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International Society of Pharmacovigilance

ABSTRACTS

5th ISoP Annual Meeting

'Pharmacovigilance – A Global Concern: East Meets West'

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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

The International Society of Pharmacovigilance (ISoP) is devoted to developing its activities on a worldwide basis towards supporting safer use of medicines in clinical practice.

ISoP aims to promote the use of all types of information and methodologies in providing optimal drug treatment for patients. The Society is not only for clinical pharmacologists, the pharmaceutical industry, epidemiologists and regulators, but also for practising clinicians and other health professionals who are interested in discovering better ways to treat patients more safely with medicines.

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1. CARDIOVASCULAR ADVERSE EFFECTS OF COX-2 INHIBITORS

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The prime object that underlies the development of cyclooxygenase (COX)-2 inhibitors had two goals. The first one was that this isoenzyme causes release of prostanoids formation in pain-induced [during] inflammatory conditions. The second one was that COX-1 is responsible for cytoprotective generation of prostanoids, predominantly, prostaglandin PGE_2 and PGI_2 in the gastrointestinal (GI) epithelium. Thus, the inhibition of COX-1 accounts for the GI adverse effects which most commonly complicate traditional non-steroidal anti-inflammatory (NSAID) therapy. However, it was postulated before their introduction in 1999 that COX-2 inhibitors may decrease vascular PGI_2 production and may disturb the balance between prothrombotic (thromboxane A_2; TXA_2) and antithrombotic (PGI_2). This process may lead to increased cardiovascular abnormalities. COX-2 inhibitors by inhibiting PGI_2 also disable one of the main defenses of the endothelium against platelet aggregation, hypertension and other cardiovascular events. Several factors may explain the blood pressure raising effects, such as inhibition of vasodilating bradykinin, PGs, altered angiotensin system and changes in sodium and water retention by the kidneys. In this regard, there might be some differences in the individual COX-2 inhibitors. COX-2 inhibitors have also been reported to cause oedema, worsening of heart failure, fatal allergic vasculitis and aggravation of doxorubicin-mediated cardiac injury. Most of these adverse reactions may be related to inhibition of COX-2. Recently, it has been reported that celecoxib, a COX-2 inhibitor, has been associated with a dose-related increase in the composite end-point of death from cardiovascular abnormalities, myocardial infarction, stroke and heart failure.[1] These finding provide further evidence that the use of COX-2 inhibitors may increase the risk of serious cardiovascular disorders. In September 2004, Merck announced a worldwide withdrawal of its popular COX-2 inhibitor, rofecoxib (Vioxx), because of the observations of an increased incidence of cardiovascular events in a trial evaluating the 25 mg dose used to prevent cancer. In conclusion, what Paracelsus, 1493-1541, described may be true: "All things are poisons and there is nothing that is harmless, the dose alone decides that something is no poison".

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2. CHALLENGES IN THE PHARMACOVIGILANCE OF ONCOLYTIC DRUGS

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In pharmacovigilance, there are several reasons for paying special attention to oncolytic drugs. The Baby Boomer generation is now entering their sixties and in the years to come unprecedented numbers of people will acquire cancer or another malignant disorder and be treated with one chemotherapy regimen or another. Fortunately the early diagnosis and treatment of many tumours have much improved and many patients will survive for a long period of time. Therefore, a thorough knowledge of the delayed adverse effects and their influence on the quality of life has become even more important.

In recent years several new oncolytic drugs have been introduced, with novel mechanisms that may possibly have as yet unidentified consequences, and many more are in the pipeline. New oncolytics can be very expensive and, since refusals by insurers or reimbursement agencies have become a reality, treatment affordability has become another concern in pharmacovigilance.

Also less structured countries with vast populations, for example India or Indonesia, have large numbers of cancer patients. Here the diagnosis is often made in a late phase and palliative chemotherapy may be the only option. In these patients special attention is needed for the effects of treatment on the quality of the, often short but important, last part of their lives.

Experience has shown that at many national pharmacovigilance centres there seems to be selective underreporting of the adverse effects of oncolytic drugs and it is uncertain how effective traditional pharmacovigilance is with regard to oncolytic drugs.

Novel oncolytics and combinations need comprehensive and prolonged data collection after their introduction, in order to obtain all the information needed for a realistic long-term benefit/harm evaluation. New strategies — regulatory, scientific and financial — may be required in order to ensure rational and beneficial cancer chemotherapy.

3. MECHANISMS RESPONSIBLE FOR CARDIAC SIDE EFFECTS OF NON CARDIOVASCULAR DRUGS: PROARRHYTHMIC, QT-PROLONGING EFFECTS OF PSYCHOTROPIC DRUGS

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This paper summarizes the experimental and clinical data showing the cardiac side effects of non cardiovascular, especially psychotropic (antidepressants, antipsychotics) drugs. The most frequent cardiac side effects of psychotropic drugs are brady- or, tachycardia, ECG alterations (prolongation of QRS, QT interval), AV-block, ventricular arrhythmias (tachycardia, torsades de pointes [TdP]) and sudden death.

Objective: to attempt to find relations between clinical data and the electrophysiological effects of antidepressants (fluoxetine, citalopram), antipsychotics (risperidone, haloperidol) obtained in isolated guinea-pig ventricular muscles and canine ventricular myocytes using the conventional microelectrode and whole cell clamp technique.

Results and conclusion: While antidepressants inhibit different cardiac ion channels (Na^+, K^+ Ca^{2+}), most of antipsychotics are associated with the inhibition of the rapid component of delayed rectifier K^+ current (I_{Kr}). Comparing the potency on K^+ channel inhibition (I_{Kr}), and the prolongation of QT interval with the therapeutic plasma levels of the drugs, the difference between the inhibitory potency and therapeutic dose is the highest in the case of quetiapine, olanzapine and risperidone, while thioridazine shows the smallest difference. All drugs that cause TdP prolong QT interval and inhibited I_{Kr} but the relationship is not precise. Some additional cellular effects of particular agents, modulating conditions, factors (disease, electrolyte disturbances, genetic damage, drug interactions) make the individual vulnerable to arrhythmias. The paper takes into consideration drug interactions that may cause risk of arrhythmia during chronic treatment of psychiatric patients. It also draws attention to the predisposing factors of TdP and lists those groups of drugs that have QT-lengthening and torsadogenic side-effects.

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4. ANALYSIS OF ADR REPORTS FOR YEAR 2004

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Objective: To analyse the reporting rate and types of ADR received by the Pharmacovigilance (PV) Unit for year 2004.

Methodology: We performed a search in the HSA ADR database to identify all reports received in 2004. Reports were analysed and information extracted included the top 15 active ingredients suspected of causing ADR and the highest 10 occurrences of ADR.

Results: In year 2004, the PV Unit received a total of 1,138 local spontaneous ADR reports. Healthcare professionals from the public hospitals submitted 60% of the total number of reports. The rest of the reports were from national specialty centres/other public health institutions (17.3%), private clinics/specialist clinics (8.9%), private hospitals (7.2%), pharmaceutical companies (5.3%) and community retail pharmacies (1.2%). Medical doctors were the main reporters (70.9%), followed by pharmacists at 21.4%.

Based on ethnic groups, Chinese patients constitute the highest proportion (63.7%), followed by Malay (10.8%) and Indian (5.5%) patients. Patients between 20 and 69 years of age made up the majority of patients reported to suffer ADRs. The trends observed above were similar to Singapore's demographic statistics.

Non-steroidal anti-inflammatory agents (NSAIDs) and antibiotics were the most commonly reported drugs causing ADRs. The top reported ADRs were skin-related disorders (41.8%), followed by body as a whole — general disorders (17.6%), gastrointestinal system disorders (8.2%).

Serious ADRs constituted 25.2% of the total reports. Serious skin-related ADRs reported included Stevens Johnson syndrome (25 reports) and toxic epidermal necrolysis (8 reports) which were mainly suspected to be associated with the use of NSAIDs, antibiotics or anti-convulsants.

Conclusion: Voluntary reporting of ADRs by health professionals is recognised as one of the important tools for monitoring the safety of marketed medicinal products. The spontaneous ADR reporting programme remains an important component of the post-marketing surveillance activities in enhancing the safe use of drugs and related health products in Singapore.

5. THE EFFECTIVENESS OF TARGETED RISK COMMUNICATION IN PROMOTING SPONTANEOUS ADVERSE DRUG REACTION REPORTS

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Objective: To investigate the effectiveness of HSA's communication on targeted drug-ADR concern through the local publication of *Adverse Drug Reaction News* bulletin, a thrice yearly publication for local healthcare professionals.

Methods: Two case studies were identified for this project: (1) doxycycline associated with oesophagitis (published in Mar 2004); (2) bisphosphonates and osteonecrosis of the jaw (published in Dec 2004). A search in the HSA ADR database was carried out to identify all reports associated with the drugs of interest and their associated ADRs highlighted. ADR reports received before and after the publication of the articles were analysed separately.

Results:

(1) "Doxycycline and oesophagitis" article was published in Mar 2004.

Prior to the publication, there were 4 reports of retrosternal pain suspected to be associated with doxycycline in the database. These reports were received in 1998 (1 report), 1999 (1) and 2002 (2). After the publication of the article in Mar 2004, 3 reports on doxycycline associated with oesophageal ulcer, retrosternal pain and doxycycline-induced oesophagitis were submitted within an 8-month period.

(2) "Bisphosphonates and osteonecrosis of the jaw" article was published in Dec 2004.

Prior to the publication, there were 2 reports received in 2004 suspected of jaw osteolysis with zoledronate and exostosis and aseptic bone necrosis with alendronate. After the publication in Dec 2004, 5 reports of osteonecrosis of the jaw were received (zoledronate = 3, alendronate = 1, pamidronate = 1) within a 4-month period. The reporting rate was increased by more than 2-fold.

