medication, the DOH requested manufacturers to change the labels of these ten drugs in May 2004. Warnings

in statement that close observation of patients with worsening depression or with suicidality tendency need to be intensively alerted.

Drafts for Pharmacovigilance: The ADR reporting responsibilities of hospitals, pharmacies, and pharmaceutical manufacturers have been enacted by 'Pharmaceutical Affairs Law' (PAL) of Taiwan in March 2004. Based on the law, DOH announced the draft of 'Adverse Drug Reaction Reporting Regulation' which clearly defines the ADR reporting regulation involving approved drugs and investigational new drugs. In addition, the issue of postmarketing surveillance has been put into the PAL. Draft of 'Drug Safety Surveillance Regulation' defining the surveillance period was also announced in June 2004. Currently, both drafts were awaited for public responses.

This paper will present detailed ADR information on the ten antidepressant drugs and the comments and potential impact of the two regulatory drafts on ADR.

315. CNS ADVERSE REACTION INDUCED BY CEFEPIME IN A FEMALE HEMODIALYSIS PATIENT: A CASE REPORT

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Serious CNS adverse reactions (ADRs) are unusual complication of cephalosporin therapy. Their early recognition and withdrawal of antibiotic therapy can avoid serious consequences. We report a case of a 42-year-old woman on chronic haemodialysis programme (three times per week) affected by urosepsis (Pseudomonas) who was treated with intravenous cefepime (2 g/day) with a good clinical response. The therapy was continued until the planned GU operation. The patient suffered from congenital dysfunction of innervations of urinary bladder (vesica urinaria neurogenes) with calculosis and obstructive uropathy. The patient had undergone plenty of urinary tract operations (uretherovesicoplastics, ileocystoplastic with implantation of artificial sphincter, right nefrectomy, stenosis of left urether, percutaneous left nephrostomy) in previous years. She also suffered from symptomatic epilepsy (grand mal). In consultation with urologist cystography, nephrostomography and operation were planned (cystectomy and left nephrectomy). During the third week of cefepime therapy the patient became somnolent, dysartric with myoclonic jerks. Computed tomography of the brain was normal. By using electro-encephalogram (EEG) status epilepticus was diagnosed. A presumptive diagnosis of cefepime CNS ADR was made and cefepime therapy immediately discontinued. Urgent haemodialysis was performed daily for a consecutive two days resulting in patient's complete recovery. After cystography was performed (showing bizarre, large urinary bladder with multiple stones) total cystectomy (the main cause of sepsis) and uretherectomy were done. The patient's clinical condition was subsequently stable and she was discharged from the hospital in a good clinical condition. Left nephrectomy was planned for the future.

The frequency of cefepime induced CNS ADRs are probably underestimated. Close neurological survey in treated patients should allow an early diagnosis of these complications. Urgent haemodialysis is the best therapeutic method for a rapid neurological improvement.

320. INCREASING COMPLEXITY OF VACCINE SAFETY SURVEILLANCE DATABASES: THE CASE FOR 'DATA MINING'

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Introduction: The US Vaccine Adverse Event Reporting System (VAERS), established in 1990, is jointly operated by the Centers for Disease Control and Prevention and the Food and Drug Administration. It is primarily responsible for detecting rare or novel vaccine adverse events that may be subject to further study. Such signals have typically been detected by manual case review, inquiries from providers and the general public, or media attention.

Aim of the Study/Objectives: (i) Describe secular trends in US spontaneous vaccine safety reports, relative to measures of vaccine usage; (ii) assess the complexity of the VAERS database using vaccine combination and symptom code data.

Methods: For 1991–2003, absolute numbers of and trends in reports to VAERS, newly reported adverse event symptoms, and the number of vaccine combinations involved in reports were reviewed. For the same time period, we also acquired data regarding changes in the number of US licensed vaccine products and distributed vaccine doses.

Results: Since the inception of VAERS the number of licensed vaccine products has tripled, from 16 to 49. Vaccine dose distribution has increased from 127.8 to 235.4 million, for an average of 7.0% per year. Reports to VAERS showed a parallel increase, averaging 6.9% annually. Through end 2003 a total of 162 606 reports have been received. Over the time period of this study, the total number of vaccines and vaccine combinations seen in reports to VAERS for both children and adults increased from 101 to 951. Total symptoms reported to VAERS increased by 8.6% annually, with a total of 1022 unique symptom codes (COSTARTs) now included in the database.

Conclusions: The disproportionate increases in both vaccine combinations and possible vaccine associated symptoms (relative to the number of reports received) reflect the increasing complexity of the VAERS database. Given the possibility of increasing difficulty in detecting vaccine safety signals, we are actively supporting development and validation of statistically based 'data mining' tools to be used in conjunction with traditional case review methods.

325. IMMUNE AGRANULOCYTOSIS AND CLARITHROMYCIN

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Introduction: Clarithromycin belongs to the macrolide antibiotics with indications including infections in the respiratory tract, skin, and soft tissues as well as for *H. pylori*. Agranulocytosis is usually not associated with macrolides.

Aim: To bring attention to this unusual but increasingly documented risk a case is outlined and given perspective by analysis of spontaneously reported adverse reaction cases to the WHO Adverse Drug Reaction (ADR) database, Vigibase.

Methods: Analysis of one clinical case and cases spontaneously reported to Vigibase up to and including 2002.

Results: The case report consisted of a 60-year-old man that had for 10 years experienced recurrent pyrexial illnesses that had no apparent cause and always with spontaneous recovery. He received 500mg of clarithromycin for five consecutive days for his illness, and after a repeated course he was clinically better. A second episode began six months later when a persistent monocytosis was noted. The third and current illness commenced three months later with a flu-like illness, drenching night sweats and rigors. Even though a normal white cell count was documented and the pyrexia was regarded as of undetermined origin, at follow up a month later, he had nevertheless been started on clarithromycin and now gave a history of confusion and vomiting of two days' duration. The total white cell count was 0.25×10^9/L of which 1% was neutrophils and the remainder lymphocytes. Blood culture showed a bacterial infection and he was treated with intravenous piperacillin-tazobactam, gentamicin, and fluconazole and started on granulocyte stimulating factor. The morphologic features were comparable with drug-induced changes. One week later total leukocyte were 4.5×10^9/L with 3% neutrophils, 1% myelocyte, 1% metamyelocyte and 49% monocytes. Repeated bone marrow check was now typical of recovery from acute injury with early myeloid series apparent. Two weeks later all haematological values had returned to normal as had cytomorphology.

The Vigibase contained 22 reports of agranulocytosis and 27 of neutropenia/granulocytopenia associated with clarithromycin. However, in eight of them other drugs known for inducing agranulocytosis were also listed. In addition there are cases linking the other macrolides, such as erythromycin and azithromycin, to agranulocytosis as well.

Conclusion: These observations taken together suggest that agranulocytosis can be associated to the treatment with macrolides. Quantification of the risk and eventual differences among individual drugs cannot be detected on the basis of spontaneous reporting data, and epidemiological studies should be structured to test this signal.

330. FOLLOW-UP STUDY USING TDM AND PHARMACOGENETIC TESTING AS TOOLS IN PHARMACOVIGILANCE

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Introduction: The importance of genetic polymorphisms and drug drug interactions in relation to therapeutic response and susceptibility for adverse drug reactions (ADR) are increasingly recognised.

Aim of the Study: Follow-up of a dynamic cohort study in psychiatric inpatients with ADRs (most of them being serious), with emphasis on plasma levels of the involved medication.

Methods: This study comprises data of an ongoing dynamic cohort study of in the meantime 250 psychiatric inpatients with ADRs: Within an ethically approved pharmacovigilance project (AMSP) in the clinic Königsfelden, we continuously and actively collect side effects meeting the criteria serious, unexpected or leading to stop of the medication. All adverse event cases are assessed for their causality in relation to disease and drug therapy. In order to better understand the impact of high plasma levels, we measure trough plasma levels during or immediately after the adverse event. If the plasma levels are at least 20% lower or higher than the expected reference plasma levels,[1] we also assess the pharmacogenetic status of the patient for the cytochrome P450 isozymes.

Results: In about 20–25% of the cases plasma levels of the medication lay at least 20% above the given reference ranges. In some drugs, we regularly find plasma levels of over 200% of the given upper reference value, hinting to a possible pharmacogenetic polymorphism for a metabolising enzyme.

Conclusion: TDM and pharmacogenetic tests are useful for causality assessments of a number of ADR cases. It is too early to give a recommendation for routine TDM and pharmacogenetic testing, with the exception of drugs like clozapine with an established therapeutic index. To understand if high plasma levels and their cause really lead to more ADRs, more and controlled studies are needed.

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335. TDM AND PHARMACOGENETIC TESTS AS TOOLS IN PHARMACOVIGILANCE

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Our hypothesis is that: (i) a relevant number of adverse drug reactions are dose dependent side effects (e.g. extrapyramidal side effects correlate with dopamine D2 receptor occupancy which correlates with plasma levels of haloperidol), (ii) plasma levels of a given drug reflect better than its dose brain concentrations, (iii) plasma levels are, amongst other, dependent on the pharmacogenetic status of the patient.

Methods: Based on this hypothesis we perform an ethically approved dynamic cohort study in the psychiatric inpatient hospital Königsfelden (400 beds, 1800 patient entries).We continuously and actively collect adverse events meeting the AMSP-criteria: serious, leading to discontinuation of treatment and unexpected. All adverse event cases are assessed for their causality in relation to disease and drug therapy. We measure trough plasma levels during or immediately after the adverse event. If the plasma levels are at least 20% lower or higher than the expected reference plasma levels (Baumann et al. Therapeutic Monitoring of Psychotropic Drugs. AGNP-TDM Expert Group Consensus Guidelines, Pharmacopsychiatry, in press), we also assess the pharmacogenetic status of the patient for the cytochrome P450 isoenzymes

In 3 years' time we have collected about 250 cases. TDM and pharmacogenetic tests helped us to elucidate difficult ADRs and to find for these patients better tolerated individualised drug treatment. Some of these cases will be presented and an algorithm for using TDM and pharmacogenetic tests in pharmacovigilance is proposed.

340. VIGIMED, AN INTERNATIONAL DRUG SAFETY E-MAIL DISCUSSION GROUP

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Introduction: National Pharmacovigilance Centres (NPCs) monitor the safety and other problems concerning medicinal products after approval. Vigimed is intended to support international collaboration, was started in 1997 by the WHO Uppsala Monitoring Centre, and now connects 76 countries. As the only world-wide pharmacovigilance e-mail discussion group, it is a new and unique IT drug safety tool.

Aim: To study the functioning and results of Vigimed.

Methods: A structured review was made of a sample of 100 subsequent questions and 576 responses.

Results: There were 51 (72%; total 71) active countries in all regions of the world. Drug-groups that emerged as frequent causes of problems were analgesics and anti-inflammatory (15%), various anti-infectious (11%), anti-obesity (5%), psycholeptics (5%), systemic antihistamines (4%) and vaccines (4%); 9% of the questions concerned herbals. Established drugs (in use since 7 or more years) predominated (89 %). NPCs with more than one connected person were more active, both in asking and answering.

Conclusion: Vigimed eases communication between NPCs and the frequent use shows that it serves a need. Continuous vigilance is needed for both new and old drugs. The study gave an interesting view of the matters encountered in day-to-day pharmacovigilance and how problems are solved. Effective communication of early suspicions and concerns needs confidentiality and trust.

345. COOPERATION BETWEEN THE NATIONAL PHARMACOVIGILANCE CENTRE AND REGISCAR IN THE NETHERLANDS: MUTUAL PROFITABLE

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Introduction: Severe Cutaneous Adverse drug Reactions (SCAR) are rare but severe drug-related diseases that include Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). A European consortium (RegiSCAR) of six countries collects comprehensive information of cases of these severe skin reactions. The data will be analysed in a case-control study.

Since September 2003, The Netherlands Pharmacovigilance Centre Lareb has collaborated with the Dutch RegiSCAR department. Lareb plays an active role in the inclusion of SCAR cases by sending a monthly e-mail questionnaire to the participating dermatologists. In return, Lareb receives all the relevant information about these included adverse drug reactions.

Objective: The objective of this paper is to review the cooperation between RegiSCAR and Lareb and to evaluate the quantity and quality of included SCAR cases before and during this cooperation.

Methods: The number of SCAR cases included in the Dutch RegiSCAR study before and during the cooperation with Lareb was analysed. The same comparison was made for the number of SCAR reports in the Lareb database. The level of documentation of the SCAR reports in the Lareb database has been quantified with the help of 15 parameters, derived from the RegiSCAR program.

Results: Before the cooperation with Lareb, the Dutch RegiSCAR program received a monthly average of 0.86 SCAR cases. In the first 10 months of collaboration, this number increased to an average of 1.6 cases per month. In addition, the number of SCAR reports received by Lareb, increased from 0.7 to 2.0 average per month.

From January 1st 2000 to July 1st 2004, 22 non-RegiSCAR cases of TEN and SJS have been identified from the Lareb-database. For all cases age, gender and drugs are known. However, information about previous infections, biopsy and lab-values is present in less then 30 percent of the cases. Regiscar requires information on all 15 parameters before filing the report in their database. As a result of this, the RegiSCAR reports are far better documented then the non-RegiSCAR reports.

Conclusion: The cooperation between Lareb and Regiscar is mutual profitable. For Lareb it results in an increase in reported SCAR and a more comprehensive documentation. Data about the occurrence of severe skin reactions in daily practice, collected for a case-control study, will also be used now for pharmacovigilance signal generation. The use of this additional source of information enables a faster identification of drugs suspected for the development of SCAR.

350. CLINICAL TRIALS OF MEDICINAL PLANTS: BIBLIOGRAPHICAL REVIEW (1980–2000) AND METHODOLOGIC ANALYSES

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Traditional medicine, one of the basis of African, Asian or South American cultural inheritance, is important. More than 80% of the population use traditional medicine.

Methods: To analyse the methodology used in clinical trials on medicinal plants, we reviewed articles published on this topic between 1980 and 2000.

Results: Forty-eight clinical trials were found. Most were carried out in developed countries. Standard methodological principles were mostly applied: randomisation (85.4%), comparison (87.5%) versus placebo (95.2 %), blind design (81.3%). The duration of the studies was short. Sample sizes were generally low, from 30 to 99 subjects; statistical tests were used in 90% of trials. Adverse effects were infrequently collected.

Conclusion: Most clinical trials included in this survey were conducted in accordance with WHO's guidelines. The respect of methodological principles and the implementation of a legislative framework are important to obtain credibility and international recognition of traditional pharmacopoeia.

355. INTOXICATION BY MEDICINAL PLANTS IN ABIDJAN: CLINICAL AND ETHNOBOTANICAL ASPECTS

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Objective: To appreciate the clinical, epidemiological and ethnobotanical aspects of intoxications, voluntary or not, with local medicinal plants.

Methods: A retrospective study was conducted to analyse all cases of intoxication, voluntary or not, with medicinal plants between 2000 and 2002 in the three University Hospitals of Abidjan.

To complete this data, an ethnobotanical questionnaire study was performed in the markets of Abidjan to identify the medicinal plants, their use and their potential toxicity.

Results: We collected 32 cases of intoxication with plants. The mean age was 24 ± 14 years (9 months to 75 years). The sex ratio is one man for three women. Most of the cases were cithes students or shopkeepers. The reasons for taking plants were abortion in 34.4% of cases, suicide attempt in 28.1% of cases (89% concerned women).

More than half of the patients (59.4%) were admitted to the intensive care unit after the 6th hour with altered consciousness.

We identified seven main clinical pictures (hepato-renal failure, infectious, haematological, neurological, abdominal pains, respiratory destress or inhalation, anaphylactic shock). 12 (37.5%) patients died. For the others, the outcome was generally favourable after 72 hours. None of the plants used were identified with certainty. In the markets, we found 34 plant families, of which six were frequently found (Euphorbiaceae, Caesalpiniaceae, Asclepiadoceae, Combretaceae, Maliceae, Rubiaceae) and 61 plant species were collected. The most frequently used were *Anogeinus leiocapus*, *Jatropha curcas*, *Gossipium hirsutum*, *Momordica charanticia*, *Nauclea latifolia* and *Vernonia colorata*. Parts of the plants used are leaves and roots to make decoctions, or infusions. Oral and rectal routes of administration are the most commonly used. The usual indications are infectious, urogenital and digestive. The side effects reported concern neurological, digestive systems and general effects.

Conclusion: Our results confirm that traditional herbal medicine can pose severe health problems in overdose or when misused. More attention must be paid to the characterisation of these drugs and their effects, and to phytovigilance and phytotoxicity.

360. SAFETY PROFILE OF PIOGLITAZONE AS USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Background: Pioglitazone is a new oral drug for treatment of non-insulin dependent diabetes mellitus. It is the third of a new class of anti-diabetic drugs known as thiazolidinediones and was licensed in the UK in November 2000. Another thiazolidinedione, troglitazone, was withdrawn from the market in December 1997 due to reports linking its use to severe liver toxicity.

Objectives: To monitor the safety of pioglitazone prescribed in primary care in England using Prescription-Event Monitoring (PEM).

Methods: An observational cohort study in which patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between November 2000 and June 2001. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Information on dosage, suspected adverse drug reactions (ADRs), reasons for stopping the drug, concomitant use of other anti-diabetic drugs and cause of death were requested. Event Incidence Densities (IDs) [number of 1st reports of an event /1000 patient-months of exposure] were calculated. Significant differences between IDs for events reported in month 1 (ID1) and months 2–6 (ID2) of exposure were regarded as potential signals. Events of clinical interest, including outcomes of pregnancies were followed-up using specific event questionnaires.

Results: The study cohort comprised 12774 patients (median age 62 years; interquartile range 52, 70; 53.1% male). 'Malaise/lassitude' was the event with the highest ID1 (6.6; n = 75). Clinical events that were reported significantly more often during the first month of treatment compared with months 2–6 included: 'malaise/lassitude', 'nausea/vomiting', 'dizziness', 'headache/migraine', 'diarrhoea', 'weight gain' and 'abnormal liver function tests (LFTs)'. 281 events in 186 patients were reported by GPs as ADRs to pioglitazone, including 'unspecified side effects' (n = 49) and 'malaise/lassitude' (n = 30). Other events of clinical interest during treatment with pioglitazone were 96 (0.8%) reports of cardiac failure, 312 (2.4%) of oedema, 101 (0.8%) of abnormal LFTs, 224 (1.8%) of weight gain and 41 (0.3%) of anaemia. Outcomes for two exposed pregnancies were ascertained: one was a live birth, and the other was a premature birth, resulting in death. Sirenomelia was present in the latter case. Four cases of bladder cancer were reported, two of which were pre-existing conditions.

Conclusions: This postmarketing surveillance study shows that pioglitazone is generally well tolerated when used in general practice in England. Further analysis of the study data is being undertaken including assessment of causal association.

Financial Disclosure Statement: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of pioglitazone. Saad Shakir has received consultancy fees from Takeda.

365. SAFETY PROFILE OF ROSUVASTATIN AS USED IN GENERAL PRACTICE IN ENGLAND: INTERIM RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Background: Rosuvastatin is a cholesterol lowering drug, the newest drug of a class of drugs called HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors or statins. Rosuvastatin was launched in the UK in March 2003. Another statin,

cerivastatin was withdrawn from the market in August 2001, due to concerns about increased risk of rhabdomyolysis associated with its use.

Objectives: To monitor the safety of rosuvastatin prescribed in primary care in England using Prescription-Event Monitoring (PEM).

Methods: An observational cohort study in which patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between August and December 2003. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Information on dosage, suspected adverse drug reactions (ADRs), reasons for stopping the drug, past medical history, previous use of other statins and cause of death were requested. Event Incidence Densities (IDs) [number of 1st reports of an event /1000 patient-months of exposure] were calculated. Significant differences between IDs for events reported in month 1 (ID1) and months 2–6 (ID2) of exposure will be regarded as potential signals. Events of clinical interest are being followed-up using specific event questionnaires.

Results: The interim cohort as of June 2004 compromised 2722 patients (median age 64 years; IQR 56, 71; 50.9% male). Starting dose was 10mg in 68.9% (n = 1875), 20mg in 11.5% (n = 312), 30mg in 0.04% (n = 1), 40mg in 4.3% (n = 117) patients. 36% (n = 979) of the patients had previously been on another statin. There were 76 cases (2.8%) of myalgia, 11 cases (0.4%) of raised creatinine phosphokinase, four cases (0.1%) of limb pain, 26 cases (1%) of abnormal liver function tests, 3 cases (0.1%) of abnormal renal function tests and 1 case (0.04%) of proteinuria reported as events. No cases of myopathy, rhabdomyolysis or renal failure were found in this interim cohort. Thirty-six ADRs to rosuvastatin were reported in 30 patients, myalgia (n = 7) being the most common. The highest ID was for myalgia (ID1 = 6.2; n = 15); it was also the most frequent reason for stopping rosuvastatin (67/446 reasons). ID analyses revealed no statistically significant results.

Conclusions: Rosuvastatin was generally well tolerated when used in general practice in England. Myalgia was the most commonly reported event and reason for stopping rosuvastatin. No new signals for ADRs with rosuvastatin were detected. This is an interim report, as the study progresses these findings will become obsolete.

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370. GENERALISED TONIC-CLONIC SEIZURES AND PROPOFOL

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Introduction: Propofol is an intravenous hypnotic with a modulating action on gamma-aminobutyric acid A receptors. Favourable characteristics of propofol are the lack of accumulation and the relatively short recovery time. However adverse effects have been reported. Among those are pain on injection, arterial hypotension, bradycardia including asystole, respiratory depression and blood stream infection. Clinical reports suggested that prorofol, like other hypnotics that modulate gamma-aminobutyric acid A receptors, may have anticonvulsive properties. Others reports on propofol suggested a drug-induced excitation of the central nervous system, including seizures in suceptible patients. We report one case of generalised tonic-clonic seizures during anesthesia by propofol in a young man.

Case Report: A 17-year-old man took irregularly since September 2003 Bronchofyline® (theophylline), Ventolline® (salbutamol) and Celestamine® (betamethasone, dexchlorpheniramine). On March 26th 2004, he had received for general anaesthesia 200mg (3 mg/kg) Diprivan® (propofol), 100µg Fentanyl® (fentanyl) and 6mg Norcuron®(vecuroniun bromure).Three minutes after beginning these medications, the patient presented generalised tonic-clonic seizures. These seizures occurred 2 minutes after stopping the drugs and then received Rivotril® and Pentothal® with favourable evolution. An electro-encephalogram was performed and it was normal.