Conclusions: The publication of specific safety concerns in the HSA *Adverse Drug Reaction News* bulletin has shown to be effective in promoting the reporting of specific drug-ADRs in Singapore.

6. RETROSPECTIVE ANALYSIS OF DRUG-INDUCED STEVENS JOHNSON SYNDROME (SJS) OR TOXIC EPIDERMAL NECROLYSIS (TEN)

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Objective: To examine reports of drug-induced SJS and TEN in Singapore as dermatological ADRs accounted for >40% of all adverse reactions reports received by the Pharmacovigilance Unit of the Health Sciences Authority in the past 5 years.

Methods: A search of the HSA ADR database was carried out to identify all reports of SJS and TEN from 1993 to 2004. In particular, we were interested in the types of suspected drugs implicated, time taken to develop the reactions, patient's profile and annual reporting rate of these reactions.

Results: Between 1993 and 2004, a total of 151 reports of SJS/TEN (120 SJS and 20 TEN cases) were identified. This comprised 2.28% of the total ADR reports received. The most common suspected drugs were carbamazepine (27 reports), cotrimoxazole (25), phenytoin (14), allopurinol (13) and amoxicillin (13). The average time taken to develop the reactions was 29 ± 61 days. Female patients were affected more (57.6%) than male (42.4%) patients and the average age reported was 48 ± 22 year-old (range 1–88). Chinese patients formed the highest group (56.3%), followed by Malays (16.6%) and Indians (9.9%). Fatal reports accounted for 15.2% of the total SJS/TEN reports and 45% of patients have not yet recovered from the ADRs when reports were submitted.

The annual local reporting rate for SJS/TEN from 1993 to 2004 ranged from 0.58% to 3.16%. Based on the reports received through the spontaneous ADR reporting programme, the estimated rates of SJS/TEN in Singapore are about 7–8 cases per million population per year for 2003 and 2004 compared to 2–4 cases per million population per year for 1993 and 1994.

Conclusions: Serious cutaneous adverse reactions namely SJS and TEN constitute about one-third of all serious ADR submitted to HSA. Preliminary data suggests a higher estimated incidence of SJS/TEN in Singapore compared reported rates in the literature. Further studies are needed to examine the reasons for this observed difference.

7. PREVENTION OF ADVERSE DRUG REACTIONS IN HOSPITALISED PATIENTS BY PHARMACIST PARTICIPATION AT A LARGE TEACHING HOSPITAL IN THAILAND

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Objectives: To determine whether clinical pharmacist participation could lead to the prevention of adverse drug reactions (ADRs) in hospitalised patients in a teaching hospital.

Methodology: Comparison of a 10 month baseline phase (with no pharmacist intervention) with the same period in which a pharmacist attended two general wards at Ramathibodi Hospital. Suspected and preventable ADRs were assessed by Roussel Ulcaf Causality Assessment (RUCAM)[1] and Schumock and Thornton criteria[2], respectively. The numbers of preventable ADRs were then compared between the intervention and baseline phases using SPSS version 11.0.

Results: A total of 1,548 (male 49.1%, age 51.6 ± 18.9 years) and 985 (male 52.2%, age 52.1 ± 18.9 years) patients were recruited to the baseline and intervention phases, respectively, there being no statistical difference between these phases in terms of gender and age. During the baseline phase, the rate of preventable ADRs was found to be 5.20 per 1,000 patient-days (95% confidence interval [CI], 5.60-4.80) compared with 1.72 per 1,000 patient-days (95% CI, 2.24-1.20) following pharmacist intervention, a difference of 70% ($p<0.001$). Clinical pharmacist intervention resulted in 143 recommendations. These included dosage modification (48.2%), avoidance of drug-drug interactions (18.9%), inappropriate medication for a disease (14.0%), the need for therapeutic drug monitoring (13.3%) and history of drug allergy (5.6%). Eighty percent of all clinical pharmacist recommendations were accepted and implemented by the medical care team.

Conclusion: Although a national ADR monitoring scheme was established in Thailand in 1984, few steps have been taken to actively prevent ADRs from occurring in hospital patients. Results of the present study indicate that the participation of a clinical pharmacist on hospital ward rounds markedly reduces the number of preventable ADRs from occurring.

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8. POST LICENSURE SAFETY SURVEILLANCE FOR PREVENAR®, A 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

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Prevenar® was approved for use in infants (2 months to 2 years old) to prevent invasive diseases caused by pneumococcus of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The French Drug Agency entrusted the Pharmacovigilance Regional Center of Tours with a pharmacovigilance monitoring to detect as early as possible, an eventual serious adverse effect not identified yet.

Two methods, an intensive monitoring based on systematic reporting and a pharmacovigilance survey based on spontaneous reporting have been used.

During the 19-month intensive monitoring period conducted by 13% of French office-based pediatricians, 32 cases of serious or unlisted adverse symptoms were collected. During the 3.5-year period of marketing, 153 spontaneous reports of serious or unlisted adverse effects

were registered in France. Incidence of serious reports was for the intensive monitoring 7/100 000 doses [4-10.5] and for the survey 4/10 000 doses [3-5]. High fever was the most frequently reported effect in the intensive monitoring (22%) and in the survey (12.4%). Febrile and non febrile seizures were the most frequently neurologic sign reported in both studies. Incidence of sudden infant death in the survey (0.09/100 000 doses [0.01-0.3]) is lower than expected in general population. Incidence of "seizures", "hypotonia-hyporesponsiveness", "erythema multiforme", "hypersensitivity type I" is lower than in the SPC. Injection site abscess or cellulitis, hypotonia, hypertonia, abnormal crying, and vasculitis, reported in our studies and in American data of postlicensure surveillance, are not mentioned in the SPC. The CI 95% of the frequency of occurrence of an adverse effect not observed yet over the 275 511 doses done in the intensive monitoring is [0.1, 1.10^{-5}], that means that only serious adverse effects occurring at a frequency over 1.1/100 000 have been detected.

No adverse effect which would trigger an alert has been detected. However, for practitioners information the French SPC of Prevenar® needs actualization.

9. POTENTIALLY LIFE-THREATENING LINGUAL ANGIOEDEMA DURING IMMUNOSUPPRESSIVE TREATMENT WITH EVEROLIMUS IN CARDIAC TRANSPLANT PATIENTS

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Objective: Everolimus is a proliferation signal inhibitor currently undergoing evaluation for combination therapy to prevent rejection after solid organ transplantation. It belongs to the class of mammalian target of rapamycin inhibitors. Everolimus has received approval for heart transplant recipients in several countries, including Germany.

Methodology: We have switched a total of 114 cardiac transplant recipients with chronic renal insufficiency due to calcineurin inhibitor therapy to everolimus at our center. Everolimus was given at doses of 1.5 mg/day to achieve serum concentrations of 3 to 8 ng/mL. The dosages of ciclosporin or tacrolimus were reduced by 50%.

Results: In 6 out of the 114 patients (5.3%) we observed the occurrence of lingual angioedema. Symptoms developed within the first weeks of treatment (range 2 to 41 days), duration was 3 to 4 days. Angioedema was accompanied by petechial bleeding and with lingual bullae at the lateral part of the tongue. Everolimus plasma concentrations were in the normal range when symptoms occurred. Concomitant medications consisted of aspirin, nystatin, pravastatin, magnesium, angiotensin-converting enzyme inhibitors or angiotensin-1 antagonists. There was a drop in red blood cell counts, while other laboratory parameters were not affected. A lack of C1-esterase inhibitor could be excluded in all patients. The reaction required hospitalization in all patients. They were treated with corticosteroids and H1-blockers. Moreover, aspirin treatment was terminated. Everolimus treatment was not terminated. ACE-inhibitor- or AT 1-antagonist treatment were also not terminated. Five patients were free of relapse under ongoing everolimus treatment (15 to 126 days), while in one patient two recurrent episodes occurred.

Conclusions: The potentially life-threatening condition of lingual angioedema should be considered a severe adverse drug reaction during therapy with everolimus in cardiac transplant recipients.

10. SAFETY OF STATINS: EFFECTS OF EZETIMIBE AND SIMVASTATIN ON COENZYME Q10 CONCENTRATIONS IN PLASMA — A RANDOMIZED TRIAL

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Objective: Statins (HMG-CoA reductase inhibitors) have been associated with a decrease in coenzyme Q10 (CoQ10) concentrations due to inhibition of the conversion of HMG-CoA to mevalonate, a CoQ10 precursor. Decreased CoQ10 levels have been associated with the muscular adverse drug reactions of statins. The cholesterol absorption inhibitor ezetimibe has been postulated to increase endogenous cholesterol synthesis. Its effect of CoQ10 levels is unknown. Purpose of the present study was to evaluate the effects of treatment with ezetimibe, simvastatin or their combination on the Q10 plasma levels of healthy men.

Methodology: Monocenter, randomized, parallel 3-group study using ezetimibe (10 mg/day), simvastatin (40mg/day) or their combination for 14 days in 72 healthy men.

Results: Baseline CoQ10 (0.97 ± 0.28 μg/mL, $P < 0.0001$, respectively). There was a correlation between the percent change in the levels of LDL cholesterol and the percent change in CoQ10 in all treatment groups ($R = 0.67$, $P < 0.0001$). While cholesterol synthesis decreased in the simvastatin group ($P = 0.37$), there was no change in the ezetimibe or in the combination group. The ratio of CoQ10 levels and LDL cholesterol was significantly increased in all treatment groups ($P < 0.0001$).

Conclusions: Simvastatin and the combination of simvastatin and ezetimibe significantly decreased plasma CoQ10 concentrations. There is a strong correlation between the CoQ10 decrease and the decrease in total- and LDL cholesterol levels in all three treatment groups, suggesting that the CoQ10 decrease reflects the decrease in the concentrations of its lipoprotein carriers and is not statin-specific.

11. SAFETY PROFILE OF PIMECROLIMUS CREAM USED IN GENERAL PRACTICE IN ENGLAND: INTERIM RESULTS OF AN ONGOING PRESCRIPTION-EVENT MONITORING STUDY

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Objective: Pimecrolimus, indicated for mild or moderate atopic der-

matitis (AD), is one of a new class of topical immunomodulators (TIMS) which acts by prevention of T cell activation via calcineurin inhibition. Our objective was to monitor the use and safety of topical pimecrolimus prescribed in primary care in England using Prescription-Event Monitoring (PEM).

Methodology: A post-marketing study using the observational cohort technique of PEM. Patients identified from dispensed prescriptions issued by general practitioners (GPs) from 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. Indication for use, drug effectiveness and reasons for stopping were also requested. Event Incidence Densities (IDs) [no. 1st reports/1000 patient-months of exposure] were calculated. IDs for month 1 (ID_1) and months 2–6 combined (ID_2) were compared for all events. A positive statistical difference at 99% confidence level was considered to indicate an association of that event with starting pimecrolimus.

Results: To date information available for 2509 patients, 58% female [median age 22 years (IQR 5-47), 3.6% aged<2 years]. 5% GPs reported off-label usage. 67% (876/1304) of GPs who opined reported pimecrolimus as effective. 16% (394) of cohort stopped due to lack of effect and 11% (266) due to condition improved. Clinical reasons for stopping were predominately skin related (skin burning/stinging), as were 9 events reported by the GP as ADRs. The only adverse event for which ID_1-ID_2 was statistically significant was pruritus. One case of skin neoplasm and one death from Mantle cell lymphoma reported.

Conclusions: This study is ongoing, and final analysis will include follow up of specific adverse events, pregnancies and deaths and stratification by disease severity, drug use and duration of treatment. At this stage, no previously unrecognised ADRs have been identified.

12. SAFETY PROFILE OF TACROLIMUS OINTMENT USED IN GENERAL PRACTICE IN ENGLAND: INTERIM RESULTS OF AN ONGOING PRESCRIPTION-EVENT MONITORING STUDY

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Objective: Topical tacrolimus, indicated for moderate to severe atopic dermatitis, is one of a new class of topical immunomodulators (TIMS) which act by prevention of T cell activation via calcineurin inhibition. Our objective was to monitor the use and safety of tacrolimus prescribed in primary care in England using Prescription-Event Monitoring (PEM).

Methodology: A post-marketing study using the observational cohort technique of PEM. Patients identified from dispensed prescriptions issued by general practitioners (GPs) from May 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. 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. A positive statistical difference at 99% confidence level was considered to indicate an association of that event with starting tacrolimus.

Results: To date information available for 2697 patients, 51% female [median age 30 years, (IQR 9-49), 1% aged<2 years]. 10% GPs reported off-label usage. 77% (1232/1602) of GPs who opined, reported tacrolimus as effective. 12% (326) of cohort stopped due to lack of effect and 8% (207) due to condition improved. Clinical reasons for stopping were predominately skin related (burning/stinging) as were the 25 events reported by GPs as ADRs. The only specified adverse event for which ID_1-ID_2 was statistically significant was pruritus. No skin cancers reported. One case of Hodgkin's disease after treatment.

Conclusions: The study is ongoing, and final analysis will include follow up of specific adverse events, pregnancies and deaths and stratification by disease severity, drug use and duration of treatment. At this stage, no previously unrecognised ADRs have been identified.

13. SAFETY PROFILE OF TIOTROPIUM USED IN GENERAL PRACTICE IN ENGLAND: RESULTS OF A PRESCRIPTION-EVENT MONITORING STUDY

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Objective: To monitor the safety of tiotropium prescribed in primary care in England using Prescription-Event Monitoring (PEM). Tiotropium bromide, a new once-daily long-acting specific muscarinic receptor antagonist, administered by inhalation for maintenance treatment of chronic obstructive pulmonary disease (COPD), binds to M_1 and M_3 receptors in bronchial smooth muscle resulting in relaxation.

Methodology: Post-marketing surveillance using an observational cohort technique, (PEM). Patients were identified from dispensed prescriptions issued August 2002 to August 2003 by General Practitioners. Questionnaires were sent to initial prescriber at least 6 months after first prescription was identified for each patient. Information on events, demographics, ADRs, reasons for stopping tiotropium, history of cardiovascular conditions, prior use of oral/iv steroids and/or hospital admission, concomitant use of long-acting β_2 agonists and/or inhaled anticholinergics was requested. Event Incidence Densities (IDs) [number of 1st reports/1000 patient-months of exposure] and differences between IDs in month 1 (ID_1) and months 2–6 (ID_2), were calculated. Results were stratified by history of cardiovascular conditions and by severity of condition, based on prior use of steroids and/or hospital admission.

Results: Cohort 13,891 patients; 55.4% male, median age both genders 70 years. Excluding indication related events, dry mouth was the most frequently reported adverse event in month 1 (ID_1 3.46). 118 events (92 patients) reported as ADRs to tiotropium including;

dyspnoea (10), malaise (10), dry mouth (8) and small numbers affecting face and mouth. 4155 patients (29.9%) were reported to have stopped tiotropium; most frequently reported reason was 'not effective' (2023; 14.6%). Clinical reasons for discontinuing tiotropium included intolerance (102; 0.7%), hospital referrals (85; 0.6%), admissions (75; 0.5%), dry mouth (74; 0.5%). Of 1017 (7.3%) deaths reported 316 were due to COPD, 64 to lung carcinoma; for 257 cause was not established.

Conclusion: No previously unrecognised ADRs have been identified. Based on this large cohort, tiotropium appears to be generally well tolerated.

14. A COMPARISON OF REPORTED THROMBOEMBOLIC EVENTS BETWEEN ROFECOXIB AND CELECOXIB USING OBSERVATIONAL DATA

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Objective: The withdrawal of rofecoxib due to increased risk of cardiovascular events raised concerns about the safety of celecoxib and other cyclooxygenase-2 (COX-2) inhibitors. Our objective was to compare the incidence of thromboembolic (TE) [cardiovascular, cerebrovascular and peripheral venous] events reported for patients prescribed rofecoxib or celecoxib in primary care.

Methodology: An observational cohort study was carried out using the technique of Prescription-Event Monitoring (PEM). Exposure data were derived from dispensed prescription written by primary care physicians in England, for rofecoxib (Jul–Nov 1999) and celecoxib (May 2000–Nov 2001). Outcome data were clinical events and information on potential risk factors, reported on simple questionnaires (posted to prescribers at least 6 months after the date of 1st prescription), that occurred within 270 days of starting treatment. Crude and adjusted rate ratios (RR) for the three TE event groups (cardiovascular, cerebrovascular and peripheral venous) were calculated using Poisson regression modeling.

Results: The rofecoxib and celecoxib PEM cohorts contained 15,268 and 17,458 patients, respectively. The RRs adjusted for age, sex and concomitant use of the combination of aspirin and/or antiplatelet/anticoagulants agents (one or other or both), for rofecoxib compared to celecoxib were: 1.04 (95% CI 0.50, 2.17) for cardiovascular TE events; 1.43 (95% CI 0.86, 2.38) for cerebrovascular TE events; 0.36 (95% CI 0.01, 1.34) for peripheral venous TE events.

Conclusions: No evidence of statistically significant difference between rofecoxib and celecoxib users was found, after adjusting for identified risk factors, for the three TE event groups. However, it should be borne in mind that we had information on a limited number of confounding variables for TE events. Further research is required to fully understand the risks and benefits of using celecoxib, meanwhile doctors should be cautious when prescribing these products, particularly to patients with risk factors for developing TE events.

15. INTERIM RESULTS FROM A MODIFIED EVENT MONITORING STUDY OF TRAVOPROST AS USED IN PRIMARY CARE IN ENGLAND

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Objective: To examine the safety of travoprost (used to treat open-angle glaucoma and ocular hypertension) and used in primary care in England, to better understand frequently and less commonly reported events.

Methodology: Travoprost is associated with adverse effects of iris pigmentation, abnormal eyelash and eyelid hair growth. This is an observational cohort study using a modified event monitoring technique focusing on the adverse effect of iris discolouration. Primary care physicians (GPs) of patients identified from dispensed National Health Service prescription data received an eligibility and then if appropriate a 12-month questionnaire. Requested data included: events experienced by patients since commencing travoprost; any reason for stopping travoprost; and the occurrence of iris discolouration. Incidence densities (IDs) [first reports of event/1000 patient-months of exposure] were calculated; differences between months 1 to 3 and later 3-month periods of therapy were examined for significant event rate change over time.

Results: Of 17,531 eligibility questionnaires sent, 7245 (41.3%) were returned. Of these, 3810 (52.6%) patients were eligible for inclusion. To date, 1505 12-month questionnaires have been sent with 1202 (79.9%) returned – valid information is available for 978 patients. Eight events were reported as ADRs by GPs in 8 patients; sore eye (4), allergy (2), conjunctivitis (1) and eye irritation (1). Of 144 reported reasons for stopping travoprost, the most frequent were; 'not effective' (55) and ophthalmic surgery (17). No significant results were obtained from the ID analyses. There were single reports of abnormal eyelash growth, eyelid hair growth and periocular skin discolouration but not iris discolouration.

Conclusions: No adverse events recognized as ADRs to travoprost occurred at a frequency during treatment above those given in the SmPC for travoprost. No signals of serious adverse events were identified from ID analyses. These interim results and any conclusions drawn may change as the study progresses.