Discussion: Propofol responsibility of this generalised tonic-clonic seizures is retained in front of: (a) absence of previous history of seizures or neurologic or psychiatric disease, (b) compatible delay of 3 minutes from drug intake to the onset of seizures, (c) favourable evolution after drug withdrawal, (d) seizures were reported only with propofol. In literature, seizure-like phenomena was most obvious during induction in neurologically healthy patients: the time point of occurrence of the seizures suggests that a change in the cerebral concentration of propofol may be causal.

375. GINGIVAL HYPERPLASIA INDUCED BY CYCLOSPORINE IN RENAL TRANSPLANT

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Introduction: The increasing use of cyclosporine A (CSA) in organ transplants and in the treatment of autoimmune diseases has increased the incidence of cyclosporine A-related adverse effects, including gingival hyperplasia (GH). GH causes esthetic, speech, mastication and tooth growth problems in the affected patients. The prevalence of cyclosporine-induced GH varies in different studies and may be as high as 85%, depending on the diagnostic criteria.

Aim of the Study: The aim of our study is to evaluate the incidence of gingival hyperplasia induced by cyclosporine A in renal transplant patients.

Materials and Methods: A retrospective study was carried out in the nephrology unit in IBN SINA hospital during December 2001 to December 2003, including renal transplant patients receiving cyclosporine A.

Results: We have included 20 cases in our series, aged 23–50 years. Our patients were treated by triple immunosuppressive therapy (cyclosporin, corticoids and anti-proliferative) The incidence of pa-

tients presenting gingival hyperplasia post cyclosporine was 15%. Dose of cyclosporine varied from 275 mg/day to 400 mg/day. Cyclosporine assay varied: 800–1398 ng/mL. Gingival hyperplasia occurred between 57 days to 48 months.

Conclusion: Drug monitoring and controlling the inflammatory component through an appropriate oral hygiene programme may benefit the patient by limiting the severity of the gingival overgrowth.

380. ADVERSE DRUG EVENTS AND POTENTIALLY INAPPROPRIATE MEDICATION USE IN THE ELDERLY

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Age-related physiological changes, high level of comorbidity and multiple medications are the main determinants of the high frequency of adverse drug reactions (ADR) in the elderly. Beers et al. proposed a list of potentially inappropriate medications (PIM), based on benefit-risk ratio in the elderly (Arch. Intern. Med., 1997, 157, 1531). A drug is regarded as inappropriate if a less dangerous one is available with the same indication. Various epidemiological studies estimated the prevalence of PIM use among community dwelling or hospitalised elderly subjects.

Objective: The objective of this study was to describe the ADR occurring in a population aged 70 years and over treated with both appropriate and inappropriate medications. A prospective drug surveillance study was undertaken in 1761 elderly 70-year-old or over admitted to an acute care medical geriatric unit from 1994 to 1999. Prescribing patterns were established on admission. PIM use was assessed according to a list derived from the Beers' criteria by a panel of French experts and suited to French practice. Adverse effects were identified.

The prevalence of ADR among patients receiving at least 1 PIM was 21% (95% CI: 18, 22). In patients with (ADR+) or without ADR (ADR–), age was similar (ADR+: 84.9 ± 6.8 years/ADR-: 84.8 ± 6.6; p = NS) but the number of drugs given was significantly higher in patients with ADR (ADR+: 7.3 ± 3.9 drugs/ADR–: 5.9 ± 2.7, $p < 0.0001$). In 72% of the patients with an ADR, at least one PIM was given, but only 31% of these ADR were related to PIM. Cerebral vasodilators and anticholinergics were the drugs most frequently responsible for orthostatic hypotension, and benzodiazepines were responsible for neuropsychiatric disorders. Drugs out of the list such as diuretics, antianginal and antihypertensive drugs were accountable for renal failure, ionic disorder or orthostatic hypotension. They were often associated.

As the Beers' list was devised in an epidemiological framework it is not suited to the peculiar treatment of a single patient. This list is not relevant enough and incomplete. The addition to this list of some drug associations, such as diuretics with antihypertensives for instance, is to be discussed. This list should be periodically updated with data derived from the pharmacovigilance database.

We acknowledge the financial support of the French drug agency AFSSAPS.

385. ARE GENERICS AS SAFE AS THEIR ORIGINAL COUNTERPARTS?

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Generics are becoming fairly common in France as pharmacists are now allowed to substitute a generic drug for a drug prescribed. This substitution should not induce any adverse effect per se as generics are presented as equivalent to their original counterparts. In order to verify this assumption we conducted a survey into the French Regional Centres of Pharmacovigilance data base over years 2002 and 2003.

Cases included consisted in treatments with the following sequence: an original drug well tolerated was substituted for a generic drug which induced an adverse effect (AE) and was consequently substituted for the original brandname drug, thus alleviating the AE.

Two generic categories were identified according to the respective compositions of the generic (Ge) and the brandname (Br). When the excipient compositions of Ge and Br were qualitatively equivalent, no serious or reliable AEs were reported. The 13 AEs reported consisted in supposed diminished action of bupivacaine for rachi-anaesthesia, skin and lung allergic reactions with fluoxetine, bromazepam, cromoglicic acid (ciomolyn sodium), dextroproxyphene-paracetamol and ceftriaxone, and gastrointestinal functional problems with spironolactone or propranolol.

When excipient compositions were different, 27 AEs were reported consisting in allergic reactions (6), change in the action of the drug (10), gastro-intestinal intolerance (3) and other symptoms (8). Of special interest were cases of modified bioavailability: more rapid absorption occurred when a Ge mebeverine replaced a long acting Br, the granules of which were coated with Eudragit E (soluble in gastric fluid) and L (resistant to gastric fluid), thus inducing an abrupt, marked and protracted fall of blood pressure.

Of special concern were three cases with tachycardia or increase of blood pressure involving a shift from Br verapamil to Ge verapamil. In these cases one can assume a better study of the excipient composition would have prevented these drugs from being absorbed too quickly.

The financial pressure on the Social Security permits and promotes substitution for generics the composition of which is at times far too different from that of their original counterparts. Although substitution for a short treatment is generally well tolerated and worth trying, substitution during a chronic treatment, when drugs with a low safety margin are used – such as cardio-vascular, antidiabetic, or anticonvulsant drugs – should be discouraged.

390. INCIDENCE RATES OF CEREBROVASCULAR ACCIDENTS AND TRANSIENT ISCHAEMIC ATTACKS WITH ANTIPSYCHOTIC DRUGS IN GENERAL PRACTICE IN ENGLAND: A RETROSPECTIVE ANALYSIS OF PRESCRIPTION-EVENT MONITORING DATA

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Introduction: Following changes in the safety information on the use of risperidone in elderly patients with dementia, data from the PEM studies of risperidone, quetiapine and olanzapine were exam-

ined. These studies were conducted in England during the immediate postmarketing period of each drug.

Aim of the Study: To compare incidence rates for events reported as Cerebrovascular accident (CVA) and Transient ischaemic attacks (TIA) during the first 180 days of treatment.

Methods: Exposure data were obtained from dispensed prescriptions written by primary care physicians (GPs): risperidone (July 1993–April 1996), olanzapine (December 1996–May 1998) and quetiapine (October 1997–July 1999). Demographic and outcome data were collected from questionnaires posted to GPs 6+ months after the date of the first prescription for each patient. Incidence rates, crude rate ratios (RRs) and RRs adjusted for age, gender and indication (dementia or other) were calculated using Poisson regression modelling. Time-to-event curves were plotted using Kaplan-Meier methods.

Results: For risperidone, quetiapine and olanzapine, 23 (0.30%), 6 (0.35%) and 10 (0.11%) patients were reported to have had a CVA/TIA event, respectively. Crude RRs for CVA/TIA by risk factor showed that rates tended to increase with age, differed according to sex and suggested that patients prescribed risperidone or quetiapine for dementia had higher rates compared with other indications. Crude and adjusted RRs for CVA/TIA for risperidone versus olanzapine were 2.8 (95% CI 1.3, 5.9) and 1.2 (95% CI 0.5, 3.0); for quetiapine versus olanzapine, 3.3 (95% CI 1.2, 9.1) and 2.1 (95% CI 0.6, 7.7); and for risperidone versus quetiapine, 0.8 (95% CI 0.3, 2.1) and 1.1 (95% CI 0.3, 3.3), respectively. The age and sex adjusted RR of CVA/TIA in patients prescribed risperidone for dementia compared with other indications was 6.7 (95% CI 2.4,18.9). The effect of indication could not be reliably examined for quetiapine or olanzapine, because the number of cases with dementia was very low (or zero), respectively. Different cumulative time to event estimates for CVA/TIA ($p = 0.0103$) were observed between the three cohorts. Indication had an important effect on time to first CVA/TIA for risperidone and quetiapine, with dementia being worse.

Conclusion: The crude RRs of CVA/TIA indicated a higher rate for risperidone and quetiapine compared with olanzapine during the first 180 days treatment. After adjustment the RRs were non-significant. The indication dementia appears to be an important risk factor. These results should be considered together with other pharmacoepidemiological studies on this topic.

Financial disclosure statement: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturers of products in this study. Saad Shakir has received lecturing fees from Eli Lilly.

395. SAFETY PROFILE OF DESLORATADINE AS USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: Desloratadine, launched in April 2001 in the UK, is the primary metabolite of loratadine. It is a non-sedating, long acting histamine H1-receptor antagonist indicated for the symptomatic relief of seasonal allergic rhinitis in adults and adolescents (12+ years). Some antihistamines have been associated with serious adverse drug reactions (ADR).

Aim of the Study: To monitor the safety of desloratadine prescribed in the primary care setting in England using Prescription-Event Monitoring (PEM).

Methods: A postmarketing study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between April and May 2001. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Information on prescribing patterns, prior antihistamine use, suspected ADR, reasons for stopping the drug, pregnancies, causes of death, and any other events of interest was requested. Event Incidence Densities (IDs) [no. of 1st reports /1000 patient-months of exposure] were calculated. Differences between IDs for events reported in month 1 (ID1) and subsequent months of exposure were examined for temporal changes in event rate.

Results: The cohort comprised 11 828 patients [median age 36 years (IQR 22,54); 61% female]. The leading primary indication was allergic rhinitis (68%, n = 7999). After month 1, 30.0% (n = 3554) of patients were still taking desloratadine. Where responses to questions were provided, regular use (daily ≥15 days) was reported for 67.4% (5893/8784) patients; 37.0% (2002/5406) had a short course (daily ≤14 days); prior antihistamine use was reported for 33.7% (3468/10 293). 'Condition improved' had the highest ID in month 1 (228.1) and most frequently reported as a reason for stopping (3179/5570 reasons). Headache/migraine occurred significantly more often in month 1 versus months 2–6 and frequently recorded as a reason for stopping (11 cases). Eighteen ADRs to desloratadine were reported in 16 patients (single reports of drowsiness and sedation). Uncommon events included depression, anxiety and dizziness. Rare events included palpitations, myalgia, dry mouth and visual defect.

Conclusion: This study shows that desloratadine is generally well tolerated when used in general practice in England. Headache/migraine was associated with starting treatment. A high proportion of patients stop treatment within 1 month of starting; thus, examination of event incidence by month rather than groups of months is required to reflect the use of this type of medication.

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400. SAFETY PROFILE OF LEVOCETIRIZINE AS USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: Levocetirizine, launched September 2001 in the UK, is the biologically active (R) enantiomer of cetirizine. It is a peripheral

histamine1-receptor antagonist, indicated for the symptomatic relief of allergic rhinitis and urticaria in adults and children (6+ years). Some antihistamines have been associated with serious adverse drug reactions (ADR).

Aim of Study: To monitor the safety of levocetirizine prescribed in the primary care setting in England using Prescription-Event Monitoring (PEM).

Methods: A postmarketing study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between November 2001 and November 2002. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Information on prescribing patterns, prior antihistamine use, suspected ADR, reasons for stopping the drug, pregnancies, causes of death, and any other events of interest was requested. Event Incidence Densities (IDs) [no. 1st reports/1000 patient-months of exposure] were calculated. Differences between IDs for events reported in month 1 (ID1) and subsequent months of exposure were examined for temporal changes in event rate.

Results: The cohort comprised 12 367 patients [median age 37 years (IQR 22,55); 59.4% female]. The leading primary indication was allergic rhinitis (66.9%, n = 8276). After month 1, 27.9% (n = 3459) patients were still taking levocetirizine. Where responses to questions were provided, regular use (daily ô15 days) was reported for 68.4% (6286/9188) patients; 38.4% (2096/5465) had a short course (daily â14 days); prior antihistamine use was reported for 36.4% (3950/10852). 'Condition improved' had the highest ID in month 1 (240.6) and most frequently reported as a reason for stopping (3121/7211 reasons). Drowsiness/sedation occurred significantly more often in month 1 versus months 2–6 and frequently recorded as a reason for stopping (56 cases) and reported as an ADR to levocetirizine (nine reports/31 ADRs; n = 26). Uncommon events included depression, anxiety and dizziness. Rare events included palpitations, vertigo, myalgia and visual defect.

Conclusion: This study shows that levocetirizine is generally well tolerated when used in general practice in England. Drowsiness/sedation was associated with starting treatment. A high proportion of patients stop treatment within 1 month of starting; thus examination of event incidence by month rather than groups of months is required to reflect the use of this type of medication.

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405. IS THE DHE – TRIPTANS CONTRAINDICATION STILL JUSTIFIED?

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Migraine is a common disabling condition that significantly limits and impairs the quality of life of patients. Despite recent advances in migraine abortive therapy, such as the availability of triptans, some patients are unable to achieve satisfactory results. In these patients, the initiation of a prophylactic medication is therefore a therapeutic option, particularly if migraine interferes with their quality of life or their daily routine.

Migraine prevention is massively under-utilised; patients are not aware preventive treatment is available and most of the available migraine prevention treatments induce significant adverse events that lead to noncompliance.

Dihydroergotamine (DHE) is a well known compound effective in the acute treatment of migraine and also effective for its prophylactic treatment. The mechanisms underlying the later effect have recently been revisited.[1,2] Moreover, a recent clinical trial (PROMISE), one of the largest trials conducted in migraine prophylaxis using the IHS criteria, has demonstrated a significant efficacy of the DHE in migrainous patients with an impaired quality of life.[3] In this context, DHE can improve the management of patients that are treated by triptans and be considered as an effective and well tolerated prophylactic treatment. Nevertheless, this association is currently contraindicated, mainly because of potential cardiovascular risks. The objective of our study is to demonstrate that this contraindication is more theoretical than factual. For this, we have analysed the data concerning the pharmacology and toxicity of DHE and triptans (>60 studies) and three studies that concluded in the absence of interaction between DHE and triptans. Moreover, 33 000 prescriptions of DHE and triptans association are notified without occurrence of serious adverse events.

These data can justify the change of the contraindication into use precaution in order to provide an official therapeutic strategy to improve the management of migraine patients.

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410. DOMESTIC SELF-MEDICATION: AN ITALIAN ATTITUDINAL SURVEY

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Introduction: Self-medication with over the-counter (OTC) drugs or complementary medicine and herbal remedies is widespread in western countries. Furthermore, in recent years many prescription drugs have been reclassified to OTC status. This has spawned new patterns of consumer self-care behaviour and raised concerns regarding proper drug usage by the public.

Aim of the Study and Methods: To investigate the habits and knowledge of consumers on use of OTC, herbal and homeopathic remedies, we performed a study, in a suburban area of Verona,

through a structured questionnaire submitted to a randomly drawn sample of people selected by telephone directory (n = 520). We interviewed, at home, 277 women and 93 men (response rate = 71.2%).

The sample characteristics (e.g. age, education, occupation), except the sex, were not different from those of the Veneto Region population (census 2000).

Results: Over 80% of the interviewees used self-prescribed drugs, mainly OTC (70%), but also prescription drugs (30%) in particular antimicrobial agents and NSAIDs. The choice of self-medication was made following the suggestions of the pharmacist (31%), the doctor (26%), friends (12%) and media (6%). In the remaining cases (25%) there was no suggestion. About 68% of the people paid attention to drug expiry date and 62% read the drug information leaflet. We found a positive correlation ($p < 00.1$) between this last habit and the level of school education.

Herbal remedies have been used by 51% of interviewees, mainly as diuretics, anxiolytics and laxatives. The main sources of information for the use were herbalists (41%) or friends (27%). Sixty percent of people considers the herbal remedies safer than drugs and the main motivation for their use was that 'are natural products'.

Homeopathic remedies have been used by 39% of the interviewees, mainly for flu, constipation and dermatological diseases. The sources of information were pharmacists (52%) and doctors (38%). To ascertain the consumer knowledge on drug risks, we asked to indicate the aspirin main adverse event: only 49% of people answered gastrointestinal toxicity.

Drug cabinet location and drugs present in the house, with their expiry date, were also checked. In 46% of cases the drug cabinet, containing an average of 19 drugs, was located in the kitchen. Ten percent of drugs had expired.

Conclusion: This study emphasises the need, at least in our context, of a greater drug education for people to limit the risk of a malpractice self-medication.

415. ERRORS IN THE DRUG THERAPY TRANSMISSION FROM DOCTORS TO NURSES: A HOSPITAL PILOT STUDY

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Introduction: A medication error has been defined as a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. Adverse drug events caused by medication errors are a particularly important group, because they are potentially preventable. The relevance of medication errors in hospital setting is well documented. Drug treatment in the hospital setting requires a series of actions performed correctly by several members of the health care team, such as the physician, the hospital pharmacist, and the nurse. Errors are possible at any step of the process, from medication selection to order transcription, drug formulation, drug dispensing, and drug administration. In the literature the prescribing errors are indicated as the most serious and common; however the errors related to other therapeutic steps also could be relevant.

Aim of the Study: We have carried out a pilot study to estimate the percentage of errors in the specific phase of drug transcription.

Methods: The study was performed prospectively, for a period of two months, in the Unit of Endocrine Surgery at the University Hospital of Verona by a trained nurse with blinded doctors.

Results: During the study period, we have analysed 1693 drug prescriptions to 304 patients (mean: 5.6 drugs/patient), as reported in the case sheets, used by the nurses for the drug administration to patients. We have registered 576 transcription errors (34.0% of prescriptions). The most frequent error was the omitted or inaccurate transcription of the drug administration route (15.7% of prescriptions) followed by omitted or wrong dose indication (14.6%), omitted drug prescription (2.4%), omitted or wrong date of the end of therapy (1.3%).

The monitor every time that determined an error intervened to prevent a wrong drug administration. So, we don't know how many of these transcription errors led to drug administration errors and how many cause an adverse drug event. A subsequent discussion with the nurse team, at the end of the study, suggests that the errors in administration route are generally corrected during the drug administration step, while it is more difficult to determine and rectify the other errors.

Conclusion: The results of this study, which have immediately produced a revision of the therapy transcription system in the Endocrine Surgery Unit, emphasises the need to develop methods to prevent medication errors.

420. ASSESSMENT OF PROLONGED-RELEASE TRAMADOL EFFICACY AND SAFETY IN GENERAL MEDICAL PRACTICE: A PROSPECTIVE OBSERVATIONAL STUDY

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Introduction: Pain is one of the most frequent symptoms leading to targeted intervention by General Practitioners (GPs). Tramadol is a weak analgesic opioid, prescribed in moderate/severe pain treatment, as 2nd ladder, according to WHO guidelines. To our knowledge, few Italian data are available concerning tramadol use in pain treatment.

Aim of the Study: To evaluate efficacy of tramadol prolonged release formulation (SR), to assess incidence and severity of adverse drug reactions (ADRs) induced by such opioid, and to identify possible ADR risk factors.

Methods: Sixty-four GPs, homogeneously distributed over all of Italy, were enrolled into this study to record, during daily clinical practice, demographic/clinical information about patients affected by chronic pain, neoplastic or less, receiving prescriptions of SR tramadol (100–200mg), for a period of at least 28 days.

Efficacy was subsequently assessed throughout validated tools (Brief Pain Inventory, Visual Analogic Scale). Also anxious-depressive component was evaluated by Zung scale. Tolerability was analysed by reviewing all data about recorded ADR.

Results: Study sample included 361 patients (mean age: 65 years, females 67%), affected by non-cancer pain in 93% of cases. Among

these, 60% showed concomitant diseases or pharmacological treatments.

Pain relief resulted complete/satisfactory in 75% of cases and the shortest period of SR tramadol treatment, enough to obtain significant complaint improvements, was 15 days. Anxiety/depression level decreased significantly only in patients affected by non-cancer pain. Regarding safety data, 47 patients (13%) reported at least one adverse reaction, all ADRs being described in drug-label. The most frequent events were: dizziness (5.3% of total ADR), vomiting (4.7%), nausea (3.5%) and confusion (2.5%). ADR clinical severity resulted mild in 24.7% of cases, moderate in 48% and severe in 22.1%. Most patients with ADR required treatment discontinuation, followed by complete resolution of the event. Among ADR patients, tramadol therapy followed another analgesic treatment: NSAIDs (75% of cases), NSAIDs/opioids (23%), and opioids (2%). ADRs occurred more frequently in patients aged 65–74 years, leading to treatment discontinuation more commonly than other age groups. Apart from age, other ADR risk factors were not identified.

Conclusion: SR tramadol use resulted effective, providing complete pain relief in 75% of cases. On the other hand, all the reported ADRs were not serious, expected, and completely reversible after treatment discontinuation, suggesting an overall good benefit-risk/ratio for SR tramadol.

Such research emphasises also the GP's role in performing drug safety evaluations, especially concerning chronic pharmacological treatment.

425. APOMORPHINE GENERALLY WELL TOLERATED IN THE TREATMENT OF ERECTILE DYSFUNCTION: RESULTS OF A PRESCRIPTION-EVENT MONITORING (PEM) STUDY

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Background: Apomorphine hydrochloride, marketed as Uprima®, is licensed in the UK as a sublingual therapy for the treatment of erectile dysfunction (ED). Apomorphine is the first ED therapy with a central mode of action, exerting its erectogenic effects via dopaminergic and oxytocinergic pathways, ultimately resulting in penile tumescence.

Objectives: To examine the safety of Uprima® prescribed in the primary care setting in England.

Methods: An observational cohort study was conducted using PEM methodology. Patients were identified from dispensed Uprima® prescriptions issued by general practitioners (GPs) in England between October 2001 and December 2002. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. A series of additional questions regarding potential confounding factors (e.g. previous history of diabetes mellitus or ischaemic heart disease, and concurrent medications) was included.

Incidence densities (IDs; the number of first reports of an event /1000 patient-months of observation) were calculated for months 1 (ID1), 2, 3, 6, 9, 12 (ID2, 3, 6, 9 or 12), and the entire study period. Statistically significant differences between ID1 and ID2, 3, 6, 9 or 12 were considered to signal a possible adverse reaction to apomorphine. Event data will also be stratified according to responses to the aforementioned additional questions.