16. CHARACTERISTICS OF TRADITIONAL CHINESE HERBAL MEDICINE RETAIL OUTLETS IN LONDON: PRELIMINARY RESULTS OF A CROSS-SECTIONAL STUDY

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Objective: In the UK, unlicensed Traditional Chinese Herbal Medicines (TCHMs) are widely available for purchase from TCHM retail outlets. Several recent safety concerns have been associated with TCHMs purchased from such outlets. This study explored the char-

acteristics of TCHM outlets in London, including medical uses/conditions for which they promote use of TCHMs.

Methods: A semi-structured questionnaire was developed to record features and information visible inside and outside TCHM outlets. All possible TCHM outlets within the W1 postcode area in London were identified via Yellow Pages on-line directory. After a screening procedure, 12 (7%) outlets were classified as TCHM retail outlets. Data were collected for the 'outside' of 12 outlets, and 'inside' observations were done for the 4 outlets consenting to this. Data were input, stored and analysed using MS Access, MS Excel and SPSS 12.

Results: Overall, 11 (92%) outlets displayed manufactured TCHMs, and 9 (75%) displayed Chinese crude herbs. Eight (67%) outlets listed medical uses/conditions visible outside the shop; the median number listed was 25.5 (Q_L = 16.25, Q_U = 59.5). In total, there were 274 occurrences of 137 different terms for uses/conditions; each term was counted once only for each shop and, when categorised in therapeutic areas according to British National Formulary (Number 49) chapter, the most frequent therapeutic categories were Central Nervous System (n = 53/274; 19.3%), Obstetrics, Gynaecology and Urinary-tract (14.2%) and Skin (13.5%) disorders. Other uses/conditions listed of particular interest included cancer, diabetes, HIV infection and contraception. In 11 shops, 38 (49%) of TCHM-related advertisements were associated with specific uses/conditions, most commonly skin problems, weight loss and hair loss.

Conclusion: TCHM outlets in London readily display names of serious medical conditions on their premises, visible to the passing public, which may give the impression that TCHMs can be used to prevent, treat or cure these conditions.

17. PREVALENCE AND PREVENTABILITY OF ADVERSE DRUG EVENTS IN HOSPITAL: IN A TRANSVERSAL ANALYSIS

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Introduction: Defining the incidence of adverse drug events laid the groundwork for policy discussions on patient safety in several countries. It has been shown that adverse drug events (ADEs) are more common in hospitalized patients. Thus, in view of the lack of consistent local data in this concern, we assessed the rate prevalence of ADE and preventable ADE (pADE) in a general teaching hospital of Rabat with 1045 beds capacity.

Methods: We performed a transversal study during 5 days in departments in which patients were hospitalized for less or more than 24 hours. The whole targeted population was surveyed during the study period. Patients experiencing ADE were identified by soliciting daily informations near practitioners in the 27 services.

Results: Among the 1390 inpatients surveyed, 59 experienced at least one ADE, corresponding to the rate prevalence of 4.4 (CI 95%: 3.2% - 5.2%). 76 ADE were observed in these 59 patients with a global prevalence of 5.5 (CI 95%: 4.7% - 7.1%). 10 ADE (13.2%) were categorized as preventable and 60% of them happened at the stage of monitoring. 28 patients exhibited serious ADE. The rate prevalence of ADE that caused admission or prolongation of hospitalization was 1.4% (95% CI: 0.78% - 2.02 %). By comparing the ADE group with the whole population surveyed during the study period, it seems that: women were more concerned, and age under 30 years was significantly associated to ADE occurrence. The rate of ADE was high in medical services compared with other departments.

Conclusion: These collected data provided some elements of response to our request. However, a long period of survey is needed to define prevention strategies to improve medication systems.

18. THE ROLE OF THE ADVISORY COMMITTEE ON CAUSALITY ASSESSMENT IN VACCINE SAFETY

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Objective: The Advisory Committee on Causality Assessment (ACCA) started in 1994 to perform causality assessment for selected serious adverse events.

The object is to describe the results of the assessments done for the period July to May 2005.

Methods: Using a SAS program, reports are selected for a possible review. After an internal review, when the case is selected, further information is requested. On receipt is presented to the committee. The WHO causality criteria are used. One member of the committee presents the case and the assignment is made by consensus. Should the committee not agree with the type of adverse event, it can change it and decide to review or not.

Results: During the period July 1, 2004–May 1, 2005, 212 reports were selected. On an internal review, 51 (24%) reports were deemed not to be fitting the ACCA criteria. Follow up information was not received for 96 (45%) reports. Sixty-five (30%) reports were presented to ACCA, of which 63 were assessed. Two were assigned to the next teleconference.

Forty four reports were on a single vaccine. Influenza was the most common single vaccine (n=22; 35%). The most common adverse event was Guillain-Barré Syndrome (GBS) (n=12). The committee changed three of these. Of the remaining nine GBS cases, four followed single flu vaccine. The assessment was one of: possible, probable, unlikely, and one as insufficient data. One other possible case for GBS followed Td, Flu, and IPV vaccination, while another possible GBS followed DaPT- Hib.

Conclusions: The ACCA committee is fulfilling its mandate and provides assurance of continued safety of Canadian vaccines.

The possible causal relationship between flu and GBS was based on

the causal relationship between Swine flu and GBS, but noted that, to date, the influenza vaccine is not accepted as a cause of GBS.

19. AN EXPLORATORY STUDY ON THE NEUROMUSCULAR JUNCTION ACTIVITY OF *CESTRUM NOCTURNUM* EXTRACT IN AN IN VIVO CAT MODEL

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Background: Muscle relaxants are an irreplaceable item within the modern surgical toolkit. Their almost universal use during surgical procedures of medium-to-long duration means that it is essential that all anesthesiologist must have a comprehensive knowledge of their history and the future prospects for their continued evolution. There are a number of naturally occurring acetylcholinesterase and buterylcholinesterase inhibitors, including the solanaceous glycoalkaloids (SGAs), which are found in plants of the family Solanaceae. In the Pharmacopeia of Philippines indigenous plants, one such plant is *Cestrum nocturnum* (Dama de Noche).

Objective: This animal study was therefore undertaken to determine the neuromuscular effect of intravenously administered *Cestrum nocturnum* to an anesthesized cat.

Methods: An N or 1 *in vivo* study was undertaken comparing the effect of *Cestrum nocturnum* and atracurium on the neuromuscular junction of an anesthesized cat.

Results: SGA prolonged the time needed for recovery from atracurium induced paralysis.

Conclusion: In light of these findings, we infer that *Cestrum nocturnum* exhibits depolarizing neuromuscular blocking properties and pharmacokinetic and pharmacodynamic (additive effect) with atracurium and neostigmine.

20. TRANSPARENCY IN PHARMACOVIGILANCE

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Objective: Transparency is a new keyword in pharmacovigilance, but little experience in practice is present up to now. We would like to share our experiences with a general accessible adverse drug reactions (ADR)-database and knowledge-websystem provided through the Internet (www.lareb.nl).

Methodology: Since January 2005 the renewed website of the Netherlands Pharmacovigilance Centre is in place. The experiences in the first half year will be demonstrated. Some thoughts will be given about the future contribution transparency can give to a more patient orientated pharmacovigilance.

Results: In the first three months over 50,000 persons consulted the new website, visiting more than half a million pages. 3000 persons registered for the e-newsletter.

The website provides information about pharmacovigilance news items, information about frequent reported ADRs, published articles and new signals. All these items were frequently visited.

The complete Dutch databank of ADRs is online available and was visited 7500 times in the first three months. About 33% of the reports to Lareb were received via the website and directly imported in our database.

In the presentation information and thoughts will be given about the impact of the new website on Lareb, not only on the number of (electronic) reports and phone calls, but also on the involvement of patients in pharmacovigilance.

Conclusion: A complete transparent way of working in pharmacovigilance does not lead to an overload of work. It supports health care professionals in their daily work and is appreciated by them. It also enables an active involvement of patients in their responsibility for balanced risk in drug use.

21. INFLUENCE OF BACKGROUND NOISE ON STATISTICAL MEASURES IN SIGNAL DETECTION

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Objective: The statistical approach has become an important tool for the detection and initial evaluation of possible signals in pharmacovigilance. Like the classical case by case approach, the outcome may be influenced by various types of bias. Symptoms resembling a possible adverse drug reaction (ADR) may lead to misclassification which influences the results of the outcome of the calculations. Alterations in the background noise, like epidemics of infectious diseases or seasonal influences, give rise to non-differential bias. It causes a change in reporting of ADRs for all suspected drugs, but not selectively to reports on a specific combination of a drug and ADR. The aim of this study was to investigate the influence of a change in background incidence of symptoms resembling ADRs on the various statistical measures currently applied in pharmacovigilance.

Methods: In a computer model we artificially changed the background incidence of symptoms ranging from 0.01 till 10 times the reported number of adverse reactions. We studied the alteration in point estimate and its corresponding 95% confidence interval of the Reporting Odds Ratio (ROR), the PRR, Yules'Q and the Information Component.

Results: As can also be shown mathematically, the ROR and Yules'Q do not change in the event the background noise is altered. Although the PRR is not influenced by a non-differential change in the number of reported drugs it shows, together with the IC, slight alterations when background noise is changed. For all measures, alterations of the 95% confidence interval were noted.

Conclusion: In the event a non-differential change in the background incidence of symptoms resembling specific ADRs occur, the reporting Odds Ratio and Yules'Q remain unchanged, reflecting the point estimates in the general population more closely. The findings

of this study may contribute in making a choice for a certain point estimate in statistical signal detection.