Results: Of 21 037 questionnaires posted to prescribing GPs, 11 180 (53.1%) valid questionnaires were returned. Thus, the study cohort compromised 11 180 patients (median age: 61 years, IQR: 54, 68; 99.9% male). The major prescribing indication reported by GPs was impotence (66.2%, n = 7347; for 32.6% of patients, the indication was not specified). Of the 7246 reports that included information on the effectiveness of apomorphine, 5090 (70.2%) stated that Uprima® was not effective. The event most frequently reported by GPs as an adverse drug reaction to Uprima® was headache (n = 7). Clinical events that were reported significantly more often during the first month of treatment compared with months two, three, six or nine included headache/migraine, nausea/vomiting, and intolerance. Selected events (e.g. cardiovascular events, hypotension, vasovagal attack/syncope, and somnolence) were followed-up via questionnaires sent to the prescribing GPs. Analyses of these follow-up data are ongoing.

Conclusion: Based on the data generated to date in this study, apomorphine appears to be well tolerated as a treatment for ED. The study did not generate any unexpected clinical event signals, with those above mentioned in the Uprima® SmPC (April 2004).

Financial disclosure statement: The Drug Safety Research Unit (DSRU) is an independent charity that works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control over the conduct or the publication of studies carried out by the DSRU. The Unit has received such funds from the manufacturer of Uprima®.

430. SAFETY PROFILE OF REPAGLINIDE AS USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: Repaglinide, launched in October 1998, is in a new class of antidiabetic drugs, the meglitinides, and acts as a prandial glucose regulator. It is indicated for the management of type II diabetes in adults (12+ years) inadequately controlled by diet and exercise, and may be given alone or in combination with metformin.

Aim: To monitor the safety of repaglinide prescribed in primary care in England using Prescription- Event Monitoring (PEM).

Methods: A postmarketing study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between December 1998 and January 2001. Demographic and clinical event data were collected from questionnaires (green forms) posted to GPs at least 6 months after the date of the first prescription for each patient. Indication for use, drug effectiveness and reasons for stopping treatment were also requested. Event Incidence Densities (IDs) [no. 1st reports/ 1000 patient-months of exposure] were calculated.

Results: Useful information was available for 5731 patients [median age 60 years (IQR 51–67), 49.9% male]. At the end of 6 months, 76% (3930) patients were still taking repaglinide. In those who re-

ported effectiveness, 71.0% (3224) reported repaglinide as effective. 113 events were reported by the GP as Adverse Drug Reactions (ADRs) to repaglinide in 83 (1%) patients. The most frequently specified ADRs were diarrhoea (10), abdominal pain (10) and nausea, vomiting (9). The most frequently recorded clinical events in the first month were diarrhoea (ID1 10.3), malaise, lassitude (ID1 8.1), and nausea, vomiting (ID1 7.9). 2223 reasons for stopping were reported in 1959 patients. The most frequently reported reason for stopping was lack of effect in 647 (11.2%) patients, followed by non-compliance (66, 1.2%) and hospital referral (66, 1.2%), with the most common clinical reasons being diarrhoea (60, 1.0%), malaise, lassitude (55, 1.0%) and intolerance (54, O.9%).

Conclusions: Repaglinide is generally well tolerated when used in general practice in England and this study did not identify any unrecognised adverse events, although the cohort was relatively small and therefore may not have had the power to identify very rare events. PEM is a useful method of postmarketing surveillance which monitors the pattern and frequency of events reported for a large cohort of patients who were amongst the first users of repaglinide in England.

Financial disclosure statement: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of repaglinide.

435. GLOBAL OVERVIEW OF VACCINE SAFETY MONITORING: PROGRESS, CHALLENGES AND OPPORTUNITIES

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The WHO's Department of Immunization, Vaccines and Biologicals has developed a comprehensive programme of activities to encourage and support national surveillance for adverse events following immunisation (AEFI) which include:

• Country training on AEFI through the Global Training Network (GTN);

• Assessment of national regulatory authorities (NRA) in their capacity to regulate vaccines;

• Technical assistance to priority countries to strengthen capacity for safety monitoring;

• Development of technical documents and training materials for in-country training;

• Dissemination of up-to-date information on safety issues of global relevance to enable countries to make informed evidence-based policy decisions on immunisation.

While significant progress has been made, national AEFI surveillance systems have not yet been universally implemented. This presentation will describe the status of national AEFI surveillance systems based on data collected through the above-mentioned activities and through other sources. In particular, WHO's programme for assessing the vaccine regulatory capacity of national regulatory authorities incorporates process and performance indicators for AEFI activities. These assessments have shown significant improvements in surveillance and management of AEFI in many parts of the world.

Challenges that face countries in developing successful AEFI programmes include a lack of political commitment, resource limitations, high staff turnover or 'unavailability' of staff to participate in implementation activities and a gap between training of central level staff and peripheral staff and the private sector.

However, in recent years, opportunities have arisen which could assist with further development of AEFI surveillance as a successful pharmacovigilance programme. Among others these include:

• Immunisation campaigns and the introduction of new vaccines into programmes as opportunities to introduce AEFI surveillance.

• Growing media and global awareness of vaccine safety as a priority in the context of the polio eradication and measles elimination programmes resulting in more political committment.

• Growing recognition of the importance of public health pharmacovigilance activities and the need for partnership between public health and pharmacovigilance programmes.

• Evolution of the GTN AEFI training curriculum to address region-specific needs.

AEFI systems will continue to evolve as the face of immunisation programmes change. Opportunities provided by global efforts to control or eradicate vaccine-preventable diseases need to be utilised to introduce sustainable AEFI systems in all countries. Lessons learnt from vaccine safety initiatives could be used to inform other public health pharmacovigilance programmes.

440. TRAINING INITIATIVES IN VACCINE SAFETY MONITORING THROUGH THE WORLD HEALTH ORGANISATION (WHO) GLOBAL TRAINING NETWORK

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Globally, there is growing attention being paid to adverse events following immunisation (AEFIs) and the need to improve the capacity to detect immunisation safety problems at country level. The need to strengthen vaccine regulatory capacity in order to ensure improved access to safe, effective and good quality vaccines was also recognised. To address these concerns the WHO Department of Immunization, Vaccines and Biologicals undertook in 1998 to introduce a training course on Adverse Events Following Immunization in its Global Training Network (GTN) curriculum. This poster describes the public health pharmacovigilance training programme and its role in strengthening national AEFI surveillance systems. Refer-

ence is made to the challenges faced by alumni after completion of the GTN AEFI training, and how these might be addressed.

WHO AEFI Training Programme: The 6-day programme combines lectures, problem-based workshops, discussions and intensive trainee participation. Lectures are presented on the safety profile of vaccines, concepts in risk-benefit assessment and decision-making, causality assessment, and communication of risk-benefit information to the public. The problem-based component actual cases of AEFI incidents reported in a number of countries. Participants are expected to develop and present investigation plans and communication reports, including press statements. Participants from different countries get the opportunity to work together collaboratively and constructively to deal with specific immunisation safety issues using the skills, resources and training provided.

Current status of the training programme:

• Since the first AEFI training course in November 1999, 12 training courses have been conducted in either English, French or Russian using standardised training material. Altogether 191 trainees from 64 countries have been trained so far.

• The GTN now includes four training centres – in South Africa, Tunisia, Sri Lanka and Russia. Additional courses in Arabic and Chinese are being prepared.

Despite the training, many countries still lack a functioning AEFI surveillance system. Limited resources, lack of political support, modest regulatory capacity and conflicting priorities within the ministry of health are amongst the factors impeding implementation. To address this, WHO in conjunction with the training centres have initiated the following:

• Mentorship of trainees after the training course;

• Political advocacy and ongoing assistance from WHO regional offices and training centres;

• Development of in-country training materials for adaptation by countries;

• Development and implementation of assessment tools to measure progress made by alumni and their institutions after training.

445. ADVERSE EVENTS TO HERBAL PREPARATIONS: ALLERGIC REACTIONS TO PROPOLIS

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Introduction: Therapeutic use of herbal preparations is increasing worldwide. Herbal medicine is considered by its users 'natural', and thus safe, and often used as self-medication. Even if evidence of efficacy has been produced through randomised clinical trials for some preparations, adverse events and interactions with synthetic drugs are also well known.

Propolis is a resinous material collected by honeybees from the buds of living plants mixed with bee wax and salivary secretions. It is a complex mixture of about 150 compounds including flavonoids, coumaric acids, lignans, etc. Propolis has been used for thousands of years in folk medicine for several purposes. Today propolis preparations are used, generally as self-medication for local treatment, in acute or chronic inflammatory diseases of the mouth, periodontitis, pharingotracheitis or other upper airways diseases. In a 'case-control' study an aqueous propolis extract, locally administered, was shown to reduce the incidence of acute and chronic rhinopharingitis in children;[1] more recently a double-blind study on six volunteers indicated the efficacy of a mouthrinse containing propolis in reducing plaque formation.[2] However, randomised clinical trials on efficacy of propolis are lacking. Propolis seems relatively safe, but cases of allergic contact dermatitis have been described.[3]

Aim of the Study: The results presented here are related to allergic reactions to propolis.

Methods: Since April 2002 a surveillance of adverse events to herbal preparations and dietary supplements, based on spontaneous report, has been set up.

Results: From April 2002 to March 2004 we received 99 spontaneous reports. Nine reports (about 9%) were related to allergic reactions to propolis containing products. A 1-year-old child visited the Emergency Department for a serious skin reaction after application of a topical propolis-containing product. Furthermore, two children (aged 4 and 5 years) reported acute asthmatic crisis associated with the intake of propolis given for influenza. All the three children were atopic.

A 16 year old boy was hospitalised for polymorphous erythema associated with the intake of propolis for laryngitis. A 30-year-old male was hospitalised for an erythematous reaction. Three oedema of the tongue, lips and mouth were also reported; one of them was life threatening. Finally one case of dyspepsia was reported.

Conclusions: Propolis is a potent sensitiser and it is contraindicated in case of allergic predisposition, especially in children.

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450. THROMBOCYTOPENIA ASSOCIATED WITH NON-CYTOTOXIC DRUG USE: A PROSPECTIVE CASE-CONTROL STUDY

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Introduction: Thrombocytopenia can be a serious condition that may occur in association with systemic diseases, and it is a well-recognised complication of cytotoxic cancer therapies. Though most

of the cases are classified as idiopathic thrombocytopenic purpura, almost any drug has been reported in association with thrombocytopenia.

Aim: To estimate the occurrence of thrombocytopenia in association to non-cytotoxic drug use in children.

Methods: Our study started in 1999 in four paediatric hospitals in Italy. We enrolled all children admitted through the Emergency Department for the following conditions: thrombocytopenia (platelet count < 100 000); neurological disorders; non-infectious mucocutaneous diseases and vasculitis; and clinically defined or endoscopically confirmed gastroduodenal lesions. Drug exposure, in a time period of 3 weeks (6 weeks for vaccines) prior to the onset of symptoms that had caused the hospital admission, was obtained by interviewing the parents with a structured questionnaire. The interview was performed by a physician during the hospital admission of the child. Informed consent was asked. To estimate the odds ratio associated with drug use the analysis was conducted according to a case control design: drug exposure of children hospitalised for thrombocytopenia was compared with drug exposure of children hospitalised for neurological disorders and gastroduodenal lesions (mucocutaneous diseases were excluded from the control group because frequently associated with drug use).

Results: Between November 1999 and June 2003, 1467 children were enrolled in the study. Out of these, 179 (12%) were hospitalised for thrombocytopenia (in 157 children the reason for admission was the occurrence of purpura/petechiae). As for the remaining conditions, 612 children were admitted for neurological disorders, and 123 for gastroduodenal lesions (553 children with mucocutaneous diseases were excluded).

The overall level of drug use was 54% for thrombocytopenia and 62% for the control group. Antibiotics were the therapeutic category most frequently used: 31% among children with thrombocytopenia and 21% among children in the control group. The crude Odds Ratio (OR) of developing thrombocytopenia was 0.7 (95% CI 0.5, 1.0) among users of any drug, and 1.2 (95% CI 0.8, 1.8) among users of antibiotics.

Conclusion: In our study the use of any drug is not associated with an increased risk of hospitalisation for thrombocytopenia. As for antibiotic use, the possibility should be considered that the indications for use (i.e. viral infections, upper respiratory tract infections, etc.) may represent a determinant of the thrombocytopenia.

455. REPORTS OF LEUKAEMIA AND LYMPHOMA DURING THE USE OF CLOZAPINE AND OTHER ATYPICAL NEUROLEPTICS

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Introduction: Clozapine is a known cause of agranulocytosis and myocarditis but not of leukaemia or malignant lymphoma.

Aim of the Study: To review reports of haematological malignancies during the use of atypical neuroleptics.

Methods: The WHO-UMC database contains worldwide case report summaries of suspected adverse drug reactions. A data mining program using Bayesian logic and a neural network architecture (BCPNN) is used to highlight drug-adverse event associations that stand out from the background.

Results: There are 113 reports stored in the WHO-UMC database of malignant haematological diseases in the UMC database, reported in suspected association with the use of the atypical neuroleptics clozapine (106), olanzepine (6) and quetiapine (1); 83 reports concern leukaemia and 30 malignant lymphoma. These numbers are considerably higher than expected from the background of the database.

Conclusion: In case reports of malignant disorders it is often difficult to assess the relationship with the suspected drugs. The connection between atypical neuroleptics and haematological malignancies is uncertain and may be erroneous. Nevertheless these reports need due attention.

460. ACHIEVING EXCELLENCE IN AVENTIS UK PHARMACOVIGILANCE

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Aventis Pharmacovigilance is committed to optimising the benefit/risk balance of all company medicinal products and devices, and facilitating early action to address safety issues, thereby contributing to patient safety and public health. To enable us to fulfil this commitment, we need to ensure that each member of the team is fully trained and competent in the practice of pharmacovigilance.

We have, therefore, developed a competency framework. The framework is based on the following performance areas: organisational structure, responsibilities, processes, resources and documentation, broken down into categories such as:

Organisational Structures: Global and local Aventis organisational structure; internal and external interactions; the Aventis Pharmacovigilance network; structure and function of regulatory authorities.

Responsibilities: How to provide training, communicate information, manage records and workload, adhere to Aventis Corporate Policy, and obtain and maintain therapeutic area and product training.

Processes: Adverse events and product technical complaints management; generation of Periodic Safety Update Reports; establishment and maintenance of third party licencing agreements.

Resources: Use of tools to perform our roles such as local Pharmacovigilance tracking databases, global Pharmacovigilance databases, AEGIS as well as use of external resources to search for information.

Documentation: Knowledge of all global and local Pharmacovigilance laws and guidelines and Aventis Standard Operating Procedures.

Since the roles of team members and therefore the level of competency required in each category differed, a simple question-approach was used to further breakdown each category into relevant levels:

For my job in Pharmacovigilance, what do I have to know from these areas?

For each level, training is provided either as background reading, shadowing, through discussions, examples, exercises, visual material or attending various internal/external training. To ensure that this process works, for each training method a range of assessment methods has been developed.

Using this approach, a competency standard, which captures all key aspects of necessary knowledge for staff working in the Pharmacovigilance department, was established.

The creation of this standardised competency framework provides a transparent method of ensuring that everyone working in the department is fully trained to undertake their responsibilities in pharmacovigilance as well as maintain the level of professionalism throughout their career.

465. ADVERSE EVENTS ASSOCIATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: A SURVEY IN HIV-INFECTED POPULATION OVER 18-MONTH PERIOD

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Introduction: HAART has resulted in remarkable reduction of morbidity and mortality of HIV infection. Antiretroviral toxicity has become a currently and increasingly important issue in the management of HIV-infected patients. With the sustained major declines in opportunistic complications, HIV infection is a more chronic disease, and so more drugs are being used in more patients for longer periods. The toxicity and tolerability of HAART are important factors in the decision to prescribe one of these drugs.

Aim of the Study: To determine the distribution of adverse effects induced by HAART in HIV-infected patients; to evaluate their severity and their repercussion on the continuation of this treatment.

Methods: Over an 18-month period, the Regional Pharmacovigilance Centre set up a systematic survey of adverse effects of HAART in HIV-infected patients in the department of infectious diseases. A procedure of notification, data gathering, evaluation and validation of the cases was instituted. Five consulting physicians and a pharmacist notified serious and non serious adverse effects. The adverse effects, the severity, the outcome and the suspected drugs were analysed and commented by the Pharmacovigilance's specialists.

Results: From 01/07/2002 to 31/12/2003, 135 adverse effects occurred in a cohort of 354 HIV-infected patients. 76 patients (21.5%) were concerned: 14 women and 62 men. At the time of adverse effect, mean age was 43.2 years (22–73). Median CD4+ lymphocyte count was 360 cells/mm^3 (1–1082) and median viral load was 65 copies/mL (<50–1 175 000). According to the WHO's classification, 11 events were notified as 'serious' and 124 as 'non serious'. From one to seven adverse effects were notified for the same patient. The majority of adverse effects concerned dyslipidemia (n = 12) and lipodystrophy (n = 20).

Conclusion: All antiretroviral drugs can induce both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient. In our survey, we have found essentially lipodystrophy and other metabolic type alterations (eg, serum lipid abnormalities). This survey revealed a relatively good tolerance of HAART in our HIV population.

470. AGRANULOCYTOSIS DURING TREATMENT WITH CYAMEMAZINE AND VENLAFAXINE

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Introduction: Cyamemazine is a phenothiazine with general properties similar to those of chlorpromazine. It is used for the management of a variety of psychiatric disorders including anxiety disorders and aggressive behaviour. Venlafaxine is an antidepressant, which inhibits the uptake of serotonin and noradrenaline.

Aim of the Study: To report a case of agranulocytosis associated with cyamemazine and venlafaxine in a young man.

Case Report: A 24-year-old man with a history of restlessness and depression presented with fever, asthenia, sore throat, gingival ulcerations, cellulitis of face and agranulocytosis, 3 months after starting treatment with cyamemazine (Tercian®) and venlafaxine (Effexor®). He was admitted in hospital. Blood count revealed haemoglobin 12.3 g/dL, white blood cell count 400/mm^3 (no neutrophils), and platelets 371 000/mm^3. The erythrocyte sedimentation rate was 73mm in the first hour. Cyamemazine and venlafaxine were discontinued, the patient received metronidazole, ticarcillin + clavulanic acid and ofloxacin. After 8 days' therapy with granulocyte colony-stimulating factor (G-CSF 300µg daily), his full blood count had recovered and his pyrexia resolved within 3 weeks. The cellulitis improved after steroidal treatment. It was not clear as to which agent was responsible for the agranulocytosis.

Discussion: Only two reports of cyamemazine-induced agranulocytosis have been found (Vial, 1996). Lucht et al. (2000) have reported only one case of agranulocytosis in an elderly woman after her treatment was changed from mianserin to venlafaxine. In this case, either mianserin or venlafaxin may have been responsible for the development of agranulocytosis. After clozapine and remoxipride, the highest risks of haemopoietic reactions appeared to be associated with the phenothiazine derivatives thioridazine and chlorpromazine. According to our findings, 52 cases of agranulocytosis have been attributed to chlorpromazine. Most cases are seen within the first 2 months after beginning treatment, but there have been a few reports in which this occurred only after many years. The phenothiazines, especially chlorpromazine, cause damage to the proliferating pool of granulopoietic precursors.

Conclusion: Even if agranulocytosis has been rarely reported with cyamemazine and venlafaxine, careful attention should be given to possible early warnings signs, such as fever, sore throat, and adenopathy. Treatment requires immediate withdrawal and preventive measures against infection.

475. PHARMACOVIGILANCE PLANS FOR EMERGING ONCOLOGY COMPOUNDS

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Introduction: The development of Pharmacovigilance Plans (PvPs) is becoming an essential component of clinical development strategy, with the aim of assessing and minimising risks to patients. Developing oncology compounds poses particular pharmacovigilance challenges, in balancing the need to rapidly deliver efficacious drugs for untreatable cancers, against the need to adequately define the safety profile of compounds that often have a high potential for toxicity and are widely used in combinations and off-label. To maximise the value of PvPs, AstraZeneca has initiated them in parallel to the first clinical development plan (CDP), i.e. prior to 'first in man' studies.

Aims and Methods: It is recognised that the small size, short duration and carefully selected populations of pre-marketing studies restrict the ability to fully understand the safety profile of a drug prior to marketing. Initiating PvPs during early development, whilst adopting a cross-functional approach, allows:

- Pharmacovigilance strategy to be documented, capturing potential and known safety signals within an ongoing issue log.
- Safety assessment activities to be targeted to particular issues with appropriate evaluations incorporated into study designs.
- Ongoing evaluation of potential gaps in safety knowledge from clinical studies and steps to mitigate.
- Better informed 'go'/'no go' decisions.
- An evolving PvP towards regulatory filing.

The basis for risk management is identification of potential safety issues in early development, through shared knowledge of pharmacology, toxicology and preclinical data, supplemented by epidemiological disease profiling (e.g. co-morbidity rates) and analysis of available data on class effects. Emerging clinical data refine these assessments, allowing fully characterised issues to be resolved and new issues evaluated. Multidisciplinary input is essential to support the generation of PvPs. Producing PvPs in accordance with ICH E2E, creates an issue log for risk minimisation strategies from early development and facilitates smooth transition into documents that may be required for filing, such as FDA Risk Minimisation Action Plans.

Conclusion: Drug safety is a key player in the multidisciplinary approach to producing the PvPs. A PvP format generated for postmarketing has been modified for emerging oncology compounds and sits as part of the CDP. PvPs for new drugs from 'first in man' studies in oncology or other therapeutic areas, should enhance safety evaluation and build a documented knowledge base during clinical development. This will help to protect patients and allow identified risks to be better mitigated during clinical development and postmarketing.

476. CHOLESTATIC HEPATITIS WITH FLUCLOXACILLIN: UK SPONTANEOUS REPORTS 12 YEARS ON

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Introduction: In 1992, the UK Medicines Control Agency published warnings about the risk of cholestatic hepatitis with flucloxacillin, especially in the elderly. In Australia, when flucloxacillin became a 'restricted benefit' in 1994 for severe staphylococcal infections [Australian Adverse Drug Reactions Bulletin. 13 (3) 1994], prescribing decreased. ADROIT reports have been re-analysed to investigate the impact of the UK warning.

Aims: To examine for flucloxacillin (i) prescribing, (ii) spontaneous reporting of hepatobiliary adverse drug reactions [ADRs], (iii) whether further hypotheses could be generated from ADR cases on risk factors or mechanisms for cholestatic hepatitis, and (iv) recent published literature.

Methods: Number of prescriptions per year was obtained from the Prescription Cost Analyses and patient data from Disease Analyzer MediPlus. UK ADROIT reports were extracted for hepatobiliary reactions associated with flucloxacillin. Published literature was searched using PubMed.

Results: We estimated 2.6 million patients per year in UK primary care are prescribed flucloxacillin, with 25% aged ≥60 years. By 31/7/2004, CSM/MHRA had received 282 suspected ADR reports with flucloxacillin, describing 309 hepatobiliary reactions; 15 (5%) of these had a fatal outcome and 23% were hospitalised. 225 (80%) reports were received after 1992 consistent with stimulated reporting. Of the cases, 63% were ≥60 years old and 57% were female. 31% of 206 (where time to onset reported) reactions occurred on flucloxacillin treatment and 68% post-treatment. Onset times ranged from 1 to 365 days but suggested a bimodal pattern (peaking at 6 and 30 days). Extra-hepatic manifestations were infrequently co-reported. Where reported in 44 cases, the median time to recovery was 44 days (range 2–165). Jaundice cholestatic/NOS were the most common terms reported (47%/25%), but hepatic failure (2%) and hepatic necrosis (1%) were also received. Co-morbidity and prescribing were examined but no new risk factors identified. Recent literature suggests the absolute risk of acute and clinically relevant flucloxacillin-induced liver injury to be very rare – 1.8 (0.9–4.6)/100 000 prescriptions [Br J Clin Pharmacol. 2004; 58 (1):71-80].

Conclusions: Stimulated reporting since 1992 indicates increased awareness of hepatobiliary ADRs with flucloxacillin. Prescriber and patient awareness is important given the wide use of flucloxacillin and the fact that early detection and withdrawal of treatment are the mainstays of management of this ADR. The mechanism for this rare to very rare ADR is poorly understood and no new risk factors have been identified.

477. PRELIMINARY COMPARISON OF 2 SIGNAL DETECTION METHODOLOGIES IN THE UK REGULATORY AUTHORITY SPONTANEOUS ADR DATABASE

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Introduction: Currently the MHRA uses Proportional Reporting Ratios (PRRs) for signal detection. The availability of newer methodologies, e.g. the Multi-item Gamma Poisson Shrinker (MPGS: calculating the Empirical Bayes Geometric Mean – EBGM), the possibility of age-sex stratification to refine expected values and increasing trends in polypharmacy suggested further exploration.

Aim: To conduct limited evaluation of MPGS signal detection on UK spontaneous ADR reports, compared with PRRs.

Methods: Assessment of age-sex-stratified MPGS (i) and numbers of signals produced, threshold dependency and time to threshold compared to standard PRRs; (ii) in random set of identified interactions using a threshold based on EXCESS2, i.e. an estimate of the number of transactions containing the item set over and above those that can be explained by the pairwise associations of the items in the item set; (iii) in subsets for identifying signals in children, with vaccines and fatal reactions.

Results: At a threshold of EBGM lower 95% CI (EBGM 05) ≥2, MGPS produced fewer possible signals than PRR from 198,084 drug-ADR combinations in the MHRA database (3.2% vs 6.5%) with ≥3 reports and serious MedDRA-PT. A threshold of EB05>1 produced similar results to PRR (6.5%). Blinded evaluation of the labelling status of a random 20 sample of each cell of the 2×2 table of drug-event-combinations, categorised by PRR/EB05 ≥2 threshold, demonstrated similar proportions to be labelled regardless of PRR or EBGM signal status. For nine selected signals, a retrospective analysis attempted to investigate which method identified signals earlier. Using EB05 ≥2, signals were on average identified earlier with PRRs than MGPS; at EB05 >1, the converse was true. A random sample of eight supra-threshold interactions identified using MGPS EXCESS2, were all known interactions. Greater numbers of interaction cases were identified when all drugs were the basis for the model rather than suspect drugs and the preferred term 'interaction' omitted. We successfully subsetted the data for performing signal detection in children, vaccines and fatal reactions, calculating PRR and EBGM values based on these subsets alone.

Conclusion: The choice of threshold is critical for signal detection and should be optimised for public health purposes. Although limited evaluation of supra-threshold drug interaction signals were identified as known interactions, this analysis does not provide a measure of the false negative rate. The use of subsets may be useful for detecting signals in children or those associated with vaccines or with fatal suspected ADRs

480. INTENSIVE ADVERSE EVENTS MONITORING ON IODINATED AND MAGNETIC CONTRAST MEDIA PARENTERALLY USED FOR DIAGNOSTIC IMAGING: A STUDY FROM TWO TUSCANY HOSPITALS

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Introduction: New contrast media have been developed in the last years. They are magnetic and iodinated agents with a better safety profile than previously used molecules, because of their lower osmolality. Nevertheless, some toxicity remains. Moreover, it is known that adverse reactions associated with the parenteral use of contrast media depend on patient's comorbidity and likely on concomitant drug administration.

Aims of the Study: The aim of this study was to assess the incidence and the type of Adverse Events (AEs) associated with the parenteral use of CM for diagnostic imaging.

Methods: Two questionnaires were administered to all subjects undergoing different diagnostic procedure on established days of the week to detect early (within 1 hour) and delayed (from 1 hour to 1 week) AEs after CM use; all data were analysed with the software SPSS 11.5 (Chicago Inc,.USA). The study was approved by the local ethics committee and informed consent was obtained from all subjects enrolled.

The study was carried out in seven Radiodiagnostic Units located in Florence (five), Pistoia and Pescia.

Results: From April 4 to July 10, 2004, 367 patients (227 males, 140 females) were enrolled in the study and 89 AEs were detected, based on the results of the questionnaires: 12 early (12.9%) and 77 delayed events (82.8%). The most frequent AEs were itching (14.0%), cutaneous rash (8.6 %), headache (12.9%) and nausea (18.2 %). Women experienced a significantly higher incidence of AEs (33.1%) compared with males (19.9%) ($p = 0.009$). Moreover, old women (≥60 years) presented more AEs than old men (30.0% vs 16.6%, $p = 0.016$).

Conclusion: These preliminary data suggest that age and gender are possibly correlated with AEs occurrence associated with parenteral use of CM in agreement with the literature. To verify these results and to better characterise the risk factors related to the type of contrast media and to the patient's conditions, the number of enrolled subjects will be increased.

485. VACCINE ASSOCIATED ADVERSE EVENT SURVEILLANCE (VAAES) AND QUALITY ASSURANCE

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Introduction: In Canada, reports on vaccine adverse events are sent by different health care providers (physicians and public health nurses) to local public health authorities, who then send them to the provincial/territorial counterparts. The latter, with vaccine manufacturers and some individual reporters, forward the reports to Health Canada.

Aim of the Study: To assess the magnitude of duplicates, suggest some causes for duplicate reporting, changes to the database and QA procedures.

Method: The analysis is based on data from an Excel spreadsheet on duplicate numbers, removed from the database. The active record number was linked to the VAAE database for information on province and reporter status. Analysis was done using SAS statistical software.

Results: Between the years 2000 and 2003, Health Canada received a total of 19 385 reports (5112 in 2000; 6194 in 2001; 4514 in 2003 and 3565 in 2003). The reporters were nurses 30%, physicians 10%, other professionals 35%, and manufacturers 11%. During this 4-year period, there were 851 (4%) duplicate sets (4% in 2000 and 2001; 6% in 2002 and 2% in 2003). For the retained reports, most of the reporters (38%) were nurses, 29% other professionals, 17% manu-

facturers and 12% physicians. Three provinces contributed 31%, 22% and 20%, respectively.

Discussion: The high numbers of reports for 2001 and 2002 were due to an unexpected reaction to the flu vaccine, now known as oculorespiratory syndrome. Enhanced surveillance was started and it took some time before the QA program could deal with duplicate reports. Since 2004 as a new report is entered into the database, it is automatically compared on date of birth, age, and date of vaccination and queried for resolution as to whether or not the new report is a duplicate.

Conclusion: Duplication of reports is a great concern. The reinforced procedures of checking and the aggressive QA from year 2002 contributed to decrease the number of duplicates. For 2004, it is expected that the systematic check on data entry or importations will decrease the number of duplicate reports found on later QA reviews.

490. COUNTERFEIT MEDICINE: MEDICATION ERROR PRONE

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Introduction: Counterfeiting of medicines is an age long fraudulent practice against public health which has assumed an alarming proportion in recent times. There have been reported cases of counterfeit medicines from every continent in the past five years and these reports cut across both developed and developing countries. For countries where counterfeit medicines have been detected either in the official or unofficial channels of drug distribution, drug safety monitoring systems can no longer afford to presume that quality of medicines is assured until it is really reassured. Safety monitoring therefore must be alert to the reality of counterfeit medicines and the extra dimension it portends to drug related problems such as increased Adverse Drug Reactions, (ADRs) and tendency to escalate medication errors.

The dilemma of counterfeit medicines as regards medication error is that by their very nature, counterfeit medicines are error prone. There is therefore no question of aiming for a fail-free practice in the prevention of medication error except by first being alert to detection and possibly sanitising the system to prevent counterfeit medicines in the healthcare system.

Aim: To sensitise participants on the need for greater alertness to the detection and avoidance of counterfeit and other substandard medicines as a strategy for prevention of medication errors.

495. ARYL CARBOXYLIC NON-STEROIDAL INFLAMMATORY DRUGS (AC) INDUCED SERIOUS RENAL ADVERSE EFFECTS: RESULT OF A FRENCH NATIONAL SURVEY

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Introduction: AC are widely used for several indications: dysmenorrhea, pain, fever, rheumatismal diseases, antiplatelet aggregation. They may be used in adult and children. Two drugs, given by oral route in France, are over-the-counter (OTC): ibuprofen and ketoprofen.

After a first alert for flurbiprofen and renal diseases, French Drug Agency (AFSSAPS) decided to undertake a national survey for the whole class.

Aim of the Study: Summaries of Product characteristics (SPC) of AC are different for adverse effects in section 4.4 and 4.8 (warnings and undesirable effects). The aim of the study was to describe the different types of renal diseases, the severity, and the risk factors, in order to modify prescribing information.

Methods: A retrospective study was made from January 1995 to December 2002 for the following AC: ibuprofen, ketoprofen, diclofenac, naproxen, tiaprofenic acid, alminoprofen, etodolac, nabumetone.

All serious spontaneous reporting of renal effects was collected from companies and French Pharmacovigilance Centers.

Other renal adverse effects as hyperkaliemia, sodium retention and oedema were analysed after a literature review.

Results: 280 observations were collected (219 acute renal failure) and analysed: adults n = 250, children n = 25, newborns n =5.

Thirty-one renal biopsies were available. Outcome was favourable in 71% of cases, unknown in 17 %, with sequelae in 5 %. There was 8% of deaths, but only 2% were related to drugs. Two mechanisms were clearly identified:

- Organic disease = tubular necrosis and/or interstitial nephritis, nephrotic syndrome, papillary necrosis; onset delay was short (a few days) in 90% of cases. Disease was unpredictable and independent of age and dose.
- Functional disease by inhibiting renal prostaglandin synthesis in patients with risk factors: congestive heart failure, hypovolemia, chronic renal disease, cirrhosis, or elderly patients. 31% of patients were co-treated with ACE inhibitors, angiotensin II receptors antagonist or diuretics.

Conclusion: Renal adverse effects may occur with all AC even with OTC drugs. Modification and harmonisation of SPC was accepted for all AC by AFSSAPS on the 30th of March 2004.

Warnings were added for 'at-risk' patients and description of adverse renal effects were modified according to the results.

500. SSRI ADVERSE EVENTS IN ITALIAN POPULATION

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Prescribing of SSRI antidepressants has increased in Italy from 5.5 DDD/1000 inhabitants day in the year 2000 to 18 DDD/inhabitants day in the year 2003. In the last year antidepressant prescription has increased more than 13%.

The prescription rate in the young population, aged <18 years, is about 2.1 per 1000 inhabitants. In the population aged 14–17 years the prescription rate is 6.6 per 1000 inhabitants. The use of SSRI is more frequent among females (8.4 per 1000 inhabitants) than males (4.8 per 1000 inhabitants). A major depressive disorder is the main indication for the use of SSRI in children and adolescents. But the effectiveness of antidepressants in childhood and adolescence is less clear.

Recently the FDA, MHRA and EMEA gave a warning about the increased risk of suicide in young people using SSRI. The data collected by Italian pharmacovigilance network from January 2000 until July 2004 showed a total number of 358 ADR related to SSRI use in Italian population. Sixty-seven events were serious: seven cases of suicide and 60 cases of other serious adverse reactions (mania or hypomania, agitation, anorexia, insomnia). 26 of these serious events occurred in children and adolescents, aged <18 years, but no case of suicide was reported in this population group. Seventeen cases occurred to young females and nine cases to young males. Twenty-one cases of serious adverse events occurred in the population group aged 0–12 years: 16 to females and five to males.

Our data suggest that a widely active surveillance for this therapeutic group is necessary because the randomised controlled trials usually underestimate the serious adverse events of SSRI. Moreover the magnitude of benefit in children and adolescents is not so evident to justify the risk related to the use of these drugs as the first therapeutic line.

505. REPORTS OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM FROM A PRESCRIPTION EVENT MONITORING STUDY OF YASMIN® IN ENGLAND

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Introduction: Yasmin® is a new combined oral contraceptive (OCP) that was launched in the UK in May 2002. Yasmin® contains ethinyloestradiol (30 mcg) and a novel progestogen, drosperinone (3mg). Some OCP have been associated with serious adverse drug reactions (ADR), including arterial and venous thromboembolism.

Aims: To monitor the safety of Yasmin® prescribed in the primary care setting in England using Prescription Event Monitoring (PEM).

Methods: A postmarketing study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between May and December 2002. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Details of suspected ADRs, reasons for stopping treatment, pregnancies and causes of death were requested. Information on selected risk factors for arterial and venous thromboembolism (prior history of: venous thromboembolism, arterial thrombosis, prothrombotic coagulation abnormality, smoking) and migraine (prior history) was collected. Event Incidence Densities (IDs) [no. of first reports/1000 patient-months of exposure] were calculated. Differences between IDs for events reported in month 1 (ID1) and months 2 to 6 (ID2-6) of exposure were examined for temporal changes in event rate.

Results: The cohort consisted of 15 684 patients. Age was known for 13 369 of the 15 645 (85.4%) female patients; the mean (SD) was 26.5 (±6.9) years. The total treatment period recorded for the 15 645 female patients was 9481.9 patient-years. Five incident cases of deep vein thrombosis (DVT) and eight of pulmonary embolism (PE) in 13 females using Yasmin® were identified. Diagnosis was confirmed by ultrasound or imaging procedures, with the exception of one case of PE where the event occurred outside the UK. None of the cases was confirmed to have both a DVT and PE during these episodes. The crude incidence rate of DVT/PE cases is 13.7 cases per 10 000 patient-years of use (95% CI: 7.3-23.4). The mean (SD) age of these 13 patients was 33.9 years (±8.2). Each of the 13 patients had one or more possible risk factors for DVT/PE (age >35 years and/or other risk factor).

Conclusions: To our knowledge, this is the first description of cases of DVT/PE in users of Yasmin® in an observational study conducted in England. Further analysis of study data is being undertaken.

Disclosure: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of Yasmin®.

510. SAFETY PROFILE OF SIBUTRAMINE AS USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: Sibutramine is a serotonin-noradrenaline reuptake inhibitor indicated for the management of obesity within a weight management programme. It was launched in the UK in June 2001.

Aim: To monitor the safety of sibutramine prescribed in the primary care setting in England using Prescription-Event Monitoring (PEM).

Methods: In PEM, patients were identified from dispensed prescriptions issued by GPs between October and December 2001. Demographic and clinical event data were collected from questionnaires posted to GPs at least 6 months after the date of the first prescription for each patient. Information on suspected adverse drug reactions (ADRs), reasons for stopping treatment, pregnancies and causes of death was requested. Data on co-morbid conditions and previous prescribing of other anti-obesity agents were also collected. Incidence Densities (IDs) [number of first reports of an event/1000 patient-months of exposure] were calculated. Significant differences between IDs for events reported in month 1 (ID1) and months 2–3 (ID2–3) of exposure were regarded as potential signals.

Results: Reports on 12 336 patients were received. The median age was 45 years (IQR 36,55); 82.9% were female. Less than 1% of patients were under 18 years of age; 5.9% of patients were over 65 years of age. Data collected on comorbid conditions indicated that 12.5% of patients had a history of hypertension, 1.9% had ischaemic heart disease and 7.3% had diabetes mellitus. Clinical events that were reported significantly more often during the first month of treatment compared with months 2–3 included: headache/migraine, malaise/lassitude, insomnia, cardiovascular tests, dry mouth, nausea/vomiting, palpitation, dizziness, intolerance, sweating and faintness. The most common clinical adverse events given as a reason for stopping treatment included: raised blood pressure, hypertension, headache and depression. 425 events in 285 patients (2.3% of cohort) were reported by GPs as ADRs to sibutramine. The most frequently reported ADRs were headache (n = 30), malaise (n = 28), palpitation (n = 23) and constipation (n = 19). Twenty-five deaths

were confirmed during the total period of observation for sibutramine; nine deaths were due to cardiovascular causes. The cause of death was not ascertained for ten deaths.

Conclusion: This study defines the safety profile of sibutramine in 'real world' patients. Further analysis of the study data is being undertaken including assessment of causal association of specific events.

Disclosure: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control over the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of sibutramine.

515. NEUROPSYCHIATRIC DISORDERS INDUCED BY ISOTRETINOIN: ANALYSIS OF CASES REPORTED IN THE FRENCH PHARMACOVIGILANCE DATABASE AND REVIEW OF THE LITERATURE

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Introduction: Isotretinoin is indicated for the treatment of severe, recalcitrant nodular acne. Spontaneous reports have suggested a possible association between isotretinoin and depression/suicide attempts.

Aim of the Study: The objective of our study was to analyse cases of neuropsychiatric disorders occurred in patients taking isotretinoin and reported to the French pharmacovigilance database as side effects.

Methods: We analysed cases of neuro-psychiatric disorders related to isotretinoin therapy notified to the French Pharmacovigilance Centers (FPC) between 1984 and 31 December 2002. Key search terms used were depression, suicide attempts, suicide, sleep disorders, memory disorders, and mental confusion. In a second time, we reviewed case reports and/or studies published in the literature.

Results: During the study period, we found 30 cases of neuropsychiatric disorders notified to the FPC: 13 cases of depression, three cases of depression with suicide attempt, two cases of suicide, two cases of sleep disorders, three cases of memory disorders, five cases of mental confusion, one case of anorexia and one case of asthenia/drowsiness. The mean patient age was 22.3 years (range: 15–49). Men represented 73% of all patients. A concomitant treatment was found in four patients: two patients were treated with psychotropic drugs for previous psychiatric illness, one patient had vaccine against yellow fever and only one patient had taken oral contraceptives. Psychiatric medical history was documented for only three patients. Median time to onset was 12.9 weeks (range: 0.5–104) after beginning of isotretinoin. Apart from two cases of death, the outcome of other cases was favourable. A treatment with antidepressant therapy was started in five cases. According to the French method of assessment of adverse drug reactions, the link between isotretinoin and psychiatric side effects was likely in one case, possible in three cases, and dubious in other cases.

Conclusion: In the literature, we found 22 cases of psychiatric side effects in patients taking isotretinoin, 19 of them being major depression or suicidal behaviour. To date, the pathophysiology of such complication remains unclear.

Although a causal relationship may exist between isotretinoin and psychiatric illness in adolescents and young people, this has not been supported by prior studies. Depression has been reported in patients with acne and is common among adolescents. Further epidemiological studies are needed to asses the possible relationship between isotretinoin and depression or suicide. Until such data are available, prescribers should exercise high caution when initiating and maintaining isotretinoin for acne in young patients.

520. SSRI-INDUCED HEPATOXICITY: REVIEW OF DATA FROM THE FRENCH PHARMACOVIGILANCE DATABASE AND LITERATURE

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New psychotropic drugs introduced in clinical practice in recent decades include new antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRI). The overall incidence of severe Adverse Drug Reactions (ADR) of SSRIs is 0.7% of exposed patients.[1] In the literature, hepatic ADRs have been scarcely reported.[2]We conducted here a retrospective study from the French Pharmacovigilance Database (FPD) and collected 158 cases of liver disturbance of various severities.

Hepatic reports represented 11.8% of total ADRs in the FPD for paroxetine, 13.1% for fluoxetine, 10.8% for citalopram, 11.3% for sertraline, and 11.2% for fluvoxamine. The hepatic reports concerned 97 women and 61 men, aged from 15 to 94 years (mean 57.3 years).

Most of the hepatic disturbances were represented by cytolytic hepatitis in 65 cases, followed by cholestatic hepatitis in 45 cases, mixed hepatitis in ten cases and elevation of liver enzymes in nine cases. The biological values were not available in 27 cases. The hepatic ADRs were considered as not severe in 75 cases, severe in 75 cases, life-threatening in four cases, and fatal in four cases. The 158 hepatic ADRs were attributed to paroxetine in 63 cases, fluoxetine in 45 cases, citalopram in 30 cases, sertraline in 18 cases, and fluvoxamine in two cases of the notification.

In the severe cases, among risk factors, we noted diabetes in 10.6%, age over 70 years in 38.6%, other hepatotoxic concomitant medications in 73.3% and chronic alcohol intake in 13.3%.

In comparison with the other antidepressants notified in the FPD, hepatic reports represented 18.8% of total ADRs for mianserine, 16.4% for clomipramine and 17% for tianeptine. In the literature, only five cases of hepatotoxicity were reported with fluoxetine, three with fluvoxamine, ten with paroxetine, and six with citalopram.

In conclusion, SSRI-induced toxicity seems to be rare with regard to their large prescription but their pharmacological proprieties and especially their action on liver cytochomes can contribute to ADRs including liver toxicities.

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525. FEEDBACK INFORMATION TO REPORTERS AS A TOOL FOR CONTINUING EDUCATION IN PHARMACOVIGILANCE

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Aims: To stimulate ADRs spontaneous reporting among GPs, to improve the quality of ADR reports filed and to provide continuing education on drug safety.

Materials: The network of reporting GPs called 'Pharmasearch' was set up in 2002 as a collaboration between the Department of Medicine and Pharmacology of the University of Messina (Co-ordinating Centre) and a group of GPs (295 until June 2004) which voluntarily forward to the Co-ordinating Centre a copy of each filled in ADR reporting form. The Co-ordinating Centre, after receiving the form, provides reporters, via e-mail, with individual feedback; this consists of a personalised and qualified comment to the ADR reported, according to data retrieved from international literature and on-line databases. Additional information about the ADR reported or a follow up of the patient may be asked.