22. REPORTS OF HYPERKALEMIA AFTER PUBLICATION OF RALES — A PHARMACOVIGILANCE STUDY

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Objective: A population-based study and other reports have indicated that the publication of Randomized Aldactone Evaluation Study (RALES) was associated with a sharp increase in hyperkalemia-associated morbidity/mortality as well as broader use of spironolactone in treatment of heart failure. Computational signal detection algorithms, also known as data mining algorithms (DMAs), are currently mainly being applied to spontaneous reporting system (SRS) databases, which are not population based, as part of a multidisciplinary approach to drug safety, in hopes of obtaining early warnings/additional insights into post-licensure safety data. We applied one such DMA to a SRS database to determine if this tool would have provided an earlier indication of the same safety issue reported from aforementioned population-based study.

Methodology: An empirical DMA (i.e. multi-item gamma Poisson shrinker [MGPS]) was applied to US FDA SRS database using a commonly cited threshold. Year-by-year analysis and analysis of increasing cumulative time intervals were performed on cases of spironolactone/angiotensin-converting enzyme (ACE) inhibitor-hyperkalemia.

Results: Initial analysis with spironolactone failed to provide a compelling signal of disproportionate reporting (SDR) of increased hyperkalemia after publication of the RALES study. However, supplementary analysis using ACE inhibitors identified SDRs with two ACE inhibitors (perindopril, ramipril) in advance of population-based time series analysis and after publication of RALES.

Conclusions: One well-described DMA failed to provide a signal of increased hyperkalemia after publication of RALES upon initial analysis possibly due to large and persistent disproportionate reporting of hyperkalemia with spironolactone, masking any post-RALES changes. However, using a supplemental and less intuitive/obvious analysis, SDRs for increased hyperkalemia post-RALES were identified. The quality and usefulness of data mining analysis is highly dependent on the knowledge and experience of the "prepared mind" of the drug safety expert.

23. POTENTIAL USE OF DATA MINING ALGORITHMS FOR THE DETECTION OF "SURPRISE" ADVERSE DRUG REACTIONS

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Objective: The objective of this paper was to examine our anecdotal observations with regard to "surprise reactions" in more systematic fashion. Formally, the question is whether these "surprise reactions" (e.g. carbamazepine-hypertension), often first reported in the literature, represent a type of adverse event (AE) most amenable to detection with the assistance of adjunctive statistical calculations on SRS data. Our hypothesis is that data mining algorithms (DMAs) could be of help in this circumstance.

Methodology: Using commonly cited thresholds, multi-gamma Poisson shrinker (MGPS) and proportionate reporting ratios (PRRs) were applied to reports in FDA Adverse Events Database (AERS) that were associated with a set of well documented "surprise reactions" compiled by the authors.

Results: There were 30 surprise reactions that were reviewed, twenty-eight of which were cited in literature, and two that never generated any reports in AERS. Using proportional reporting ratios (PRR>2, χ^2>4, N>2), 10 drug event combinations (DECs) signaled before first year of literature reporting, two concurrently, and twelve after. With EBGM (EBGM>2, N>0), eleven occurred before, three concurrently, and eleven after. With EB05 (EB05>2, N>0), eight occurred before, three concurrently, and nine after.

Conclusions: Identification of surprise reactions may serve as an important niche for DMAs. These adverse events are more likely to be discounted in manual review of AE lists because they are less "clinically dramatic", are less characteristic and less serious than the classical Type B hypersensitivity adverse reactions and may have subtle pharmacological explanations. DMAs may identify in this circumstance what the human mind is likely to overlook. The findings also emphasize the importance of a holistic approach to signal detection using a comprehensive suite of signal detection strategies including the importance of focused reviews of the published literature as a source of early "signals" since DMAs were not always successful in identifying these associations.

24. A NEW TAXOMONY OF ADVERSE DRUG REACTIONS INSPIRED BY AUTOMATED SIGNAL DETECTION

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Objective: Pharmacovigilance employs multiple techniques, tools, and datasets to detect new adverse events. Central to these activities is the need to assess individual reports. Traditionally, adverse events have been generally categorized by pathomechanism, severity or by body system for this purpose. These approaches may have some limitations. Our objective was to develop a new taxonomy that provides a conceptual framework to determine applicability and assess performance of automated and non automated pharmacovigilance tools in naturalistic settings.

Methodology: Based on the authors experience and expertise the authors considered various categories. A principle factor in formulation of the taxonomy was the relative error cost of misclassification of the event, the potential for the event to have a subtle pharmacological explanation, and the potential for discounting it as a drug-related effect.

Results: The eight categories developed include designated medical events (DMEs), commonly reported potentially drug-induced events, events due to a primary extension of the therapeutic action of the drug, indication-related events, events that are difficult to distinguish from an underlying age-related or comorbidity-related disorder, paradoxical reactions, withdrawal reactions, and "surprise reactions."

Conclusions: For signal detection, a new taxonomy for AEs was developed for performance assessment of everyday pharmacovigilance tools. Seven of the eight categories are readily apparent. The eighth one, surprise reactions, are rarely reported, often of intermediate seriousness, not typical of adverse drug reactions in general, do not have the classical hallmarks of "idiosyncratic" adverse drug reactions, and are not obviously explainable based on the primary pharmacological activity of the drug. These associations are "surprising" since the individual reports are often well documented and because they could be easily overlooked or discounted based on manual review of AE lists.

25. SPONTANEOUS REPORTS OF ASTHMA-RELATED ADVERSE EVENTS WITH ACETAMINOPHEN: RESULTS OF A DISPROPORTIONALITY ANALYSIS

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Objective: A possible association between acetaminophen and asthma has been suggested. This has occurred mainly in the context of case reports and observational studies; various mechanistic frameworks have been postulated. Our objective was to determine if the statistical calculations from a disproportionality analysis significantly illuminated the initial signals based on the clinical data in the case reports.

Methodology: Two forms of disproportionality analysis (proportional reporting ratios [PRRs] and the multi-item gamma Poisson shrinker [MGPS] using commonly cited thresholds were applied to the FDA AERS database. Events specific to asthma and more generally to bronchospasm and acetaminophen-containing products were selected.

Results: There were 73 separate drug listings for suspect drugs where acetaminophen was listed alone or in combination with other products. Despite the presence of up to 47 reports of asthma/individual drug (i.e. acetaminophen), the selected statistical thresholds were not exceeded for 71 of the 73 listed suspect drug preparations/combinations for asthma-specific events. Only two drug preparations exceeded the selected thresholds and thresholds were exceeded with both analyses. Two drug(s) exceeded statistical thresholds for PRR only when more general event terms (e.g. wheezing) were examined.

Conclusions: The numerical information using a very specific case definition did not significantly strengthen the potential "signal" that may have existed based on case reports and epidemiological investigations. This is not to say that the relevant event is not drug related only that the original hypothesis based on the index clinical and epidemiological data doesn't seem to be substantially enhanced by these numerical calculations. SRS data represent convenience samples without a clear probability structure and as such cannot be used for risk calculations or qualitative or quantitative inter-drug risk comparisons. This may be especially pertinent for a drug that is in so many over-the-counter combination medicinal products. Other limitations will be presented.

26. ADR 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) and hypertension. The aim of our study is to evaluate the frequency of hypertension and gingival hyperplasia induced by cyclosporine A in renal transplant patients.

Material and methods: We led a retrospective study on cyclosporine A induced hypertension disease and gingival hyperplasia 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 and gingival hyperplasia post transplanting.

Results: We have included 20 cases in our series, aged 23 to 50 years old. Our patients were treated by triple immunosuppressive therapy (cyclosporine, corticosteroid and anti-proliferate).

The incidence of patient presenting gingival hyperplasia post cyclosporine was 15%. Dose of cyclosporine varied 275mg/day to 400mg/day. Cyclosporine blood level varied 800 to 1398ng/ml. Gingival hyperplasia occurred between 57 days to 48 months.

The incidence of hypertension post cyclosporine was 40%. Dose of cyclosporine varied 275mg/day to 300mg/day. Systolic pressure varied 170 mm Hg to 220 mm Hg occurred on the average of 4 days. Cyclosporine assay varied 500 to 1000ng/ml.

Conclusion: Hypertension and gingival overgrowth were the principal adverse effect of cyclosporine. This may be severe, appear to be dose related; monitoring is the main method to prevent ADR induced by cyclosporine in renal transplant.

27. SELF-MEDICATION AMONG FIRST-YEAR MEDICAL STUDENTS: A QUESTIONNAIRE BASED STUDY

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Objective: To determine the knowledge, attitude and practice of

self-medication among first-year medical students of Arabian Gulf University, Bahrain.

Methodology: This was an anonymous, questionnaire-based, descriptive study. A pre-validated questionnaire, containing open-ended and close-ended questions, was administered to the subjects. Data were analyzed using SPSS version 12 and the results expressed as counts and percentages.

Results: Out of the 134 respondents, 43 (32.1%) were males and 91 (67.9%) were females. The mean age in years ± SD was 18.01 ± 0.78. Knowledge about appropriate self-medication was poor but knowledge of the benefits and risks of self-medication was adequate. The respondents found self-medication to be time-saving, economical, convenient, and providing quick relief in common illnesses. Important disadvantages of self-medication mentioned were the risk of making a wrong diagnosis, wrong drug use and adverse effects of drugs. Majority (76.9%) of the respondents had a positive attitude favouring self-medication. Self-medication was practiced by 44.8% of the subjects. The most common indications for self-medication were to relieve the symptoms of headache (70.9%), cough, cold and sore throat (53.7%), stomach-ache (32.8%), and fever (29.9%). Analgesics (81.3%) were the most common drugs used for self-medication. The practice of self-medication was appropriate in only 14.2% of cases.

Conclusion: Knowledge about appropriate self-medication was poor, attitude towards self-medication was positive, and practice of self-medication was common and often inappropriate.

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

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Objective: To explore and describe the current practices of national pharmacovigilance centres (NPCs) with regard to spontaneous reporting of ADRs associated with herbal medicines.