Collective feedback is also provided: GPs receive monthly, quarterly and yearly reports about the state of the art of the network, containing the number and geographical distribution of reports, classification of ADRs received according to systems/organs involved, drugs most frequently implicated, etc. All cases of interest are studied in depth and distributed to all participating physicians. Furthermore, regular updates are performed, drawing inspiration from topics or signals coming from international literature (e.g. Neuropsychiatric reactions to Coxibs). This is in order to sensitise physicians about the importance of reporting ADRs and to keep them updated on the safety profiles of drugs, based on news and warnings coming from international regulatory agencies. To achieve this goal, a specific section of the pharmacovigilance website www.farmacovigilanza.org has also been created. After registration, physicians are included in a mailing list, and receive news and extensive abstracts of articles of major interest translated into Italian.

Finally, GPs weekly receive on their email accounts the CIOMS definition of ADRs (also translated into Italian) in order to help them to appropriately identify (and report) adverse events.

Results: The increasing number of GPs joining to the Pharmasearch network and the constant improvement in the quality of their reports (evaluated according to the completeness of information provided in the forms filed and the rate of serious and/or unexpected reactions reported) highlights the importance of providing feedback information to reporters to stimulate ADRs reporting. Although this approach isn't able to prevent reactions reported, we think that it might be the way forward to educate physicians about the risks of inappropriate use of medicines.

530. WWW.ECM.FARMACOVIGILANZA.ORG: AN ITALIAN WEBSITE FOR CME IN PHARMACOVIGILANCE

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Aims: The website www.ecm.farmacovigilanza.org has been set up since June 2002, with the support of the Clinical Section of the Italian Society of Pharmacology (SIF). The site belongs to the no-profit foundation 'Gianfranco Ferro', whose aims are to promote the culture of pharmacovigilance among healthcare professionals, and is financially supported thanks to an educational grant from Farmindustria, the Italian association of drug manufacturers.

Materials: The website provides a free online course of pharmacovigilance, prepared by several experts in the field, structured into 14 lessons, concerning topics such as: methods in pharmacovigilance, Italian and European regulations, how to recognise an ADR, etc. Users, after registration, receive a password and are invited to undergo a preliminary test, in order to assess their competence in this field. After that, they have access to the 14 lessons whenever they want. Each lesson provides a test related to, which users are asked to do before going further to the next lessons. They are also allowed to repeat the tests each time they want. After reading and learning all the lessons, users make a cumulative test (containing questions randomly picked out from the lessons), that, if passed, allows them to access to the final test. This final exam is made in an academic setting (users can agree by email for the closest available), in presence of a professor of pharmacology, who has to witness that the candidate actually underwent and passed the test.

Results: Until May 2004, users registered were 1 480 408 (27.5%) of them are pharmacists, 199 (13.4%) General Practitioners, and 189 (12.7%) work in the pharmaceutical industry. Only in the year 2003, users registered were about 600. Up until now, 65 users passed the final test, and 12 are waiting to do it. Most frequently involved Universities for the final exam were Rome 'La Sapienza' (11 final tests), Pisa (10) and Milan (9).

Conclusions: Aims of this course are to allow all healthcare professionals interested in pharmacovigilance to achieve a correct and updated education in this field, which is often missed during academic regular courses; furthermore, this can be obtained without moving from home, just using a PC connected to the Internet. The rising number of people joining the course confirms the success of the initiative and further shows the helpfulness of Information Technology also in the field of Continuing Medical Education.

535. ENHANCING PATIENT SAFETY: (RE-)DISCOVERY OF VACCINE ADMINISTRATION ERRORS IN THE VACCINE ADVERSE EVENT REPORTING SYSTEM USING DATA MINING

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Introduction: Medical errors are increasingly recognised as a public health problem. In 2000, the code 'MED ERROR' was added to the US Vaccine Adverse Event Reporting System (VAERS). To aid manual review of the large, complex VAERS database (>170 000 reports), we developed statistical techniques to detect temporal clus-

tering of adverse events needing further evaluation. In April 2004, one of the tools (Poisson Probability Screening, PPS) flagged a cluster of local reaction reports following a tetanus toxoid (TT) vaccine that were also coded as medication errors. Reports from one clinic described inadvertent administration of TT in place of purified-protein derivate (PPD) used for tuberculosis testing.

Methods: In PPS, for each vaccine-symptom pair in the database, total reports over the period of surveillance are divided by the number of months in the period to obtain expected number of reports per month. This number is used with the Poisson distribution to obtain a p-value for the actual number of reports in a month. Pairs with low p-values are flagged for further review.

Because 'MED ERROR' was not introduced in VAERS database until 2000, to identify other reports of substitutions of TT containing vaccines and PPD we searched for a combination of key words ('PPD', 'TB test', 'Tubersol', etc.).

Results: We identified 30 clusters and single cases of PPD and vaccine substitutions (over 100 affected persons from various states) resulting in local and systemic reactions. One report described several patients (exact number unknown) in whom Isoniazid treatment was initiated due to erroneous interpretation of PPD reactivity. Although there was no clustering by TT containing vaccine brands, this review identified a remarkable similarity in TT and PPD product packaging for one current manufacturer.

Discussion: We successfully demonstrate the utility of the new routine automated signalling method for detecting a (previously reported) medical error. Two factors contributed to its detection in this instance: (i) the introduction of a new problem specific code for medication errors, and (ii) the reporter filed separate VAERS reports for each patient with adverse events observed in the clinic. The results of this review prompted development of several communication messages targeted at vaccine providers to raise awareness and prevent future recurrences. Additional solutions to avert similar errors include revising product packaging and use of barcode scanning.

540. CLINICO-TOXICOLOGICAL ASSESSMENT OF ATYPICAL ANTIPSYCHOTICS

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Introduction: Since the introduction of clozapine – the prototype of atypical antipsychotics – especially in the last ten years new antipsychotics have come into the market, aimed at efficacy against negative symptoms and a lower incidence of adverse effects (e.g. extrapyramidal symptoms) than conventional antipsychotics. In consequence of the increasing prescription accidental and intentional poisonings by atypical antipsychotics also increased.

Aim of the Study: The analysis of poisoning cases should give more information about the toxicity of atypical antipsychotics and the poisoning patterns.

Methods: All sufficiently documented cases with atypical antipsychotics reported to the Poison Information Centre Erfurt from 1994 to 2003 were analysed retrospectively.

Results: Calls concerning poisoning with atypical antipsychotics (including multiple drug overdose) rose from 26 in 1994 to 187 in 2003 (corresponding to 1 and 2.7 % of the total number of calls for drug overdose in these years). Altogether, over these 10 years 865 cases were registered; 343 of them were single drug ingestions of atypical antipsychotics (adults: 309, children: 29, unknown age: 5). Suicide attempts represent the main proportion of all cases (78%); the others were accidental overdoses (approximately 17%), cases of drug abuse or adverse effects. The age of the patients and the dose ingested ranged from four months to 85 years and from 0.2 to 200-fold DDD, respectively.

The clinical feature of poisoning is similar for all atypical antipsychotics and predominantly characterised by CNS depression (68%), in some cases alternating with agitation. Furthermore, tachycardia (20%), hypotension (8%), and gastrointestinal disturbances (7%) occurred. Patients presented both peripheral anticholinergic (dry and warm skin and mucosa, mydriasis) and muscarinergic symptoms (hypersalivation, miosis). Miosis was more frequent than mydriasis. Extrapyramidal disturbances (14 %) were observed at doses of 2- to 5-fold DDD, with amisulpride already at therapeutic doses. In most cases doses up to the 5- to 10-fold DDD caused minor symptoms. Above this threshold loss of consciousness may be possible, however, respiratory depression and seizures rarely occurred. Fatality was registered with amisulpride (343 mg/kg, e.g. 60 DDDs).

Conclusion: Generally the newer atypical antipsychotics appear to have the same overdose profile as phenothiazines and butyrophenones. Essentially, the toxic-therapeutic ratio is not much better, but acute overdose seldom results in death. First of all clozapine seems to be more toxic than the others, since this drug caused unconsciousness, tachycardia and cardiac arrhythmias even at doses below DDD.

545. TIME REQUIRED FOR FOLLOW UP INFORMATION ON SPONTANEOUS REPORTS

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Introduction: Initial reports of suspected adverse drug reactions submitted to national centres are often not yet optimally documented. Additional information is frequently required and time needed for an adequate assessment varies considerably. For example, concerning serious reports which have to be forwarded to the Marketing Authorization Holders within 15 days after reception, follow-up information often cannot be included initially.

Aim of the Study: To study possible factors influencing the number of reports requiring follow up and the time needed to gather this information.

Methods: All reports from health professionals received by The Netherlands Pharmacovigilance Centre Lareb in 2003 were included. Logistic Regression Analysis was used to study possible factors influencing the need for follow up: seriousness, type of reporting health professional, involvement of individual assessors, and the fact whether the reported adverse drug reactions were labelled.

Of all reports of which follow up has been received, the time between the reception of the initial report and the most recent information was

established. For this subset, Cox Proportional Hazard Analysis was used to determine possible differences in the time needed to get follow up information for the above mentioned covariates.

Results: A total of 2929 reports were included in the study. Of these, 426 concerned reports with follow up information. Multivariate logistic regression analysis showed that reports submitted by hospitals (hospital pharmacists and specialists) [OR 1.5 (95% CI 1.1, 1.9)] and serious reports [OR 2.5 (95% CI 1.9, 3.2)] more often required follow-up information.

The overall median time to receipt of follow-up was 34 days, for serious reports 38 days. Only the type of reporting health professional influenced the time needed for follow up ($p < 0.001$). Pharmacists and general practitioners sent in follow up information sooner than specialist or hospital pharmacists.

Discussion: The number of reports requiring follow up information depends both on the seriousness of the reports and the type of the reporting health professional, but the time needed to collect all available information only depends on the latter. There appeared to be no difference concerning the time needed for follow up between various assessors involved. This suggests that collecting this information is difficult to influence. Since for serious reports the majority of information is received after the official '15-day period' we would suggest extending this period to decrease the administrative burden and optimise the amount of initial information.

555. A CASE REPORT OF RHABDOMYOLYSIS WITH PENTAMIDINE: SIGNAL REPLICATION UTILIZING A NEW PHARMACOVIGILANCE TOOL UNDER INVESTIGATION

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A report on an association between pentamidine and rhabdomyolysis caught our interest, as this association is not listed as an adverse effect by drug manufacturers or in reviews of pentamidine. To enhance our capability to detect novel adverse events, we studied computational signal detection algorithms (data mining algorithms-DMAs) in postmarketing safety databases to determine whether these methods might complement our strategies.

DMAs consist of two techniques: simple disproportionality analysis [proportional reporting ratios (PRRs) and reporting odds ratios (RORs)]; methods using statistical adjustments and Bayesian modelling [Bayesian Confidence Propagation Neural Network (BCPNN) and multi-item gamma-Poisson shrinker (MGPS)]. All methods use the background frequency of drugs and events as internal control, rather than external datasets for exposure data and calculate an observed to expected ratio for each drug-event combination (DEC). Bayesian methods down-weight the observed to expected ratio scores, thus, a performance gradient between disproportionality analyses and Bayesian methods is expected.

To compare time to appearance of replicated findings in the published literature (i.e. >2 drug-specific case reports) of anti infective-induced rhabdomyolysis to the timing of first signal in a large post marketing safety database using two data mining algorithms.

Cases of anti infective-induced rhabdomyolysis from MEDLINE were reviewed to identify relevant citations. Two data mining techniques (PRR and MGPS) were used to retrospectively screen data from US FDA database.

Four relevant drugs were identified (pentamidine, isoniazid, sulfamethoxazole/trimethoprim, lamivudine). PRR appeared to outperform MGPS in that a signal was generated for all four drugs from one to 17 years in advance of publication of a second published case report for PRR. This was compared to the signal generated in MGPS for two of the four drugs, five and six years in advance of publication of a second case report. For pentamidine, PRR signalled myopathy 17 years in advance of a second case report based on one case.

Results of this analysis illustrate potential of simple forms of disproportionality analysis to identify potentially meaningful associations that fail to be identified by certain empirical Bayesian methods such as MGPS that utilise various statistical procedures or to identify signals highlighted by both at earlier time points. PRRs might have special utility for identifying rare or under-recognised adverse events to anti-infectives used by infectious disease specialists in diverse but circumscribed clinical settings.

560. POSTMARKETING SURVEILLANCE OF POTENTIALLY FATAL REACTIONS TO ONCOLOGY DRUGS: FINDINGS FROM TWO DATA MINING ALGORITHMS

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A recently published compilation of potentially fatal adverse drug reactions for cancer drugs concluded that there was a need for continued vigilance for such reactions. In hopes of enhancing the ability to screen large databases of adverse events (AEs) reports, several computer-assisted statistical signal detection algorithms, also known as data mining algorithms (DMAs), are being studied in hopes of improving safety surveillance. Two such algorithms are multi-item gamma Poisson shrinker (MGPS) and proportional reporting ratio (PRR).

To apply and compare two DMAs (MGPS and PRR) to the FDA AERS database to see if signals of potentially fatal adverse events (AEs) to cancer drugs contained in a recent publication would have been identified earlier than with use of traditional methods.

The data extract used for the current analysis was the FDA AERS database through the second quarter of 2002. The screening algorithms used for this analysis were MGPS and PRR. An EB05>2 and a PRR>2 with c2>4, respectively, were the signal metrics used. A recent peer-reviewed publication summarising all AEs associated with oncology drugs reported from 2000 to 2002 using a predefined search strategy provided the sample of drug-event combinations (DECs) for this analysis.

The peer-reviewed published analysis contained 21 drugs and 25 DECs that were considered sufficiently specific for data-mining. Twenty-three of the DECs generated a signal with PRR and 19 with MGPS, twelve signalled with PRR one to seven years prior to signalling with MGPS, seven cases in which PRR and MGPS signalled in the same year, and four cases where only PRR signalled. There were no DECs generated with MGPS only and in two cases, no signal was generated with either algorithm.

Commonly cited DMAs generated signals of disproportionate reporting for 23/25 of DECs in advance of publication of a case series and/or labelling change for selected cancer drugs. For fifteen drugs one could conclude that a signal generated well in advance (>2 years) of standard techniques in use. PRR and MGPS might be useful in complementing traditional surveillance strategies with oncology drugs (i.e. drugs that may be approved on an accelerated basis, are known to have serious toxicity, are administered to patients with substantial and complicated comorbid illness, are not available to the general medical community, and have a high frequency of 'off-label' use).

565. USE OF A NEW PHARMACOVIGILANCE TOOL UNDER INVESTIGATION TO EVALUATE AN UNEXPECTED STRUCTURE-ADVERSE EFFECT RELATIONSHIP INITIALLY IDENTIFIED BY LABORATORY RESEARCH

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Data mining algorithms (DMAs) are being studied to screen large databases of adverse events to determine whether these automated methods might supplement traditional surveillance strategies. DMAs include simple disproportionality analysis [e.g. proportional reporting ratios (PRRs)] and algorithms that use additional statistical adjustments/Bayesian modelling [e.g. multi-item gamma-Poisson shrinker (MGPS)]. Validation of performance characteristics of these DMAs is a current issue. A potential but as yet untested source of data for assessing performance of DMAs is potential associations between drugs and adverse events where suspected association is based on a previously unrecognised pharmacological/chemical characteristic of drug (structure-adverse event relationship) identified from non-clinical research.

We questioned whether application of DMAs to such safety data sets could be a useful reference standard to evaluate DMA performance and/or be of potential use in identification of drug-event associations that might be fruitful areas for studying structure-activity relationships.

MGPS and PRR were used to data-mine on drug-event combinations in the US FDA drug safety database relating to an association of Parkinsonism with drugs containing diethyl amino methyl moiety. This structure-adverse event relationship was substantiated by recent published animal/molecular pharmacological research. Timing of signals in relation to publication dates of research and relevant anecdotal case reports were evaluated.

For four of nine drugs studied by researchers, a signal of disproportionate reporting was generated with PRR and/or MGPS prior to publication. For three drugs, a signal was generated concurrently or after publication. PRRs appeared to outperform MGPS in that a signal was generated with PRR for all seven drugs compared to three for MGPS. For three drugs, there were no reports; for two drugs, there were reports but no signals. There were seven anecdotal case reports for five of seven drugs generating signals. A signal predated publication of a case report for three drugs.

A signal of disproportionality was generated for seven of the nine drugs for which there were reports. Our retrospective analysis especially with PRRs suggests that similar data-sets may provide useful reference standards for evaluating performance of DMAs. It's unlikely that this particular association could have been identified prospectively without prior knowledge of research. Findings from DMAs might provide data that would be fruitful for studying structure-adverse activity relationships.

570. AUTISM AND PAEDIATRIC VACCINES

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The present work is a review, which intends to approach a controversial and current topic: the possible causal association that has been suggested between autism and paediatric vaccines. Beginning in the last decade of the twentieth century, a series of changes in the classification, nomenclature and diagnostic approaches of autism has occurred. The results of the epidemiological studies, performed according to these new concepts, showed that the prevalence rates of autism at the present time are higher than 15 years ago. Vaccines are among the factors that have been considered for explaining this phenomenon. The mechanisms invoked to try to involve vaccines in the aetiology of autism are: the excess of mercury derivatives from tiomersal, which is used as vaccines preservatives, autoimmune processes that act on the CNS, direct or indirectly by inducing lesions at the intestinal level of the mucous membrane, which increase the absorption of macromolecules, antigens and toxins that once in the bloodstream may reach the CNS producing the lesions responsible for the genesis of autism there.

580. FLUOROQUINOLONE-ASSOCIATED ANAPHYLAXIS IN SPONTANEOUS ADR REPORTS: OCCURRENCE AFTER FIRST USE AND APPARENT DIFFERENCES IN REPORTING RATES BETWEEN FQS

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Introduction: Anaphylaxis has been reported associated with the intake of fluoroquinolone (FQ) antibiotics. According to pathophysiology such reactions may be immune-mediated (anaphylactic) or result from direct stimulation of effector cells (anaphylactoid). Both mechanisms produce the same clinical picture of anaphylaxis; however, anaphylactoid reactions may occur after first intake since no sensitisation phase is necessary. In Germany, numerous cases of suspected adverse drug reactions (ADRs) are reported spontaneously to the Federal Institute for Drugs and Medical Devices (BfArM) and registered in a large ADR data base.

Aim of the Study: The aim of the present study was to analyse all cases of FQ-associated anaphylaxis contained in the BfArM database with respect to previous exposition, time to onset and other determinants.

Methods: All FQ-associated cases of anaphylaxis, anaphylactic shock, anaphylactic/anaphylactoid reaction reported to the BfArM between 1993 and 2004 were identified and assessed with regard to correctness of diagnosis and causal relation. Further analyses were performed in defined subgroups.

Results: 172 cases reporting the aforementioned terms were identified. In 152 cases correctness of diagnosis and causal relation was considered at least as possible and further analyses were restricted to this subgroup. Administration of moxifloxacin was reported in 75/152 cases (49%), and this figure did not seem to be matched by a comparable high number of exposed patients. Levo-, cipro-, and ofloxacin accounted for 25 (16%), 21 (14%) and 17 (11%) of the 152 cases, respectively. Intake of other FQs was reported in 14/152 cases (9%). Occurrence of the ADR after the first dose or within the first three days was reported in 63/152 cases (41%), but no information on pre-exposure with this or any other FQ was provided with these reports. In 20/152 cases (13%) the reaction occurred within the first three days and it was stated that the respective FQ has never been taken before, although previous administration of a different FQ was not explicitly excluded. In 1/152 cases (0,7%) it was stated explicitly that no FQ has ever been taken before.

Conclusions: Anaphylaxis appears to be an ADR of the class of FQs. Time to onset is compatible with an underlying anaphylactoid mechanism in a relevant number of cases. Differences in reported frequencies constitute a signal for the true differences and should be further investigated. Physicians should be aware that FQ-associated anaphylaxis may already occur after first intake of an FQ.

585. PRESCRIPTION ERRORS IN PRIMARY CARE: TYPES, DETERMINANTS AND THERAPEUTIC IMPLICATIONS

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Prescribing errors are preventable and hence are considered an important target for improving health care. The aim of this study was to identify prescribing errors and their determinants in a primary care setting. Prescriptions with errors collected on a daily basis by pharmacy staff during the first two weeks of September 2003 at 18 out of 20 primary care health centres in Bahrain. Data was analysed using Statistical Package for the Social Science (SPSS/PC+, version 9.0) and prescribing errors were classified as non-drug-related and drug-related (omission, commission and integration) errors.

Out of 77 511 prescriptions dispensed, 5959 (7.7%) were identified to contain errors. The frequency of prescribed medication items in 5959 prescriptions was 16 091. Of these 13 630 (84.7%) were with errors and 13.2% were written using generic names. Non-drug-related errors such as physician's stamp, date, and information about patients' address and sex were not specified in 34.5% 9.8%, 5.8%, and 0.5% of prescriptions, respectively. Rate of omission errors (missing informations) was as follows: strength/dose (53.9%), duration of treatment (51.3%), dosage form (34.3%), frequency of dosing (23.3%), and direction of use (15.5%). Omission errors associated with topical preparations were significantly higher than with systemic preparations. However, prescriptions with systemic preparations were having a higher rate of commission errors (incorrect information).

A significant difference in errors was found in prescriptions ordered by family physicians and general practitioners. In 9.2% of prescriptions with errors, potential drug–drug interactions were expected.

This survey at the national level revealed that in primary care a considerable proportion of prescriptions contained errors. Strategies to minimise medication errors by improving the prescribing skills, adherence to essential drugs list, and use of National Formulary are needed to enhance rational use of drugs.

590. ADVERSE DRUG REACTION SPONTANEOUS REPORT IN RURAL DISTRICTS OF MOZAMBIQUE

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Aim: The aim of this study was to describe the feasibility of creating an adverse drug reaction spontaneous reporting system in two rural districts in Mozambique where remote location, poor telecommunication services, and low level of education of health professionals are ongoing challenges.

Method: Namaacha and Matutuíne are two pilot districts for the introduction of Artesunate + Sulfadoxine-pyrimethamine, a new combination drug therapy as first line treatment for uncomplicated malaria in Mozambique. Health professionals in these districts were trained to diagnose, treat and report adverse drug reactions to all medicines. A standard report form was distributed to all health professionals in these districts. There were routine site visits to identify and clarify any problems in filling the forms and sending them to the National Pharmacovigilance Unit (PU). One focal person was identified in each district to facilitate communication between the health professionals and the PU. Retraining of the health staff was carried after 4 months to improve the quality of reports submitted.