Method: A structured questionnaire for data collection was designed and developed. The final sampling frame comprised the NPCs of 71 official and 13 associate member countries of the WHO Uppsala Monitoring Centre (UMC) programme. Seven follow-up mailings were sent to non-responders at 4-week intervals after the initial mailing. Data were entered into Microsoft Excel version 10 for storage and analysed using SPSS version 13. Preliminary results have been presented previously.[1]

Results: Responses from 62 countries (74%) were received. In total, 54 (87%) respondents accept spontaneous ADR reports for herbal medicines. Of these, 17 (31%) specifically encourage certain reporter groups to report suspected ADRs associated with herbal medicines and 2 (4%) said they have a separate spontaneous ADR reporting form for herbal medicines. In response to statements regarding herbal ADR reporting, 61% of respondents agreed/strongly agreed that their current ADR reporting form needs modifying in order to effectively collect data on suspected herbal ADRs, 27% agreed/strongly agreed that there should be a separate ADR reporting form for herbal medicines, and 61% disagreed/strongly disagreed with the statement that there should be a separate ADR reporting scheme for herbal medicines. Of the 59 spontaneous ADR reporting forms and 45 sets of guidelines obtained, 5 (8%) forms and 14 (31%) guidelines specifically mentioned the term herbal medicines.

Conclusion: Current practices of NPCs for spontaneous reporting of ADRs associated with herbal medicines vary. Few NPCs undertake activities specifically to encourage reporting of suspected ADRs associated with herbal medicines. However, there is support from NPCs for modifying existing spontaneous ADR reporting forms to improve the collection of information on herbal medicines.

Reference

1. Barnes J, Aggarwal AM. Spontaneous reporting of ADRs associated with herbal medicines: a cross-sectional survey of national pharmacovigilance centres [abstract]. ISoP 2004. Drug Saf 2004; 27 (12): 917

29. INVESTIGATING ADVERSE EFFECTS OF CHINESE HERBAL MEDICINE

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There has been a considerable increase in the use of Chinese and other herbal medicines in the UK. These are often considered natural and therefore safe, but adverse effects are regularly reported in the literature. The traditional medicines project at the Medical Toxicology Unit investigates suspected adverse effects of Chinese herbal medicines (CHM) and identifies safety concerns.

Enquiries are taken from healthcare professionals in the UK who suspect a patient has suffered an adverse effect from using CHM. As well as details of medical history and time course, case investigation includes botanical identification of the herbs, review of the prescription and reasons for use of CHM.

As these are spontaneous enquiries, the incidence of adverse effects cannot be estimated. Relatively minor effects included nausea, abdominal pain and diarrhoea. Serious effects included cardiac, hepatic and renal damage. It was not possible to identify the causative herb(s) in all cases. Toxicity was also caused by the inclusion of synthetic and other non-herbal ingredients such as fenfluramine, tadalafil, corticosteroids and heavy metals.

Investigating suspected adverse effects is difficult owing to the use of complex herbal formulae in CHM. In China there is considerable experience of safely using CHM, however use of the herbs has spread to many other countries without this knowledge This may lead to identification of previously unreported effects due to differences in practice (eg dose, herb combinations) and patient genetics, susceptibilities, lifestyle and diet. Health professionals rarely have the expertise or resources to fully investigate suspected herbal adverse effects

and they have little understanding of issues such as botanical identification or nomenclature leading to inadequate reports. Improved reporting and investigation of such effects associated with CHM and other herbal medicines is needed to ensure accurate reporting and to address the safety concerns of healthcare professionals and patients.

30. SUCCESS FACTORS FOR REGISTRY STUDIES IN RISK MANAGEMENT PROGRAMMES

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Background: Registries (product-or disease registries) play an increasing important role in late phase development and risk management programs of medicinal compounds. These programs can be complicated in nature and management.

Objectives: This study was undertaken to investigate the success factors and limitations of registry studies with the objective to determine recommendations for successful registry studies for all involved parties.

Methods: A literature review was undertaken in Pub Med. 160 articles were identified on various published registry studies. Strengths and limitations were subtracted and translated in recommendations for successful registry studies.

Results: Registry studies are used to: increase awareness and burden of disease or condition; highlight the deficiencies of current treatments; show the potential impact of products on disease prevalence, incidence, progression and outcomes; develop relationships with community-based physicians and cultivate support from key opinion leaders; obtain competitive intelligence; establish sponsor reputation as a therapeutic leader and/or commitment to franchise development; demonstrate commitment to product risk management strategy.

Registry designs can meet both clinical and marketing objectives; always let science lead; early planning and continuing flexibility are key; start planning registry outputs during the design phase and be creative; the best registries evolve over time.

Conclusions: Successful and less successful registries have been initiated. In order to be successful the following recommendations can be made: brand the registry; issue initial and ongoing press releases; establish a registry steering committee at inception; identify ongoing and ad hoc analyses; determine likely forums for results; build key relationships; integrate other peri-approval activities like Phase IIIB/IV studies; reimbursement strategy; market research activities; incorporate a disease screening tool; host investigator meetings and provide bench marketing reports.

31. ISOLATED SYSTOLIC HYPERTENSION IN DIABETES MELLITUS: RISK FACTORS AND ANTIHYPERTENSIVE PRESCRIBING PATTERN IN PRIMARY CARE

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Objective: To determine the prevalence of isolated systolic hypertension (ISH) in diabetes mellitus, and to evaluate antihypertensive drug prescribing pattern by primary care physicians.

Design and Methods: Retrospective review of medical record charts from 15 primary care health centers in Bahrain during 2002. ISH was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure <90 mm Hg.

Results: In a cohort of 768 patients with hypertension, 13% (n=100; 28 male and 72 female) had ISH and diabetes mellitus. The mean systolic blood pressure was 156±16 mm Hg, diastolic blood pressure 79±4 mm Hg and pulse pressure 76.2±16.4 mm Hg. Mean age of the group was 62.6±16.4 years with a body mass index 29.8±6.7 kg/m^2 and a waist : hip ratio 0.99. The relevant laboratory findings included fasting blood glucose 10.8±3.8 mmol/L, glycated hemoglobin 9.2±2.2%, total cholesterol 5.8±1.1 mmol/L, triglycerides 1.73±0.8 mmol/L and creatinine 72.6±19.8 µmol/L. Mono- and combination drug therapy was prescribed in 54% and 44% respectively, and in 2% of patients, nonpharmacological measures alone were used. In terms of overall drug utilization (as monotherapy and combination therapy) antihypertensives prescribed were angiotensin converting enzyme inhibitors (51%), beta blockers (41%), diuretics (31%), calcium channel blockers (29%) and others (5%). Similar prescribing pattern was also observed with monotherapy.

Conclusions: Patients with ISH and diabetes did not achieve optimal blood pressure control in primary care setting. Risk factors should be considered while prescribing antihypertensive drugs to patients with ISH and diabetes mellitus.

32. HEALTH PROFESSIONAL USERS OF A REGIONAL PHARMACOVIGILANCE CENTRE: TRENDS OVER TIME

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Objective: To describe health professionals (users) contacting the Bordeaux pharmacovigilance centre and to assess temporal trends.

Methods: The Bordeaux pharmacovigilance centre has in charge a region including 5 million inhabitants. Users were defined as health professionals having contacted the centre at least once for a question or to report an adverse drug reaction during the period 2000 to 2004. The internal database of the pharmacovigilance centre was used. Variables analysed are sex, profession, geographic localisation, type of exercise, number of questions and number of reports, etc. Analysis was performed with the software SPSS and Excel.

Results: General practitioners (28.7% of users) and specialists (53.4%) represented the greater part of the 2758 users of the centre; pharmacists, dentists, nurses and midwives represented together 17.2% of the users. Among the users, 46.4 % were in community practice settings, 26.1% worked in the Bordeaux university hospitals whereas 15.8% worked in non-academic hospitals. Most users (60%)

were from the urban area of Bordeaux. During the first semester of 2000, the difference between entrance/exit was positive of more than 200 users. However, in the last semester of 2004, this difference was negative by more than 200 users.

Conclusion: Users are not representative of health professionals in the region. User distribution reveals "active profiles" (general practitioner in community settings, specialist in hospital…) and "inactive profiles" (nurse in clinic, doctor or pharmacist in pharmaceutical firm…) among other users. A semi-annual analysis of user entrance/exit during the study period shows a decrease of the absolute number of users. This is worrying for the centre's activity, particularly in the long term.

33. SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND WITHDRAWAL SYNDROME: A CASE/NON CASE STUDY

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Objective: The selective serotonin reuptake inhibitors (SSRIs) are associated with withdrawal reactions. The objective is to evaluate the risk of an association between reports of withdrawal syndromes with the SSRIs in a spontaneous report database.

Methods: The study used data from the French Pharmacovigilance database of case reports until February 2005 inclusive. This database includes all adverse drug reactions reported to the French National Pharmacovigilance system by health professional. All reactions are coded according to the WHO ART dictionary. Cases are reports of reactions of interest (withdrawal syndrome). Non-cases are all reports of reactions other than those being studied. The odds ratio (OR) is the ratio of the odds of the association of reports of withdrawal syndrome with SSRIs in cases and non cases.

Results: A total of 121 suspected cases of SSRIs-induced withdrawal syndrome had been notified. SSRIs are clearly associated with a higher risk of withdrawal syndrome (OR = 6.16, 95%: CI: 5.01-7.36). This risk is major for venlafaxine and paroxetine (OR = 11.78, 95%: CI: 7.75-17.78 and OR = 9.07, 95%: CI: 6.75-12.15, respectively). Sixteen cases were neonatal withdrawal syndrome, six with paroxetine.

Conclusion: The risk of withdrawal syndrome appears to be greater with short half-life drugs such as paroxetine and venlafaxine. Practician's information should be more developed on that risk.

34. METHYLPHENIDATE USE IN CHILDREN AND ADOLESCENTS IN FRANCE

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Methylphenidate is the only one psychostimulant approved in France in Attention Deficit Hyperactivity Disorder (ADHD) for children over six, since July 1995. ADHD is a childhood disorder characterised by inattention, inappropriate impulsivity and hyperactivity. Recently, the use of methylphenidate in children was increased. Medication doesn't cure ADHD, it only controls symptoms on the day they are taken.

Objectives: Describe the pattern of methylphenidate prescribed to French children.

Methods: In France, prescription and distribution of methylphenidate are restricted, with initial hospital prescription each year. Neurologists, psychiatrics and paediatricians are allowed to prescribe methylphenidate ("narcotics" schedule). The study used data from French Pharmacovigilance Database of adverse drug reactions spontaneously reported by health professionals from 1985 until may 2005.

Results: Forty adverse events were reported with methylphenidate of which four in adults. Among the eleven serious cases, nine occurred in children (four convulsions). The more frequent adverse reaction were neurological psychiatrics (n=16) and cutaneous reactions (n=10). Two growth suppressions were observed. Only one thrombopenia was notified. The number of children treated by methylphenidate in France is estimated at 8000 children.

Conclusion: Our findings suggest that the prevalence of growth-suppressive effects of methylphenidate are unknown. Effects on growth with methylphenidate are discussed in contradictory studies. Until more information is available concerning the long term effects of methylphenidate and in order to limit misuse, the current dispensation and dispensing regulation must be maintained in France.

35. PRE-EMPTIVE, TIME CONTINGENT PARECOXIB VERSUS KETOROLAC FOR POSTOPERATIVE PAIN RELIEF IN PATIENTS FOR GYNECOLOGIC OPERATIONS

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This study was designed to determine if pre-emptive, per-incisional doses of parecoxib sodium 40 mg IV given in time-contingent manner (every 12 hours) can prevent postoperative pain in gynecologic patients for lower abdominal surgery as compared to the non specific anti inflammatory drug, ketorolac given in the same manner.

Methodology: Study population consisted of 40 gynecologic patients, ASA 1-2, 18-65 years old. Patients were assigned by block randomization to either group 1 (parecoxib) or group 2 (ketorolac) given pre-emptive, 45 minutes prior to surgery. Efficacy analyses assessed the drug to prevent postoperative pain. Analgesic efficacy was based on four key points: 1) the proportion of patients who require rescue medication with VAS ≥3; 2) the median time to rescue medication; 3) pain intensity; and 4) the patients' global assessment of the test medication.

Result: Overall statistical analysis showed that 40 mg IV parecoxib sodium is more effective as compared to the 30 mg IV ketorolac sodium. The time to rescue medication at VAS ≥ 3 is earlier in the ketorolac group than parecoxib group. Sufficient evidence showed a higher pain scores in the ketorolac group than in the parecoxib group.

In both groups, the global assessment ratings showed no statistical difference.

Conclusion: Pre-emptive administration of parecoxib sodium 40 mg IV, given twice daily in time contingent manner in gynecologic operations is more effective in providing analgesia and symptom-control as compared to ketorolac given four times daily and with an improve side effect profile.

36. SAFETY OF ANTI-MALARIALS

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Let us not be mistaken, falciparum malaria is not a deadly disease like some other infectious diseases such as occasional epidemics of Lassa fever with a case-fatality rate of up to 50%, clinical tuberculosis with a cumulative all-cause mortality rate in 14 months of up to 28% or SARS for which an average case fatality rate of 15% was reported. Of course, the burden of disease caused by malaria is vast. Recently estimates of 500 million new infections per year were published. Some 1 to 2 million of these patients die, which means that the fatality rate of falciparum malaria is approximately 0.2–0.4%. In consequence, for anti-malarials the requirements of safety have to be high and it must be proven that the drug's benefits outweigh its risks.

The malaria parasite is increasingly resistant to many agents and this poses serious problems. Recently the combination of chlorproguanil and dapsone (Lapdap) has been licensed in the UK. It still has efficacy against parasites that are no longer sensitive for sulphadoxine-pyrimethamine and Lapdap is now used in sub-Saharan Africa. However, it has been questioned if the risks associated with dapsone use in areas with a high prevalence of G6PD deficiency are acceptable. This debate has made one thing certain and that is that there exists an urgent need to establish in these countries rigorous pharmacovigilance programmes.

37. SELF-MEDICATION USE IN COMMUNITY DWELLING ELDERLY IN FRANCE — RESULTS FROM THE THREE-CITY STUDY

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Objective: The aim of this study was to examine the pattern of self-medication use and related-factors in a large prospective French community-dwelling elderly.

Methodology: The study population was composed of 1972 noninstitutionalized participants aged 65 years and over, a sub-sample from the Three-City study, in Dijon, France. This cross-sectional study was performed between November 1st 2003 and December 31st 2004. Information on prescription and self-medication drug use, socioeconomic, lifestyle and health-related variables including depression scale were collected in the study examination center or in participants' homes, by trained psychologists. Self-medication included drugs available over-the-counter, drugs previously prescribed and stored at home, and alternative medicines. Subjects were considered as self-medication users if they consumed drugs at least once a week without any current medical prescription.

Results: A preliminary analysis shows that 38% of the subjects reported self-medication use at least once a week: 11% used alternative medicine and 31% consumed drugs regularly. Among drugs, the most common classes used for self-medication were analgesics (27%), non-steroidal anti-inflammatory drugs (21%), antacids (15%), stomatological preparations (15%), laxatives (11%) and psychotropic drugs (11%). In the multivariate analysis, the main predictors of high drug self-medication were female gender (odds-ratio (OR)=1.9; 95% confidence interval (CI): 1.4-2.4], to live alone (men only, OR=1.6; 95%CI: 1.0-2.5), birth in a foreign country (OR=1.6; 95%CI: 1.1-2.3), depressive symptoms, assessed by CES-D scale (OR=1.5; 95%CI: 1.1-2.0), poor self-perceived health (OR=1.3; 95%CI: 1.0-1.6), regular visits to a medical specialist (OR=1.4; 95%CI: 1.1-1.8) and the number of drugs prescribed. At least one hospitalization during the last two years was significantly associated with low drug self-medication (OR=0.7; 95%CI: 0.5-0.9).

Conclusion: Self-medication is a common behavior in elderly and increases with depressive symptoms and the number of prescribed drugs. The medical community should pay particular attention to lonely persons with depressive feelings.

38. WHO, WHERE, AND WHAT IN SPONTANEOUS REPORTS

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Objective: Is there a difference in spontaneous reports regarding gender and age, the most commonly reported suspected drugs and adverse drug reactions (ADR) from six continents entered in the World Health Organization (WHO) database, Vigibase, from January 2000 until December 2004?

Methodology: Vigibase is a unique source with international information holding over 3 million individual spontaneous reports of suspected ADRs from 75 countries. Report data from 1 January 2000 until 31 December 2004 was extracted from Vigibase including country of origin, gender, age, drugs, and ADRs. Report information from the different countries was grouped by six continents: Africa (AF), Asia (AS), Europe (EU), North America (NA), Oceania (OC), South America (SA, including Latin America).

Results: A total of 1 217 372 reports were received from 73 countries during these 5 years. The majority of reports originated from NA, followed by EU, AS, OC, SA, and AF. Women accounted for more reports than men, and adults constituted the most frequently reported age group and adolescents the least. This pattern was consistent for all continents. The most reported drug classes, grouped by Anatomical Therapeutic Chemical (ATC) classifications (3rd level) were:

- AF, OC, and SA, non-steroidal anti-inflammatory/anti-rheumatic products
- NA, viral vaccines
- AS, beta-lactam antibacterials, penicillins
- EU, antidepressants.

The most reported ADRs from AS, AF, SA, and OC belonged to the 'skin and appendages disorders' system organ class (WHO-adverse reaction terminology). For NA and EU, ADRs within the 'body as a whole-general' system organ class were most commonly reported.

Conclusions: The overall pattern for gender and age, and the most frequently reported ADR groups were similar among the different continents. More variations were seen among the reported suspected drug groups.

39. ARE ERECTILE DYSFUNCTION DRUGS (PHOSPHODIESTERASE 5 INHIBITORS) ASSOCIATED WITH NON-ARTERITIC ISCHEMIC OPTIC NEUROPATHY (NAION)?

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Background: The FDA is examining the link between erectile dysfunction drugs and nonarteritic ischemic optic neuropathy (NAION) after receiving about forty reports of varying degrees of vision loss among users of phosphodiesterase (PDE) 5 inhibitors drugs, mostly with sildenafil.

Methodology: We conducted a literature search in the Medline database by using the Mesh terms "phosphodiesterase inhibitors" AND "Optic Neuropathy, Ischemic/chemically induced".

Results and Conclusions: Until June 2005, 9 publications concerning 17 cases (15 with sildenafil and 2 with tadalafil) were published. Median age of patients was 60 (range: 42 to 69). Dose varied from 50 to 100 mg for sildenafil and 20 mg for tadalafil. Adverse events (acute visual loss and visual field loss) occurred between 30 min and 45 h after ingestion of the last tablet. In 5 cases, sporadic treatment was taken for more than one year. Funduscopy revealed optic disc edema with nerve fiber layer hemorrhage. Two patients experienced positive rechallenge (4 with tadalafil and one with sildenafil). In all cases the symptom did not improve despite several months of follow-up later. Several patients had known risk factor for NAION. No NAION was reported during clinical trials. Retinotoxicity of PDE inhibitors could be explained by: (i) high c-GMP levels in the retina due to inhibition of PDE6 and/or (ii) alteration of the retinal vascular flow. Even if risk factors are present, the rapid onset delay of NAION and some positive rechallenges cannot exclude the responsibility of the drugs. In the French pharmacovigilance system, visual adverse events including one NAION have been reported. Nevertheless, underreporting is probable. Physicians should be aware of this potential adverse event of PDE5 inhibitors.