Results: Thirty health professionals received training. Apart from two medical doctors, the other health professionals were technicians (1), nurses (24) and basic health care agents (4) from the 2 districts. The education level of the other health professionals is medium and basic that consists of standard 10 + 3 years and standard 7 + 2–3 years. The two focal persons were pharmacy agents. Eight months after the training, 45 adverse reactions reports were received by the PU, two of which were rejected because the reporters didn't mention any reaction. Twenty-two drugs were mentioned in the reports, 14 of which were causally linked to the reaction. Most reported ADRs were skin reactions (86%). There were eight reactions that the reporters considered serious. Four resulted in hospitalisations and four prolonged hospitalisations. Only four of the 43 reported ADR resulted in sequelae, mostly skin pigmentation. There were no fatal reactions reported. All ADRs reported were evaluated to assess causality according to WHO categories. Seven out of the 43 reactions were classified as certain.

Conclusion: Health professionals with basic and medium level of education from rural areas could contribute to ADR spontaneous reporting systems. Training, quality assurance visits and the ongoing presence of focal persons can promote reporting and improve the quality of reports submitted.

600. REPORTING OF ADRS IN POLAND

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The Centre for Monitoring of Adverse Drug Reactions was established in 1971. Cooperation with WHO Programme for International Drug Monitoring began in 1972. Centre until 2002 was a part of Drug Institute. In 2002 new drug law in Poland come into force – the competent authority was reorganised and Pharmacovigilance Unit is now situated within the structure of Office for Medicinal Products, Medical Devices and Biocides. Although there are legal obligations by law to report adverse drug reactions for pharmaceutical companies and the healthcare professionals, the number of Polish reports is very low – approximately 600 per year. In contrast the number of foreign reports received by our Unit is very big – approximately 300 per day. We have decided to focus on new chemical entities and other certain group of drugs – oral anticoagulants (acetylsalicylic acid, acetylsalicylic lysine, ticlopidine, clopidogrel, acenocoumarol), COX-2 inhibitors (rofecoxib, celecoxib), leukotriene receptor antagonists (zafirlukast, montelukast), HMG-CoA reductase inhibitors (statins).

We had analysed the reports to this group of products for 2001–mid-2004. The numbers are as follows: oral anticoagulants 24 reports; statins, 137; COX-2 inhibitors, 108; leukotriene receptor antagonists, 112.

The profile of reported adverse drug reactions is in line with current knowledge about these drugs. We have too small numbers of reports to generate signals and we do not use quantitative methods for evaluation of incoming reports.

Probably with electronic exchange of information and with one unified system for collecting all reports there will be a possibility to analyse data concerning pharmacovigilance in a more comprehensive way.

605. IS WEEKLY ADMINISTRATION OF PACLITAXEL LESS TOXIC THAN 3-WEEKLY? A PROSPECTIVE PHARMACOVIGILANCE STUDY BASED ON PATIENTS' AND PHYSICIANS' REPORTS

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The usefulness of cancer chemotherapy is often limited by toxic reactions. However, spontaneous reports of adverse drug reactions (ADRs) in oncology are exceptional. Extending ADR reporting to patients should contribute to enhance our knowledge on the safety of chemotherapy. Paclitaxel (PAC) is a major anticancer drug, used against a broad range of cancers. In France, PAC is authorised in ovarian, breast and non-small lung cancer at 175 mg/m² every 3 weeks (3-weekly). However, as low-dose weekly PAC (80 mg/m²) has shown its efficacy in several clinical studies, it is also currently prescribed.

The aim of our study was to compare the safety of weekly and 3-weekly PAC administration. We performed a prospective pharmacovigilance study in two centres and included patients receiving PAC from December 2003 to May 2004. To assess PAC safety, ADRs were systematically collected by two methodological approaches: physicians' and patients' reports. A specific questionnaire about PAC's ADRs was created and distributed individually to patients after each PAC administration. Safety of PAC was expressed by the number of ADRs and their intensity.

During the study period, 108 patients were included: 42 '3-weekly' and 66 'weekly'. Adhesion of patients to our questionnaire was 85%. The response rate was lower with 355 responses/663 (53%). Prior chemotherapy was more frequent in weekly (median = 1.5) than in 3-weekly administration (median = 0.5) [$p < 0.001$]. The number of ADRs in patients' questionnaires was significantly lower in weekly (median = 3) than in 3-weekly administration (median = 4.5) [$p < 0.001$]. Intensity of ADRs was also lower in weekly (median = 8) than in 3-weekly administration (median = 13). Furthermore, we demonstrated that the dose of PAC administrated at each cure has a stronger influence on the number and intensity of ADRs than the total cumulative dose. As expected, the number of reports for neuropathy, myalgia, arthralgia and onycholysis was significantly higher in the patients' questionnaires (n = 479) than in the medical board's (n = 103) [$p < 0.001$]. Moreover this study quantified and evaluated PAC in current French oncological practice. 88% of the 108 patients included were treated out of French marketing authorisation: 61% because of PAC schema (weekly) and 27% because of PAC indication (head and neck cancers and urothelial cancers).

Conclusion: In conclusion, our study, the first prospective pharmacovigilance study in oncology based on patients' questionnaires, confirms the interest of patients reporting ADRs. It enables us to assess that weekly PAC is safer than 3-weekly administration even taking into account prior chemotherapy.

615. PHARMACOVIGILANCE OF CHILDHOOD VACCINATION IN ITALY, 2001–2003

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Introduction: In Italy, the childhood vaccination schedule consists of three doses of DTPa, Hib, HBV and polio vaccines by 24 months and an MMR dose at 12–15 months. Vaccination coverage is >95% for all vaccines except for Hib (87%), and MMR (77%). Recently, new combined vaccines have been licensed, including hexavalent vaccines introduced in 2001. Postmarketing surveillance of suspected adverse vaccine reactions (ADR), started in the 1970s, was improved in 2001 by introducing web-based reporting and, in 2003, by modifying the reporting form.

Aim of the Study: Describe the spontaneously-reported ADRs for routine infant vaccines particularly for hexavalent and MMR vaccines.

Methods: We reviewed all ADRs following vaccine administration to children <24 months reported to the Italian Pharmacovigilance System during 2001–2003. Information on patient's age and sex, vaccination date and product type, date of onset, diagnosis, severity according to clinical diagnosis, and outcome of the event were collected. ADR rates/100 000 newborns by year, type of vaccine, and severity were calculated.

Results: Of the 785 ADRs reported, 179 occurred in 2001, 228 in 2002, and 378 in 2003. Hexavalent vaccines accounted for 378

(48.1%) and MMR for 186 (23.7%) ADRs. The median ages were 5 and 15 months for hexavalent and MMR vaccines, respectively. Annual ADR rates/100,000 newborns ranged from 33.5–70.6 for all vaccines, from 4.3–48.0 for hexavalent products and from 8.6–13.8 for MMR vaccines; for severe ADRs, the corresponding ranges were 18.7–44.9, 2.1–18.9, and 2.6–3.5, respectively.

Conclusion: An increase of ADR notification was observed for all vaccines, probably as a consequence of improvements in the reporting system. Nevertheless, the increase for hexavalent vaccines was more pronounced than for other products. In 2003, the total and severe ADR rates for hexavalent vaccines were 3.5, and 5.4 times higher than corresponding rates for MMR vaccines.

Differences between the vaccines can be explained by: increases in hexavalent product use (from 400 000 doses sold in 2001, to 1 600 000 in 2003); the greater attention paid to newly introduced products; differences in vaccination schedule (three doses for hexavalent and one for MMR vaccines, respectively); the different age of administration (first vs second year of age).

Although the passive pharmacovigilance system is crucial for detecting signals, the inference on the actual reactogenicity of vaccines should take into account detailed age and number of vaccinees.

620. HYPERSENSITIVITY TO GLUCOCORTICOIDS

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Introduction: The steroidal anti-inflammatory drugs (SAID) are used in many pathologies requiring a suppressive, anti-allergic, anti-inflammatory, anti-exudative or anti-proliferative effects. The main side effects reported are endocrine, metabolic effects and peptic ulcer risk. Hypersensitivity reactions are also reported.

Aim: The aim of the study was to estimate the responsibility of glucocorticoid in the appearance of immuno-allergic reactions and to clear a conduct to hold in similar situations.

Materials and Methods: It is a retrospective study carried on 91 observations in which corticoid drugs were suspected of hypersensibility reaction. These cases were notified to the National Centre of Pharmacovigilance between January 1990 and December 2003 and were analysed according to the Begaud et al. method. Among these 91 observations, we selected only 10 cases where the responsibility of glucocorticoid was retained. The other cases were not included because of doubtful or excluding intrinsic imputability.

Results: Our series consisted in five women and five men. The age varied from 16 to 54 years. Four patients presented an atopy. In all cases, only one drug were contra-indicated: methylprednisolone (four cases), dexamethasone (two cases), bethamethasone (two cases), prednisone (one case).

The kind of lesions were: anaphylactic reaction (three cases), urticaria (four cases), facial oedema with diffuse erythema (two cases) and dyspnoea with raucous voice (one case). The delay between the beginning of treatment and the event onset was short (a few minutes to 10 hours). There were a positive rechallange in three cases. The evolution was favourable in all cases. The intrinsic imputability scores were very likely: I4 (two cases), likely: I3 (five cases) and plausible: I2 (three cases).

Discussion: The symptomatology developed in each case was evocative of the drug origin because of the short delay, the favourable evolution after stopping suspected drug and the accidental positive rechallenge in three cases.

In all cases, allergic reactions were probably caused by the steroids themselves because suspected drugs didn't contain well-known allergic vehicles like: benzylic alcohol, polyethylene glycol, sulfites, parabens, carboxymethylcellulose. Only the responsible glucocorticoid was contra-indicated, since the cross allergy wasn't described in literature between different SAID.

These reactions described above seem to be type I hypersensitivity which is the manifestation of an IgE mediated response, primarily of mast cells, to a specific allergen. The process by which initial sensitisation occurs is the consequence of a direct prior exposure and probably by many others routes like topical steroid preparations, food or other unidentified cross sensitising agents.

625. WHO SIGNALS FROM 1998 TO 2001: A FOLLOW-UP

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Introduction: One major aim for the Uppsala Monitoring Centre (UMC) is to detect early signals from the WHO data base, Vigibase, which holds international data of suspected Adverse Drug Reactions (ADRs). This study is part of an improved routine follow-up of WHO signals at the UMC. The signals in this study had mainly been highlighted by the BCPNN (Bayesian Confidence Propagation Neural Network) and reviewed clinically. However, they had not routinely been screened in the triage system, which is a filtering process to narrow down the number of associations for review introduced relatively recently at the UMC.

Aim of the Study: To evaluate the literature status in 2003 of drug-ADR combinations included in the restricted circulation document 'Signal' between the years 1998 and 2001.

Methods: Drug-ADR combinations, included in 'Signal' from 1998 to 2001, were followed-up and checked for occurrence in the Physicians' Desk Reference (PDR), Martindale, DrugDex and the Summary of Product Characteristics for the UK in 2003. The PDR was used to check the status of the combination at the time of signal.

Results: A total of 285 drug-ADR combinations were included in the 'Signal' document during the study period. For 60% of all signalled combinations, the same or a less specific term were found in at least one of the sources investigated in 2003, and 39% were found in two or more sources. Several combinations were already listed in the PDR the same year as the signal was issued. For 40% of the combinations, the ADR or the drug was not found in any of the four reference sources in 2003.

Conclusion: Expectantly, the routine screening of the literature before the signal is published, which is part of the triage system, will reduce the number of signalled combinations already known. A WHO signal is a suspicion and preliminary in nature and the situation may change substantially over time. The combinations not found in

the literature may refer to 'false' signals; others may require more time than 2–5 years before having been evaluated to be established ADRs with a subsequent labelling change.

As part of the implementation of a routine follow-up process of signals, this study will provide a scientific baseline for the evaluation of the triage system and thereby further improve the quality of WHO signals.

630. ADVERSE DRUG REACTIONS RELATED VISITS AND ADMISSIONS TO A HOSPITAL IN RAWALPINIDI, PAKISTAN

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The association between Adverse Drug Reactions and its impact on hospitals visits, admissions, morbidity, mortality and economic burden on health care is well established. This has led to considerable concern about the monitoring and prevention of ADRs. It is important to have estimates of ADRs within the country for a better management of health care system. However, accurate and independent data about the prevalence of ADRs and its impact on public health is not available in Pakistan. ADRs can be reduced by multidisciplinary prevention strategies among physicians, pharmacists, other healthcare professionals, and patients. One way of reducing this problem is by creating clinical pharmacy services and education of health professionals along with better patient counseling. Availability of a national ADR reporting system can play an important role in monitoring and creating preventive strategies.

This thesis primarily aims at proposing a protocol for a study to assess the magnitude, preventability and patterns of Adverse Drug Reactions in order to inspire the health authorities to develop a national ADR reporting system in Pakistan.

A cross-sectional study will be conducted to address this objective. The study will focus on one hospital department at a time for one week and this study will be performed at all departments of the hospital. All patients visiting and admitted to that particular department will be included in the study. Certain exclusion criteria are also adopted. Adverse Drug Reactions will be evaluated in two sessions. First patients will undergo inquiry by physicians and information will be recorded on pre-developed reporting form. After that a study pharmacist will interview the same patient. Pharmacists will collect the data on special patient interview forms.

635. AGRANULOCYTOSIS ASSOCIATED TO CARBIMAZOLE: A CASE REPORT

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Introduction: The favourable effect of antithyroid drugs may be due to their suppressive effect on lymphocytic into thyroid and thereby they directly modulate the basic disorder of autoimmune hyperthyroidism. Allergic agranulocytosis is the most dreadful adverse effect observed in the few months of therapy. Although periodic leukocyte counts are considered to be little help regarding the rapid development of the agranulocytosis, recent studies have revealed that weekly leukocyte counts can detect presymptomatic cases and allow more rapid intervention.

Method: We report here a case of agranulocytosis that happened 2 weeks after the administration of Neomercazole (carbimazole).

Results: The concerned patient, a 41-year-old woman, is a physician. She was treated by Neomercazole for hyperthyroidism. She has been warned by the occurrence of a severe fever up to 40°C associated to sore throat with resistance to current antibiotics (beta lactams, macrolides). White cells count was evaluated to 600 cells/mm3, which confirmed the diagnosis of agranulocytosis and led to her hospitalisation in a sterilised room.

Neomercazole was stopped and the patient received Bolus of Solumedrol (methylprednisolone sodium succinate), Neupogen (filgrastim) and antibiotics. The white cells count improved one week later. During the hospitalisation, the patient lost around 22kg of weight and developed a sinusitis. She left the hospital after 32 days.

640. COMPLEMENTARY MEDICINES: CASE REPORTS OF ADVERSE REACTIONS DUE TO ADULTERATION

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Introduction: Herbal medicinal products are becoming popular worldwide. While there is evidence supporting the health benefits of certain herbal preparations, there are prevailing concerns about the safety and quality of herbal products arising from adulteration, contamination and toxic herbs. There have been reports of adulteration in herbal preparations with some instances of patients experiencing serious harm. To ensure the safety of herbal products in Singapore, the Health Sciences Authority (HSA) implements effective postmarketing surveillance programmes comprising spontaneous adverse reaction (AR) reporting, routine inspection and testing of products from the marketplace.

Aim: We would like to share HAS's experience in detecting adulterated complementary medicines arising from signals obtained from local AR reports.

Method: All AR reports are assessed by professional staff in the Pharmacovigilance Unit and reports with a serious AR are further reviewed by the Pharmacovigilance Advisory Committee which advises on causality assessment. Samples may be sent for analytical testing if a possible product-AR causal relationship can be established or/and the impact to public safety is assessed to be significant.

Results: We have discovered several products labelled as herbal medicine but which contain undisclosed 'western' drugs. The following 3 case studies illustrate our experience with these adulterated products. We received a report of a 52 year old patient who developed Stevens-Johnson syndrome after taking Serbuk Jarem® (Encok) for 2 months. The product label claimed to treat rheumatism and various pains. The sample was found to contain phenylbutazone. The second case is based on 2 reports of Cushing's syndrome associated with the consumption of Pil Ajaib®. Both patients had been taking Pil Ajaib® for several months. The purported indications for Pil Ajaib® include relief of various pain and numbness. The first set of samples was found to contain

dexamethasone and indomethacin but the second batch was adulterated with prednisolone. For the last case, a patient was reported to suffer from diabetic ketoacidosis. The patient has diabetes mellitus but stopped her prescribed medications and started Kenis Pil® for the past 3 years. Kenis Pil® claims to cure symptoms of diabetes. A small amount of glibenclamide was detected.

Conclusion: We have developed a working process from detecting AR to the screening of suspected adulterated complementary medicines. An AR reporting programme continues to be a valuable tool to safeguard public safety from unscrupulous practices.

645. DRUG-INDUCED BULLOUS TOXIDERMIA NOTIFIED TO THE TUNISAN PHARMACOVIGILANCE CENTRE

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Introduction: Bullous toxidermia such as toxic epidermal necrolysis (TEN), Stevens Johnson Syndrome (SJS), bullous erythema multiform (BEM) and bullous fixed drug eruptions (BFDE) are usually dangerous because they exhibit patients to several complications especially dermatological and ophthalmic complications, and death. Drug responsibility is usually suspected.

Aim of the Study: The aim was to analyse all cases of serious bullous toxidermia notified to Tunisian Pharmacovigilance Centre, to determine drug responsibility and the outcome of these lesions.

Methods: We conducted a retrospective study that included 44 cases of bullous toxidermia notified between 1990 and 2000. We analysed our cases with the Begaud et al. method.

Results: The 44 patients aged between 1 and 85 years were 28 females and 16 males. They used 115 drugs. They presented TEN in 15 cases, SJS in nine cases, BEM in seven cases, BFDE in four cases and not identified bullous lesions (BLNI) in nine cases. In 30 cases, the responsible drug has been identified (positive rechallenge in eight cases, drug used alone in 13 cases and very suggestive chronology in nine cases). One case was induced by trihexypheniyl and an other by isoniazid with positive rechallenge. In these 30 cases, antibiotics were incriminated in 11 cases, nonsteroidal anti-inflammatory drugs in six cases, anticonvulsivants in five cases and antihypertension in three cases. In the other 14 cases, several drugs have the same chronological and evolution score.

Outcome was favourable in 24 patients (54%). Cutaneous sequelae (hyperpigmenation) were observed in 11 cases, ophthalmic sequelae such as blindness were observed in one case, synechia in three cases and symblepharan in one case. Both cutaneous and ophthalmic sequelae were observed in one case. Four cases of TEN died, by septic shock in 3 cases and by staticus epilepticus in one case.

Discussion: Drugs incriminated in our serial are such described in literature: antibiotics, nonsteroidal anti-inflammatory drugs and anticonvulsants. Isoniazid and trihexyphenidyl were retained with positive rechallenge in each case. In literature bullous lesions have never been described with trihexyphenidyl and they were described with isoniazid in three cases only.

In the literature bullous lesions exhibit patients to several complications. Death was observed on an average of 30% in most studies and it attained 50% in some studies. Mucosal sequelae were more frequent than cutaneous sequelae and they affect particularly ophthalmic mucosa.

650. NEUROLOGICAL DISORDERS ASSOCIATED WITH VACCINE USE: A PROSPECTIVE CASE-CONTROL STUDY

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Introduction: Vaccinations have reduced the mortality and morbidity of infectious diseases more than any other measure, including the improvement of public health and the introduction of anti-infectious drugs. Neurological adverse events represent a rare complication induced by vaccine administration and are usually not detected in pre-approval clinical trials.

Aim of the Study: To estimate the risk of neurological disorders related to vaccine administration in children.

Methods: Our study started in 1999 in four paediatric hospitals in Italy. We enrolled all children admitted through the Emergency Department for the following four conditions: neurological disorders, thrombocytopenia (platelet count <100 000); non infectious mucocutaneous diseases and vasculitis; clinically defined or endoscopically confirmed gastroduodenal lesions. Vaccine exposure, in a time period of 6 weeks prior to the onset of symptoms that had caused the hospital admission, was obtained by interviewing the parents with a structured questionnaire. The interview was performed by a physician during the hospital admission of the child. Informed consent was asked. To estimate the odds ratio associated with vaccine exposure the analysis was conducted according to a case control design. Vaccine exposure of children hospitalised for neurological disorders was compared with vaccine exposure of children hospitalised for the three remaining conditions (thrombocytopenia, muco-cutaneous diseases, gastroduodenal lesions).

Results: Between November 1999 and June 2003, 1467 children were enrolled in the study. 612 children (42%) were hospitalised for neurological disorders (in 275 children the reason for admission was the occurrence of apyretic seizure), 179 for thrombocytopenia, 553 for mucocutaneous diseases, and 123 for gastroduodenal lesions. Children exposed to vaccines were 69 among the neurological disorders (11%) and 72 among the other conditions (8%). Overall, the most frequent exposure was to exavalent (21%), pentavalent (18%), and MMR (18%) vaccines.

The crude odds ratio (OR) of developing neurological disorders for any vaccine was 1.4 (95% CI 1.0, 2.0). Among children of <2 years, the crude OR was 1.5 (95% CI 1.0, 2.4). The crude OR of developing apyretic seizures for any vaccine was 1.5 (95% CI 1.0, 2.3).

Conclusion: Neurological events possibly associated to vaccine administration are particularly worrisome for parents. In our study we found an increased risk of developing neurological events, and in

particular apyretic seizures, following the administration of any vaccine.

655. ADVERSE DRUG EVENTS IN EMERGENCY DEPARTMENT POPULATION: A PROSPECTIVE ITALIAN STUDY

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Introduction: Several studies were performed to evaluate adverse drug events (ADEs) incidence among inpatients, while few data are available on ADEs in outpatient setting and on related hospital admissions. Particularly, only one investigation was conducted on this important health issue in Italy.

Aims of the Study: To determine ADE incidence and ADE-related hospital admissions among Emergency Department (ED) visits, and to identify risk factors of developing ADE requiring ED visit.

Methods: During the year 2000 we conducted a prospective study in 2 observational periods of 10 days each in 22 Italian EDs. Demographic, clinical and pharmacological data about all patients visiting ED were collected by trained and qualified monitors. Records related to ADE were analysed and validated by a specific scientific committee.

Results: Among 18 854 patients included into the study, 629 (3.3% of total sample) reported at least one ADE, of which 244 resulted in serious events. Patients affected by ADE were significantly more likely to be hospitalised compared with the total sample (30.7% vs 23.7%, $p \leq 0.0001$), and accounted for 4.3% (193 cases) of total hospitalisations. Female gender and old age were factors significantly associated with an ADE, while patients with serious ADEs were more likely to be male and older than the ADE sample. NSAIDs and antibiotics were the drug types most involved in ADE with 104 (16.5% of total ADE visits) and 81 cases (12.9%), respectively. ADE affected mostly skin (213 ADE visits) and the gastrointestinal system (211).

Conclusion: Older patients and females result to be at higher risk to develop ADE leading to ED. The high ADE-related hospitalisation incidence highlights need for prevention planning targeted to reduce impact of ADE within general population.

660. HAEMORRHAGIC GASTRITIS AND SEVERE BLEEDING FOLLOWING ROFECOXIB ADMINISTRATION: A CASE REPORT

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Introduction: Digestive disturbances account for the most frequent complications associated with use of non-steroidal anti-inflammatory drugs (NSAIDs), known to act via inhibition of cyclooxygenase. Presently, two isoforms of cyclooxygenase (COX-1 and COX-2) have been identified and early studies pointed out distinct features of these isoenzymes which encouraged the development of selective COX-2-inhibitors: COX-1 appeared to be expressed constitutively and involved in gastroprotection, while COX-2 was regarded as being inducible in the presence of inflammation. Celecoxib and rofecoxib represent the first selective COX-2-inhibitors (coxibs) developed on the basis of these assumptions.

Aim of the Study: To present a case of upper gastrointestinal bleeding after treatment with rofecoxib.

Methods: The case was reported to the Section of Tuscany of SIMG-Pharmasearch, an Italian network for spontaneous reporting of adverse drug reactions in general practice.

Case Report: A 76-year-old woman, affected by bilateral gonarthrosis, diffuse osteoarthritis, and low back pain, was treated for 20 days with rofecoxib 25 mg/day for a flare of osteoarthritic pain. Few days after suspending rofecoxib treatment, due to a full relief of osteoarthritic pain, the patient began to develop severe epigastric pain accompanied by the emission of dark stools, and she experienced also one episode of coffee-ground emesis. One month later the patient referred for these symptoms to her physician, who prescribed a treatment with lansoprazole 60 mg/day, and requested a stool haemoccult and an upper digestive endoscopy. The stool haemoccult was positive for blood, and the endoscopic examination revealed an haemorrhagic-erosive gastritis, with the body and antrum mucosa being extensively affected by flat or protruding erosions and broad intervening areas of intramucosal bleeding. The patient's medical history indicated the occurrence of digestive disturbances in concomitance with NSAID use. Lansoprazole treatment promoted a full relief of the patient's digestive symptoms.

Conclusion: The present case report is consistent with a selective prescription (channelling) of rofecoxib to a patient with pre-existing digestive risk factors (sex, advanced age, and history of NSAID-related digestive disturbances). Recent studies have challenged previous assumptions underlying the development of coxibs, since COX-2 can be induced in proximity of ulcerative lesions, where it contributes to healing processes. Under these circumstances, COX-2 blockade can hamper ulcer healing. Overall, coxibs should be prescribed with caution to patients with risk factors for adverse digestive events, and a protection of gastroduodenal mucosa should be ensured in these patients when they are treated with coxibs or conventional NSAIDs.

665. POSTMARKETING SURVEILLANCE OF RISEDRONATE IN FILIPINO PATIENTS WITH OSTEOPOROSIS

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Introduction: There is increased public awareness on risk factors and complications associated with osteoporosis. Osteoporosis is a bone metabolic disorder leading to increased risk of fractures arising from several factors like genetic make-up, hormonal status, age, diet, lifestyle, and drug intake. Pharmacologic agents are developed to prevent bone loss and treat established osteoporosis. Risedronate, a biphosphonate, inhibits osteoclastic bone resorption. The efficacy

and safety of risedronate in osteoporosis have been proven by recent clinical trials.

Aim of the Study: This PMS Study was done to determine the safety and tolerability of the prescribed dose of risedronate among Filipino patients with postmenopausal and corticosteroid-induced osteoporosis.

Methods: This study was required by the Philippine government health-regulatory authority on risedronate (Actonel), a drug licensed for marketing since 2001. This is the first-ever post-registration study undertaken for risedronate in Filipino patients. Eligible patients with osteoporosis were prescribed risedronate 5mg tablet, which was taken once daily for 30 days. Tolerability and safety of the drug were evaluated by global questionnaire using a 5-item Lickert scale. A comprehensive inventory of risk factors and complications was made. The clinical experience on risedronate of both the physicians and the patients was analysed. The occurrence of adverse events was monitored.

Results: Eight hundred and fifty-four (854) patients out of 869 who entered the study were able to complete the 30-day observation period. Majority were women in their menopausal years. Leading risk factors among these patients were sedentary lifestyle, estrogen-deficient state, and family history of osteoporosis. The common presenting complaints were low-back pain, deformity, and disability. Almost half (48%) of the patients had concomitant illnesses. Most of them (86.4%) had previously taken medications for osteoporosis that included alendronate, raloxifene, calcitoni/calcitriol, and calcium supplements. Seventeen patients (1.99%) reported mild adverse events. Both the physicians and the patients rated their experience with risedronate favourably (>99%).

Conclusion: The study presented the spectrum of risk factors and sequelae of osteoporosis. Women in their postmenopausal years constituted the group at high risk for osteoporosis which was attributed to estrogen deficiency and loss of mediators for programmed cell death in osteoclasts. Chronic administration of supraphysiologic doses of corticosteroid is a recognised risk for osteoporosis and its complications. Risedronate has been proven to be safe, well-tolerated, and widely-accepted in this particular group of Filipino patients.

670. NONSTEROIDAL ANTI-INFLAMMATORY AGENT AND OEDEMA: RESPONSIBILITY OF HOSPITALISATION IN 50% OF CASES

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Introduction: The nonsteroidal anti-inflammatory drugs (NSAID) are heterogeneous group of organic acids that have analgesic, anti-inflammatory and platelet-inhibitory actions. More than 100 NSAIDs are marketed worldwide. Their use is constantly expanding and the search for more efficacious and better tolerated compounds is still being pursued. The well-known adverse effects of NSAIDs are essentially gastro-intestinal, but they have also haematological, dermatological and cardiovascular toxicity.

Methods: A recent case notified to the Centre Régional de Pharmacovigilance in Besançon by a cardiologist alerted us. It concerns a 64-year-old woman, with only an aortic valve as medical history. After 4 days of treatment by nimesulide, she presented an aggravated dyspnea and severe oedema in inferior limb, with a gain of weight of about 4kg. No other new medication was introduced recently.

Results: We asked if NSAIDs could be responsible for such adverse effects. Concerning nimesulide, no data bank (VIDAL, Martindale, Drugdex, side effects of drugs) gave oedema. Nevertheless, we found 11 notifications in our national French database for which it was described oedema, cardiac dysfunction, dyspnoea or gain of weight with nimesulide.

We wanted to know if a relation existed between others NSAIDs and oedema. For 22 patent medicines out of 38 sold in France (out of generic drugs), no oedema was found in their French 'résumé caractéristique du produit' which are official references for medical doctors. Moreover, in our national data bank, for each molecule, we found between 1 to 25 notifications of oedema. In all relevant cases, oedema occurred at the beginning of treatment (<5 days) and necessitated a hospitalisation for 50% of patients.

Conclusion: Oedema with NSAID is not benign adverse effects and each prescription must be followed with attention, essentially for patients with medical history of cardiac insufficiency.

680. THE DRUG SAFETY UNIT IN A CRO

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The main task of the Drug Safety Unit in a CRO is to ensure the sponsor that the safety profile of the drug is understood, the labelling is correct, and that proper advice on actions is given in the event new adverse events are discovered. If there is a problem with a particular drug the courses of action vary from withdrawal of the drug to amendment of the safety section in the summary of product characteristics. At the extreme the company could be advised to withdraw the drug from the market.

Tasks: Compiling and analysing of adverse event data of the company's drug; compiling and analysing of adverse event data from similar drugs for comparative purposes; preparation of reports; liaison with licensing authorities; liaison with the medical profession; liaison with the industry; participation in industry initiatives in the field of drug safety.

The Drug Safety Unit should be involved in the design of Phase III and Phase IV studies to ensure that relevant safety controls are part of the study design. The Drug Safety Unit should maintain a database of all adverse events reported directly to the company and provide necessary resources to follow-up on patients reported as having experienced serious or potentially serious adverse events throughout the world. The Drug Safety Unit should take all steps to ensure it knows of all adverse events reported to licensing authorities directly and reconcile the two ways of reporting. The Drug Safety Unit should explore the possibility of using data from sources such as the General Practitioners Research Database (GPRD), Prescription Event Monitoring (PEM), PHARMO (Pharmacy Database), Health Maintenance Organisations (HMOs), Authority databases, etc. for monitoring adverse events of drugs in large populations.

In addition to maintaining an adverse event database for the company's drugs it is essential to maintain a library of relevant published material

– including reprints of articles both on the company's drugs and closely related products marketed by other companies. In order to function efficiently it is likely that the following resources will be required as part of the Drug Safety Unit: medical manager of drug safety; one or more medical advisors; data analysts; statisticians; clerical and secretarial staff. Additionally, adequate computing facilities should be available. Except for very large projects most of the work can be undertaken with large capacity PC type equipment and appropriate software.

685. LOW MOLECULAR WEIGHT HEPARINS: REPORTING RATE INCIDENCE AND PROFILE OF ADVERSE REACTIONS REPORT IN SPAIN

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Introduction: The B01B group (ATC classification) has been modified by introduction of new Low Molecular Weight Heparins agents (LMWH). In the last years, new agents like Bemiparin, Dalteparin, Enoxaparin, Nadroparin and Tinzaparin have been introduced in the Spanish market with a very important increase on the utilisation of these drugs afterwards.

Aim: To analyse case reports and reporting rate incidence concerning LMWH notified to the Spanish Pharmacovigilance System via yellow card scheme until December 2003.

Methods: Low molecular weight heparin adverse reactions reported via yellow card to the Spanish Pharmacovigilance System (SPS) until December 2003 were obtained from the SPS Database. The notified incidence of adverse reactions linked to LMWH was estimated by examination of spontaneous report 'yellow cards' included in the database. To estimate numbers of patients exposed, we used data from drug sales reimbursed by the Spanish National Health System.

Results: According to the data registered, there were 281 reports of suspected adverse reactions (sADR) to LMWH; six of them were linked to more than one LMWH, seven linked to Bemiparin, 62 to Dalteparin, 162 to Enoxaparin, and 50 to Nadroparin. There were no sADR associated to Tinzaparin. Out of the 281 reports, 145 (51.60%) have occurred in women, 132 (46.98%) in men and in four cases the sex of the patient was not documented (1.42%). The average age of subjects (n = 275) was 65.07 years.

The 281 reports were described in 409 adverse reactions. The adverse reactions notified were non serious in 44.84% of the cases, mild in 31.67%, serious in 15.30% and with a fatal outcome in 8.19% of reports. The most frequent systems affected were skin and appendages (31.78%), platelet alterations (20.54%) and body as a whole (10.27%). The reporting rate per million DDDs was 1.37 (CI 95%: 0.55, 2.82) for Bemiparin, Dalteparin: 3.31 (2.48, 4.13), Enoxaparin: 2.05 (1.73, 2.36) and 1.35 (0.98, 1.73) for Nadroparin. Reporting rate incidence related to number of pharmaceutical forms (one pharmaceutical form is the daily treatment of a patient) was higher for all agents, Bemiparin: 3.19 (CI 95% 0.83, 5.55), Dalteparin: 7.99 (CI 95% 6.00, 9.99), Enoxaparin: 4.69 (CI 95% 3.97, 5.41) and Nadroparin: 2.56 (CI 95% 1.85, 3.27).

Conclusions: LMWH adverse effects reported to the Spanish Pharmacovigilance System are, in general terms, according with the SPC of the products; and there are not differences in the reporting rate of these drugs.

690. SUICIDAL ATTEMPTS IN YELLOW CARDS REPORTED TO THE SPANISH PHARMACOVIGILANCE SYSTEM

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Introduction: Some drugs have been recently related with suicidal behaviour, especially in some special populations. The role of spontaneous adverse drug reaction (ADR) reports in monitoring the safety of marketed medicines in relation to this reaction has been criticised due to the difficult detection and an important under-reporting rate.

Aim: To analyse reports concerning suicidal attempt notified to Spanish Pharmacovigilance System (SPS) via Yellow Card from 1983 to June 2004.

Methods: Information on potential adverse reactions (ADR) was obtained from the SPS Database of all suicidal attempt reports. The search did not include a different origin than yellow card via scheme.

Results: 28 case reports of suspected ADR were found on SPS Database: 4 (14.29%) were fatal, 11 (39.29%) were severe, 12 (42.86%) were moderate and 1 (3.57%) was non serious. Sex distribution was the same in male and female (50%). Median age was 46.2 years (CI 95% 39.8, 53.4). The 28 reports contained a total of 74 reactions. The number of suspected pharmaceutical preparations was 37, with a mean number per report of 1.32. The most frequently reported therapeutic groups were N (Nervous System): 43.2% and L (Antineoplastic and immunomodulating agents): 21.6%. Most frequently pharmacological subgroups reported were antidepressants (six cases) and interferon (seven cases). In 67.8% the ADR was judged to have been well documented in previous publications, in 17.8% the relationship between drug and reaction was supported only by anecdotal information and in 14.3% there were no references in the literature about it.

Conclusions: Suicidal attempt is not a common adverse reaction reported in Spain, via the yellow card system.

695. DRUG-INDUCED HYPONATREMIAS (DIH): A 5-YEAR SURVEY OF THE FRENCH PHARMACOVIGILANCE DATABASE

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Introduction: Hyponatremia is the most frequent electrolyte disorder and a potential cause of morbidity and mortality. A variety of drugs have been implicated as a possible cause of this disorder.

Aim of the Study: To describe the main characteristics and to identify predisposing factors of DIH.

Methods: Cases coded with hyponatremia or similar terms in the French Pharmacovigilance database over a 5-year period (January 1997–December 2001) were analysed. In addition, age, sex and seriousness in cases of DIH were compared to other reports computerised during the same period.

Results: Of 83 614 computerised cases, 1057 (1.3%) were reports of DIH. Patients were mostly women (70%) and the mean age was 73 years. Female patients were significantly older than males (77 vs 64 years). The time to occurrence of hyponatremia related to the suspected drug(s) was <8 days in 32% of cases or <1 month in 76%. The mean serum sodium level was 120 mmol/L (83–134 mmol/L) and there was no significant difference between genders. 56.8% of cases were moderate hyponatremias (120–134 mmol/L), 31.7% were severe (110–119 mmol/L) and 11.5% were life-threatening (<109 mmol/L). Concomitant symptoms were found in 45% of cases, with neurological symptoms as the most frequently coded (confusion in 104 cases, seizures in 54 and coma in 15). The adverse effect was considered as serious (i.e. inpatient hospitalisation, prolongation of hospitalisation, or life-threatening) in 72% of reports, and seriousness was related to age independently of gender. A single drug was suspected in 634 reports with diuretics (mostly thiazides) in 35%, antidepressants (mostly selective or mixed serotonin reuptake inhibitors) in 31%, antiepileptics (mostly carbamazepine and oxcarbazepine) in 14%, neuroleptics in 3.3%, omeprazole in 2.5%, ACE and desmopressin in 2.4%. As compared to other adverse effects reported during the same period of time, patients with DIH were significantly older (mean age: 73 years vs 50 years), more likely females (70.3% vs 53.5%), and DIH was more frequently coded as serious (72% vs 46%) after taking into account age and gender.

Conclusion: DIH is a common problem in pharmacovigilance with a significant level of seriousness. According to other studies, female sex and old age were possible predisposing factors. As most cases occurred early after the suspected treatment is introduced, close monitoring is warranted particularly when prescribing diuretics or serotonin reuptake inhibitors in elderly patients.

700. MEDICATION ERRORS: EXPERIENCE OF A POISON CENTRE

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Introduction: Medication errors are frequent and can result in potentially severe adverse drug events. A number of errors can be prevented by education, appropriate conditioning or labelling of drugs, and pharmacist interventions.

Aim of the Study: To describe medication errors reported to a Poison Centre (PC).

Methods: All medication errors recorded by Lyon PC in 2001 were retrospectively analysed. A prospective study using a detailed questionnaire was also conducted during a 6-month period to better identify their characteristics.

Results: Of 24 693 phone calls analysed retrospectively, 2187 (8%) were related to medication errors. The error occurred at home in 90% of cases or in health care institutions in 7.3%. Children were involved in 48% of errors. In 66% of cases, no treatment was recommended. Actually, only 10% of patients were managed with activated charcoal (6.5%), symptomatic measures (2 %), local decontamination (0.7%), or antidote treatment (0.3%). Less than 10% of patients were hospitalised and 2 deaths occurred in elderly inpatients (70 and 90 years) who previously had a severe pathological condition. The prospective study included 407 cases of which 93.4% occurred in outpatients. The population age was less than 1 year in 14% of cases, 1–5 years in 27%, 6–15 years in 9%, 16–64 years in 38%, and >65 years in 12%. The most common types of errors were wrong drug or improper dose administration by the patient of a prescribed/dispensed drug (60%), inappropriate self-medication (30%), dispensing (3.5%) or prescription (1%) errors. The error was made by the physician in only 2.2% cases. The causes of the error were inattention (30%), inadequate storage (11%), similarities in packaging (9.5%), unread prescription (8.3%), misunderstanding between the parents when a child was concerned (8%), confusion with another product (3.3%), omission (2.5%), miscomprehension (2,5%), change of packaging (2%), and analphabetism (1%). Patients were asymptomatic in 79% of cases and the most frequently reported symptoms were digestive (45%) or neurologic (30%) adverse effects. Only 3% of patients required medical surveillance, and one patient was hospitalised in an intensive care unit for 24 hours. All patients fully recovered.

Conclusion: Most medication errors recorded by Lyon PC were reported by the patients themselves and the patients or their family were the most frequent source of errors. Data from PC can help to identify other types of medication errors than those usually identified in hospital or pharmacy studies.

705. SEVERE TOXICITY ASSOCIATED WITH A DRUG CONTAINING DIETHYLENE GLYCOL ETHYL-ETHER (DEGEE) AS AN EXCIPIENT: REPORT OF SIX CASES

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Introduction: Since 1999, several cases of acute renal failure and neurotoxicity attributed to an herbal drug formulation have been reported to the French Pharmacovigilance centers and raised the issue of the possible hazards of DEGEE, an excipient of the suspected formulation.

Aim of the Study: To describe reports of severe adverse effects associated with oral liquid drug formulations that contain DEGEE.

Methods: Suspected cases were provided by the manufacturers, Poison centres, or extracted from the French Pharmacovigilance database. Clinical, biological and pathological data were examined with particular attention to the circumstances of drug intake.

Results: Six cases were considered for analysis (four women and two men aged 35–89 years). Four patients had a previous history of psychiatric disorders. All six patients were admitted for acute renal

failure, and five had severe metabolic acidosis. Although promptly managed with renal dialysis, five patients subsequently developed neurological complications, e.g. coma, respiratory failure, polyradiculopathy, or neurosensorial disorders. Kidney biopsy in five patients showed acute proximal tubular necrosis. A detailed medication history revealed that all patients had consumed Pilosuryl®, an OTC liquid oral formulation of pilosellae and phyllantus which contains 6% DEGEE. A recent ingestion of large doses of the product was suspected in five patients with a total DEGEE amount of 7.5 g/day to 38 g/day over 3 days. Toxicological screening in four patients was unable to identify ethylene glycol, diethylene glycol or DEGEE. Urinary oxalate crystals were found in only one. One patient died from infectious complication 2.5 months later when partial recovery of renal function was noted. Four patients developed chronic renal failure requiring chronic ambulatory dialysis, and the last patient had abnormal serum creatinine values. Four patients also suffered from various neurological or ophthalmological sequelae.

Conclusion: Repeated intake of large amounts of DEGEE was the likely cause in our cases because (i) the herbal drugs of the formulation had been used since 1962 without identified hazard; (ii) our cases occurred only after DEGEE was added to the formulation in 1999; (iii) the clinical findings were reminiscent of epidemics due to diethylene glycol contaminated drugs; and (iv) no other causes were identified. Accordingly, Pilosuryl® was withdrawn from the market. Urosiphon (orthosiphon), another phytotherapeutic drug, was also withdrawn as a precautionary measure because the total amount of DEGEE per packaging (10g) was close to that of Pilosuryl® (15g).

708. SAFETY AND TOLERABILITY OF ASPIRIN IN RANDOMISED CONTROLLED CLINICAL TRIALS

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Safety and tolerability of aspirin in short-term acute pain therapy with single doses of max. 1g and daily doses of max. 3g is of particular importance for patients using over-the-counter (OTC) analgesics. Aspirin has been known to be an effective analgesic for many years and is commonly used throughout the world for many pain conditions. It is important for healthcare professionals and patients to have the best possible information about efficacy but also about safety and tolerability of this analgesic. Prospective, randomised, placebo-controlled clinical trials provide data on the safety and tolerability of aspirin by analysing adverse events. In those trials the assessment of adverse events is done by a physician. The determination of the relationship of adverse events to the study medication, the intensity of adverse events and their classification according to system organ classes is routine procedure in clinical trials.

Results of a meta-analysis of nine clinical trials with single-doses of 1000mg aspirin in typical OTC indications of migraine, episodic tension-type headache and dental pain will be presented and discussed. All adverse events, including drug-related adverse events and gastrointestinal adverse events of aspirin reported by the patients and coded according to MedDRA are compared with placebo. In total, 2852 patients were analysed (1581 on aspirin, 1271 on placebo). 14.9% and 11.1% of patients treated with 1000mg aspirin and with placebo, respectively, reported adverse events. For drug-related adverse events the corresponding numbers were 6.5% and 4.0%, respectively. Intensity of adverse events and gastrointestinal adverse events for aspirin and placebo were also compared. Most of the adverse events were of mild or moderate intensity. Only 3.1% of patients treated with aspirin and 2.1% of patients treated with placebo reported drug-related gastrointestinal adverse events. Data of the individual studies showing adverse event comparisons of aspirin with sumatriptan, paracetamol and ibuprofen will also be presented.

710. THE IMPORTANCE OF REPORTING MEDICATION ERRORS WITH VACCINES

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Introduction: Medication errors do occur with both drugs and vaccines. Compared to vaccines, there is much more experience with medication errors with drugs where the focus is on the problem with look or sound-alike names. A report from VAERS mentioned seven categories of medication errors on 49 vaccine reports received over seven years. In Canada, medication errors are not expected to be reported to the Vaccine Associated Adverse Event Surveillance System (VAAES). However, some are received, particularly from one manufacturer, and through the international reporting by manufacturers.

Aim of the Study: The objective is to review the types of errors presented to Health Canada since 2002.

Methods: Health Canada received 130 reports of medication errors. These were reviewed and coded along 15 types of errors (dose adult for child, dose child for adult, expired, extra doses, frozen vaccine, partial dose, pregnant, route wrong, schedule error, splashed with vaccine, split dose, wrong diluent, wrong dose, wrong vaccine, and other).

Results: 118 (91 %) reports were from manufacturers. Among the reporters, pharmacists ranked highest (30 %) then nurses (22 %) then doctors (23 %). The highest number of reports occurred in children (29 %) then adults (26 %) and adolescents (18 %). Around 70% of the reports involved hepatitis A and/or hepatitis B vaccine, followed by MMR (15 %) and varicella vaccine (9 %). Of the 17 reports where the schedule was wrong, 15 (88%) involved hepatitis A and/or B. Twenty-seven persons had an adverse event. The number ranged from 1 to 4. Three persons got chickenpox, four were therapeutic failures and one was therapeutic response decreased.

Discussion: A previous review on 76 reports divided the errors in 12 different types; now with a further 54 reports there are 15 different types. Of concern is the possibility that an incorrect schedule for the hepatitis A and/or B vaccine can lead to lack of efficacy leaving the person unprotected. It has not been the practice in Canada to request reports on medication errors. From this preliminary analysis, it may be necessary to revise this practice and encourage reports on medication errors for vaccinations. The best way of categorising these types of 'vaccination' errors still needs to be determined so that these terms can be added to the coding thesaurus (WHO-ART, COSTAR or MedDRA).

715. ELUCIDATING THE MECHANISM OF LITHIUM ACQUIRED NEPHROGENIC DIABETES INSIPIDUS

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Introduction: Acquired nephrogenic diabetes insipidus (NDI) is a well-known complication of lithium treatment, occurring in 12–54% in chronic users. NDI is defined by the kidney's inability to concentrate urine in response to vasopressin (AVP), resulting in the production of large quantities of hypotonic urine. In normal physiology vasopressin is released from the pituitary gland in response to increase in serum osmolality or strong decrease in circulating volume. AVP is bound to vasopressin-type-2 receptors (V2R) on the basolateral side of the kidney distal tubular cells. Via second messenger cAMP this results in apical insertion of aquaporin-2 (AQP-2) that act as water channels. This results in production of concentrated urine by increasing water reabsorption from pre-urine. After AVP mediated V2R stimulation ends, cAMP and AQP-2 are partly excreted into urine. In the present study we compared, in a group of patients under chronic lithium treatment, the kidney concentrating activity, in a situation of minimal V2R stimulation (water loading induced) to a situation of maximal V2R stimulation (induced by desmopressin administration). We measured the kidney concentrating capacity (maximal urine osmolality) and response (cAMP, AQP-2 excretion).

Aim: To elucidate the mechanism of lithium acquired NDI.

Methods: We conducted a cross-sectional study in a cohort of patients under chronic lithium treatment. Included were ten patients suffering from polyuria (24-hour urine volume at least 3L) and ten patients not suffering from polyuria. We monitored the kidney's response (maximal urine osmolality and rise in urinary cAMP and AQP-2) to water loading followed by desmopressin. Urine was collected every hour, starting 2 hours before until 4 hours after desmopressin (40μg intranasal) administration. Each urine sample was investigated for volume, osmolality, creatinin, AQP-2 and cAMP.

Results: Since rise in cAMP excretion paralleled maximal reached urine osmolality in polyuric and non-polyuric groups without a clear dichotomy, we decided to perform a linear regression analysis for the difference between minimal and maximal reached urine cAMP and maximal reached urine osmolality. The rise in cAMP was found to correlate (R2 = 0.784) to the maximal reached urine osmolality. Overall, possibly due to high interindividual variability, no significant relation could be found for rise in AQP-2 and maximal reached urine osmolality. On an individual basis, however, low cAMP levels corresponded to low AQP-2 levels in urine.

Conclusion: Our study shows that patients with lithium induced NDI have an impaired cAMP production in response to desmopressin V2R stimulation.

720. A COHORT STUDY TO MONITOR THE MANAGEMENT AND OUTCOMES OF SELECTED ADVERSE DRUG REACTIONS WITH CARVEDILOL WHEN USED FOR CARDIAC FAILURE IN ENGLAND

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Introduction: Carvedilol is a β-adrenoceptor antagonist initially licensed for hypertension and angina. The efficacy and safety of carvedilol in cardiac failure is well documented in clinical trials. In 1998 cardiac failure was added to its license.

Aim: To monitor the management and outcomes of selected adverse drug reactions in patients prescribed carvedilol for cardiac failure in England.

Methods: An observational cohort study using a modified Prescription-Event Monitoring (PEM) methodology. Patients were identified from dispensed prescriptions issued by primary-care physicians (GPs) between August 1999 and July 2001. GPs were sent eligibility questionnaires to ascertain if the indication for carvedilol was cardiac failure. Three further questionnaires were sent to the GPs of eligible patients over a 2-year period requesting information on demographics, initiation of treatment, supervision of care, severity of cardiac failure (NYHA), concomitant medications and any events reported. Incidence Densities (IDs), expressed as number of 1st reports of an event/1000 patient-months of exposure, were calculated for month 1, months 2–6, 7–12, 13–18, 19–24 and the entire treatment period. Data on supervision of care were analysed using descriptive statistics.

Results: 1454 patients had questionnaire-1 returned; 987 (68%) were males; median age 66 years, median age of females 72 years. Treatment was initiated by hospital specialists for 86% (1244) and by GPs for 13% (183). By questionnaire-3 (1286 returned), supervision was by shared care (hospital and GP) for 48% (621), by GPs for 25% (320) and hospital specialist 20% (260). NYHA status had improved for 48% (618), remained unchanged for 33% (420) and deteriorated for 5% (70). Malaise/lassitude were the events most frequently reported as ADRs (11), as the reason for stopping carvedilol (91) and with the highest rate in the first month of treatment (22.4/1000 patient-months treatment). There were 163 deaths including ten from cardiac failure.

Conclusion: From the information available, carvedilol appears to be reasonably well tolerated. No serious ADRs not mentioned in the SmPC were identified within the limitations of the size of this study. Guidance on the introduction and use of carvedilol seems to have been implemented well. Further studies may be warranted to identify risk factors for those who stopped treatment due to cardiovascular problems.

This modified PEM technique has enabled the safety and management of patients with selected ADRs to be monitored for carvedilol used for cardiac failure in everyday clinical practice. Such monitoring of outcomes of ADRs is important for the risk management of medicines.

Financial Disclosure Statement: The Drug Safety Research Unit is an independent charity, which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU.

The Unit has received such funds from Roche Products Limited, the manufacturer of carvedilol. SAS has received lecturing and consultancy fees from Roche Products Limited unrelated to carvedilol. The study was conducted to address a regulatory request from the MCA (now the MHRA) to Roche Products Limited.

725. SAFETY PROFILE OF TIOTROPIUM USED IN GENERAL PRACTICE IN ENGLAND: INTERIM RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Introduction: Tiotropium bromide is a new once-daily, long-acting specific muscarinic receptor antagonist (anticholinergic bronchodilator), administered by inhalation, for maintenance treatment of chronic obstructive pulmonary disease (COPD). Tiotropium binds to the muscarinic receptors in bronchial smooth muscle, resulting in relaxation and reduced mucus secretion.

Aim: To monitor the safety of tiotropium prescribed in primary care in England, using Prescription-Event Monitoring (PEM). A final cohort size of 10–15 000 patients is anticipated.

Methods: A postmarketing surveillance study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) between August 2002 and August 2003. Questionnaires requesting clinical event data and demographic information were sent to the initial prescriber approximately 6 months after the date of the first prescription for each patient. Information on suspected adverse drug reactions (ADRs), reasons for stopping tiotropium, causes of death, past medical history and concomitant use of other respiratory medications was requested. Event Incidence Densities (IDs) [number of first reports/1000 patient-months of exposure] and the difference between IDs for events reported in month 1 (ID1) and months 2–6 (ID2) of exposure, were calculated. Follow-up questionnaires were sent if more information was required to evaluate causal association of specific events with tiotropium.

Results: Data on 5199 patients has been received; 55.1% were male, with a median age for both males and females of 70 years. At the end of 6 months, 74% of the 4371 patients for whom duration of treatment was known were continuing treatment. The most frequently reported events in the 1st month of treatment were other respiratory conditions (lower respiratory tract infections (ID1 5.14), dyspnoea (ID1 3.74) and hospital referrals (ID1 1.87) that may reflect background events in this population. Excluding indication related events, dry mouth was the adverse event most frequently reported in the first month of treatment. 18 events in 16 patients were reported as ADRs to tiotropium, including dyspnoea (3), malaise (3) and dry mouth (2). 1187 reasons for stopping tiotropium were reported, of which 'not effective' was the most frequent (833; 16% of cohort). Clinical reasons for discontinuing tiotropium included intolerance (31; 0.6%), hospital referrals (23; 0.4%) and dry mouth (18; 0.3%). 211 deaths (4%) have been reported, including COPD (54) and malignancies (19) but for 95 the cause has yet to be established.

Conclusion: To date, no previously unrecognised ADRs have been identified but data on follow up of specific events is yet to be evaluated. At this interim stage, tiotropium appears to be generally well tolerated. As these are interim results, it is important to state that the study is ongoing, and that any conclusions drawn from the data presented may be subject to change as the cohort continues to grow

Financial Disclosure Statement: The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of tiotropium.

730. THE MANAGEMENT AND OUTCOMES OF SPECIFIC ADVERSE DRUG REACTIONS IN PATIENTS PRESCRIBED PIOGLITAZONE IN PRIMARY CARE IN ENGLAND: INTERIM RESULTS

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Introduction: Pioglitazone is the third thiazolidinedione, a new class of oral drugs for the treatment of non-insulin dependent diabetes mellitus, marketed in the UK. The first drug in this class, troglitazone, was withdrawn from the market due to concerns over hepatotoxicity.

Aim: To monitor the management and outcomes of specific adverse drug reactions (ADRs) in patients, included in the Prescription-Event Monitoring (PEM) study of pioglitazone.

Methods: A postmarketing surveillance study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) in England. Questionnaires requesting clinical event data were sent to prescribers approximately 6 months after the date of the first prescription for each patient. For those with abnormal liver function tests (LFTs), oedema, weight gain, cardiac failure or anaemia reported on the original questionnaire with no alternative cause given, GPs were sent follow up questionnaires. These requested information on patient's medical history, concurrent medications, investigations, how the event was detected and managed, and its outcome. Data were analysed using descriptive statistics.

Results: Of 303 questionnaires returned for patients with one or more of the 5 events in the PEM cohort (9009 patients), 250 contained clinical data. 150 patients (60%) had pioglitazone started by GPs and 96 (38%) by hospital doctors. The proportion that stopped treatment varied with the event: oedema (60, 67%); heart failure (19, 56%), as did resolution of the condition on stopping pioglitazone; oedema (37), heart failure (5). The condition was detected mainly during routine follow up for LFTs abnormal (28, 97%), weight gain (78, 84%) and anaemia (3, 60%) but cardiac failure (25, 74%) and oedema (46, 52%) were detected mainly when the patient presented with a problem. GPs managed the care of most patients: abnormal LFTs (22, 76%), oedema (61, 69%), weight gain (48, 52%). The pattern of interventions varied, with no action taken for 20 (69%) with abnormal LFTs and treatment with drugs for 24 (71%) with cardiac failure. Most patients recovered – oedema (63, 71%), cardiac failure (20, 59%) – but some did not – anaemia (2, 40%), weight gain (30, 32%), abnormal LFTs (9, 31%).

Conclusion: This methodology permitted information to be collected on how specific adverse events are managed within the primary care setting. The method is useful for postmarketing risk eval-

uation and management. These are interim findings and numbers of reports are expected to increase by completion of the study.

Financial Disclosure Statement: The Drug Safety Research Unit is an independent charity, which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of the product included in this study. Saad Shakir has received consultancy fees from Takeda.

735. THE MANAGEMENT AND OUTCOMES OF SPECIFIC ADVERSE DRUG REACTIONS IN PATIENTS PRESCRIBED ROSIGLITAZONE IN PRIMARY CARE IN ENGLAND

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Introduction: Rosiglitazone is a thiazolidinedione, a new class of oral drugs for the treatment of non-insulin dependent diabetes mellitus. The first drug in this class, troglitazone, was withdrawn from the market due to concerns over hepatotoxicity.

Aim: To monitor the management and outcomes of specific adverse drug reactions (ADRs) in patients, included in the Prescription-Event Monitoring (PEM) study of rosiglitazone.

Methods: A postmarketing surveillance study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions issued by primary care physicians (GPs) in England between June 2000 and July 2001. Questionnaires requesting clinical event data were sent to prescribers approximately 6 months after the date of the first prescription for each patient. For those with abnormal liver function tests (LFTs), oedema, weight gain, cardiac failure or anaemia reported on the original questionnaire with no alternative cause given, GPs were sent follow up questionnaires. These requested information on patient's medical history, concurrent medications, investigations, how the event was detected and managed, and its outcome.

Data were analysed using descriptive statistics.

Results: 913 questionnaires were posted for patients with one or more of the 5 events, in the PEM cohort of 14 418 patients; 600 of the 713 (84%) questionnaires returned contained clinical data. 389 patients (65%) had rosiglitazone started by GPs and 199 (33%) by hospital doctors. The proportion that stopped treatment varied with the event – LFT abnormal (72, 80%), anaemia (10, 39%) – as did resolution of the condition on stopping rosiglitazone – LFT abnormal (32), anaemia (5). The condition was detected mainly during routine follow up for LFTs abnormal (87, 97%), anaemia (17, 65%) and weight gain (100, 63%) but cardiac failure (56, 70%) and oedema (133, 54%) were detected mainly when the patient presented with a problem. GPs managed the care of most patients: oedema (175, 71%), abnormal LFTs (58, 64%), weight gain (88, 56%). The pattern of interventions varied, with no action taken for 68 (76%) with abnormal LFTs and treatment with drugs for 55 (69%) with cardiac failure. Most patients recovered – weight gain (72, 46%), cardiac failure (52, 65%) – but some did not – cardiac failure (8, 10%), abnormal LFTs (43, 48%).

Conclusion: This study permitted information to be collected on how specific adverse events are managed within the primary care setting. The method is useful for postmarketing risk evaluation and management.

Financial Disclosure Statement: The Drug Safety Research Unit is an independent charity, which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of the product included in this study.

Saad Shakir was an employee of GlaxoWellcome between 1994 and 1997.

740. THE GENERAL PRACTICE RESEARCH DATABASE – AN IMPORTANT RESOURCE FOR PHARMACOVIGILANCE PLANNING

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The implementation of risk management strategies and pharmacovigilance plans coupled with earlier access to medicines through conditional approvals will require the wider application of epidemiology to postmarketing surveillance. As the focus of pharmacovigilance broadens to include more explicit consideration of 'what diseases do to patients' as well as 'what drugs do to patients', the value of databases which provide comprehensive, high quality longitudinal patient records will increase.

The General Practice Research Database (GPRD) is the world's largest computerised database of anonymised longitudinal clinical records from primary care, containing data on a demographically representative sample of 3 million patients in the UK. It has been widely used to study a broad range of diseases, outcomes associated with therapy with most major drug classes used in primary care and in the field of drug safety signal evaluation where the results of GPRD-based pharmacoepidemiological studies have been used to inform regulatory decision-making.

In addition, for medicines prescribed widely in primary care, the GPRD will provide a rich source of data to inform many components of pharmacovigilance plans. Specifically, it will support analysis of the:

- incidence and prevalence of disease (indication for the drug) and its natural history;
- incidence and prevalence of concurrent illnesses in the population;
- drug utilisation in normal clinical practice including: demographics; dose; duration; indication (including off-label); switching (including characteristics and risk profile of first-time users and switchers to new therapies) and co-medication;
- prospective monitoring of patients for events identified from clinical trials as weak signals of drug safety issues;
- outcomes of treatment, including changes in risk over treatment duration;
- comparison of event rates between drugs of the same class and those used for the same indication;
- comparative drug effectiveness (benefits in real life setting), enabling clinical impact to be confirmed in target population.

Databases like the GPRD in which longitudinal data are collected without a priori hypotheses provide rapid, economical access to information on real life usage and outcomes and provide an important complement to clinical trials.

745. ADVERSE DRUG REACTIONS IN THE ELDERLY: RESULTS OF TUNISIAN NATIONAL CENTRE OF PHARMACOVIGILANCE

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Introduction: Many reports tried to study the incidence of adverse drug reactions (ADR) in old people and the type of these ADR in this special category of population. Many procedures were followed to achieve these studies and the population differed according to these procedures.

Aim: The aim of the study was to determine the rate of ADR in the elderly in the cases notified to Centre National de Pharmacovigilance (CNPV), the number of drugs used by each patient, the type of most frequent ADR and the class of drugs most involved in these ADR. We tried to explain the rates found and we compared them with the literature.

Material and Method: We performed a retrospective study of about 630 cases notified to the CNPV between 1991 and 2003 and validated according to the Begaud et al. method of imputability. These cases represent 11% of the total cases notified to the CNPV during this period. We kept only 573 cases and we eliminated 57 cases because of lack of data or non-medicinal cause.

Results: They were 321 women (56%) and 252 men (44%). This difference is similar to that found in all the cases notified to the CNPV (60% and 40%) [$p > 0.05$].

At least one chronic disease in 80% of the cases was found, especially arterial hypertension (282 cases), diabetes (164 cases) and cardiopathy (80 cases). The number of drugs used by each patient varied from 1 to 15 drugs. In about 62% of cases, at least three drugs were used. The most frequent suspected drugs were the ones belonging to the cardiovascular class. Cutaneous ADR were the most frequent manifestations (78%), followed by hepatic manifestations (11.5%).

Discussion: The rate of ADR in old people (11%) found in this study is twice the rate in old people in Tunisia (5.6% in 1997). These data indicate that the old people are probably more exposed to have ADR. The ADR are more often observed with polytherapy: 62% of ADR happened with 3 drugs or more. These data are similar to those found in the literature (>60%).

The drugs most involved in the ADR are the class of cardiovascular. This is probably due to the high frequency of cardiovascular diseases found in this part of the population. The cutaneous ADR are the most common.

750. THE IMPACT OF RISK COMMUNICATION STRATEGIES ON NEFAZODONE PRESCRIPTION TRENDS IN CANADA BETWEEN 1994 AND 2003

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Introduction: Between May 1994 when nefazodone was first marketed and November 2003 when it was withdrawn from the Canadian market, Health Canada issued several articles/letters to communicate the risk of hepatic injury associated with nefazodone to both the public and health care professionals. These include: (i) April 1996: an article addressing all nefazodone related adverse drug reactions (ADRs) reported to Health Canada in the Canadian Adverse Reaction Newsletter (CARN); (ii) August 1998: the Product Monograph (PM) changes to include new safety information; (iii) July 1999: an article focusing on hepatic injury and nefazodone use in CARN; (iv) June/July 2001: a combination of Dear Health Care Professional Letter (DHPL) and a public advisory (PA); and (v) January 2003: an article regarding hepatic ADRs associated with nefazodone in CARN.

Aim of the Study: The objective of this study was to describe nefazodone prescription trends in Canada between June 1994 and December 2003 and to evaluate the impact of these risk communication strategies on the trends.

Methods: Aggregated monthly data on the total number of prescriptions of nefazodone were extracted from the Canadian CompuScript Audit. Time Series Analysis (TSA) method was used to evaluate the impact of the various risk communication strategies on the prescribing trends.

Results: The total number of prescriptions increased steadily in the first four years and reached a peak in December 1999. Since then the number of prescriptions decreased continuously with 19 000 prescriptions in October 2003, 10 000 in November (the product was withdrawn from the market), to only 1000 in December 2003. The results from TSA indicated that the first, the second and the fifth interventions did not cause any significant change of the prescription volume. On the other hand, the third and fourth intervention was significantly associated with a continuing drop of the total number of prescriptions. The drop was 128 prescriptions/month after the third intervention and 803 prescriptions/month after the fourth intervention.

Conclusions: A significant drop in nefazodone prescription rate was not observed until after the third (article published in CARN) and fourth (DHPL+PA) risk communication intervention. These results suggest that risk communication strategies that employ multiple interventions over time may be needed in order to be effective in changing prescribing practices.

755. DRUG SURVEILLANCE AND INFORMATION CENTER: EFFICACY ON ALERT SIGNAL DETECTION

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Introduction: Adverse drug reactions are as old as medicine itself and have to be considered between the major causes of iatrogenic diseases. The detection of an unknown and unexpected connection between drug exposure and adverse events is one of the major problems of pharmacovigilance. The 'spontaneous reporting system' is the primary method for signal detection in Italy, but it presents several difficulties and limitations.

Aim of the Study: In order to improve the spontaneous reporting system, some action should be implemented with the aim of stimu-

lating reporting among prescribers. In this context, a drug surveillance and information centre is an important tool to achieve the development of a positive attitude towards pharmacovigilance. The existence of a drug surveillance and information centre can lead to a better adverse reaction reporting both qualitatively and quantitatively, which in turn may start the rise of alert signals. Our centre analysed all the reports of spontaneous adverse reaction received.

Methods: We selected the ADRs of some scientific and clinical interest. We evaluated the hypothesis of a possible association between drug exposure and adverse events considering arguments in favour and against the hypothesis, providing feedback information to the reporter.

Results: A patient affected by gastrointestinal stromal tumour (GIST) developed cutaneous adverse drug reactions (ADRs) during treatment with imatinib and lansoprazole. A 60-year-old White female affected by GIST developed bilateral palpebral oedema with hyperaemic conjunctiva and labial oedema after 2 months of imatinib treatment, when lansoprazole was introduced to treat dyspeptic symptomatology. Treatment was discontinued, and on reintroduction of both drugs the patient developed Stevens-Johnson syndrome. Two months later, generalised cutaneous reactions appeared immediately subsequent to reintroducing low dose imatinib with corticosteroid therapy plus lansoprazole treatment. After discontinuation of all drugs, with the exception of the corticosteroid, the progression of cutaneous lesions stopped. According to Naranjo's algorithm, imatinib and lansoprazole may be considered as the possible cause of the ADRs observed.

Conclusion: This report represents an example of the efficacy of a drug surveillance and information centre in the detection of a signal.