40. AN ASSESSMENT OF UNDERGRADUATE PHARMACY STUDENTS' KNOWLEDGE OF SPONTANEOUS REPORTING FOR SUSPECTED ADRS ASSOCIATED WITH HERBAL MEDICINAL PRODUCTS

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Objective: In the UK, community pharmacists are specifically encouraged to report suspected ADRs associated with herbal medicines (HMs), yet pharmacists' knowledge of ADR reporting may be inadequate, particularly with respect to HMs.[1,2] Most UK schools of pharmacy include teaching on spontaneous reporting in their undergraduate pharmacy programmes, but only one also teaches this subject with respect to HMs.[3] This study assessed undergraduate pharmacy students' knowledge of spontaneous reporting for HMs before and after an educational intervention on this topic.

Method: A test was developed to assess pharmacy undergraduate students' knowledge of spontaneous ADR reporting, with a focus on HMs. The test comprised 65 true/false questions and an exercise involving completion of a 'yellow card' report for a suspected ADR associated with the use of a single-ingredient HM on the basis of details provided in a vignette. The maximum score was 100. All third year pharmacy undergraduate students undertaking the Natural Products elective (n = 18) were asked to complete the test immediately before and 7 weeks after an educational intervention comprising lectures, a workshop and a course-work exercise (total 6 hours). Test papers were marked independently by both authors. Data were analysed using SPSS version 13.

Results: In total, 13 students completed both tests; 9 (69%) were female and 11 (85%) said they had received teaching on ADRs before the baseline test. Median (semi-interquartile range) scores for the 'before' and 'after' tests were 60 (12.5) and 75 (2.5), respectively ($P < 0.05$; Wilcoxon Signed Rank Test for two related samples).

Conclusion: Students' test scores were higher following an educational intervention on spontaneous reporting for ADRs associated with HMs. Further work is required to assess the reliability and validity of the test and, ultimately, to test the effects of the educational intervention using a randomised controlled study design.

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41. *CIMICIFUGA RACEMOSA* L. NUTT. (BLACK COHOSH) AND ANAPHYLACTIC REACTIONS, INCLUDING FACE AND ORAL OEDEMA

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Objective: To review the suspected association between the use of *Cimicifuga racemosa* (L.) Nutt. (also known as black cohosh or *Actaea racemosa* L.) and suspected spontaneous reports of anaphylactic reactions including facio-oral oedemas.

The roots and rhizomes of *Cimicifuga racemosa* are used as a non-hormonal alternative in the treatment of menopausal symptoms. Consumers may assume *Cimicifuga racemosa* to be safer than hormone replacement therapy due to its natural origins, but data to support this are scarce.

Methodology: The WHO Adverse Drug Reaction (ADR) database, Vigibase, contains 122 suspected spontaneous ADR reports for Cimicifuga racemosa from twelve countries, mainly from 2001–2004. Anaphylactic reactions were reported to the database more often than statistically expected and therefore these case reports were extracted from the database and clinically reviewed.

Results: Vigibase cites various allergic reaction terms, but this review focuses on five case reports from three countries from different parts of the world on 'anaphylactic reaction' and facio-oral oedemas, not previously reported in literature. The terms reported included the oedema of the face, tongue, mouth and pharynx, angioedema and dyspnoea. One of the patients recovered from her symptoms on dechallenge. In two of the cases no other drugs were used concomitantly. The ADRs occurred after 1 to 7 days of using *Cimicifuga racemosa* (onset date not listed on one report).

In addition, in a report on a combination product, which contains *Cimicifuga racemosa* and *Hypericum perforatum* L. (a.k.a. St John's wort), the patient developed face oedema and abnormal vision. A possible causality was confirmed with positive de- and rechallenge.

Conclusions: The data suggests that there is an association between the use of *Cimicifuga racemosa* and anaphylactic facio-oral oedema, but further studies are needed to determine causality.

42. WHY DO BOYS STOP CRYING?

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Objective: Do spontaneous reporting patterns differ for males and females in various age groups?

Method: The WHO Adverse Drug Reaction database, Vigibase, is a unique global source of over 3.3 million suspected spontaneous reports from 75 countries. This study shows the reporting pattern by gender and age for cases entered in the past five years (2000–2004) with focus on children and adolescents.

Result: A total of 1 217 372 reports were received from 73 countries. In total, females accounted for more reports than males (57% vs. 37%), but in the youngest age group (0 – 13 years) reporting of male patients was slightly higher. Female predominance in reporting started at the age of 13 and became even more distinct for the adult patients.

Vaccines, penicillins and NSAIDs were amongst the most reported drug classes for both genders in the age group 0–13 years. Psychostimulants also featured strongly in young males.

Vaccines, followed by isotretinoin, were the most reported drugs for female patients aged 14 – 20. Isotretinoin was the most frequently reported drug for the male patients. Other prominent ATC groups differing from the youngest age group, included the antipsychotics, antidepressants, antiepileptics, and in females, contraceptives.

A male majority in the reporting of critical terms is only found in the youngest age group. The most reported critical terms did however not differ between the genders: 'convulsions', 'apnoea', 'hypertonia', 'purpura', 'death', 'hypokinesia' and 'face oedema'. Most reported critical terms in the age group 14 – 20, were 'convulsions' and 'suicide attempt'.

Conclusion: There is a male majority of the reports amongst the youngest patients, and these male patients also have a larger portion of the critical terms. The female predominance in reporting starts at the age of 13. Similar ATC groups were reported within the age groups.

43. ADVERSE DRUG REACTIONS RELATED TO INTRAVENOUS IMMUNOGLOBULIN. ANALYSIS OF BORDEAUX PHARMACOVIGILANCE CENTRE DATA

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Objectives: To describe adverse drug reactions (ADRs) of intravenous immunoglobulin (IVIG) and to assess the appropriateness of IVIG prescription according to the French marketing approval.

Methodology: All cases of ADRs with IVIG spontaneously reported to the Bordeaux Pharmacovigilance Centre from January 1, 2002 to April 30, 2005 were reviewed.

Results: During the study period, 74 cases have been reported. There were 39 women and 35 men. The mean age was 36.3 years (range: 4 days–90 years). Causality assessment was certain in 2.7%, probable in 51.4%, possible in 12.1% and unlikely in 33.8% of cases. The most frequently reported ADRs to IVIG were infusion-related reactions (48.6%), cutaneous reactions (18.9%), aseptic meningitis (12.2%), renal (9.5%), cardio-vascular (6.8%) and haematological reactions (4.1%). ADRs were serious in 31% of cases and involved mostly central nervous and renal systems. Indication was known in 94.6% of cases. Prescriptions according to the French marketing approval represented 39.2% of cases whereas off-label indications represented 10.8% of cases. In 32.4% of cases, IVIG were used according to recommendations based on the literature. In 12.2% of cases, the indication on the ADR reporting forms was not sufficiently precise to conclude.

Conclusions: The profile of ADRs in the present study was similar to literature data. However, ADRs were frequently serious (almost 1/3 of cases). IVIG were often used in miscellaneous indications not specified in the French marketing approval. However, only a few cases occurred during IVIG treatment without evidence-based guidelines.

44. ADVERSE DRUG REACTIONS REPORTING IN A HOSPITAL, KARACHI, PAKISTAN

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Introduction: The association between Adverse Drug Reactions (ADRs) and its burden on health care is well established. Accurate and independent data about the prevalence of ADRs and its impact on public health is not available in Pakistan.

Aim: This study was aimed to analyse the ADR reports received in a university hospital Pakistan.

Method: The ADRs are reported on an anonymous and voluntary basis in our hospital. ADRs reporting forms are available in every department of the hospital. The data from these forms are added to a central computerised data base. This database was reviewed from 1999 to 2004 for all ADRs related events to determine the frequency, specialty of person reporting, age, sex of the patient and associated drugs. Each report was evaluated individually. Using a structured process, the reports were coded by two independent reviewers.

Results: In all, 350 adverse drug reactions were reported during the period from 1999 to 2004. From our analysis, the year-to-year number of ADR reports received from 1999 to 2004 has been increasing steadily. For 2004, we received 78 reports; this represented a 98% increase in the number of reports received in 2003. The physicians reported 51% of the reports compared to 44% from pharmacists and 5% from the nurses. The maximum age of the patient with an ADR was 84 years while minimum age was 8 months. The prevalence of ADRs was most common in females (54%) than males (46%). The most offending drugs were broad spectrum antibiotics, heparin and diuretics. The top three reported ADRs include skin disorders, electrolyte imbalance and thrombocytopenia.

Conclusion: Our study shows that adverse drug reaction reporting is increasing with our promotional work at the hospital. ADRs remain a major threat to patient safety in Pakistan. This issue needs national recognition in Pakistan. Availability of an active national ADR reporting system can play an important role in monitoring ADRs and creating preventive strategies.

45. A NEW ADVERSE EFFECT WITH ANTI-TUMOUR NECROSIS FACTOR-ALPHA?

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Objective: To describe four cases of lupus chilblain, an unlabelled adverse effect of anti-tumour necrosis factor-alpha drugs (TNF-alpha).

Methodology: Clinical and biological patterns of four cases of lupus chilblain with anti-TNF-alpha recently reported to the regional Pharmacovigilance Centre of Bordeaux are described.

Results: The cases involved a 47-year-old woman treated with adalimumab for seronegative rheumatoid arthritis, a 52-year-old woman treated with etanercept for rheumatoid arthritis, a 54-year-old woman treated with infliximab for seronegative rheumatoid arthritis and a 72-year-old man treated with infliximab for psoriatic arthritis. They presented with necrotic peri-ungual lesions and punctiform, violaceous papules on proximal inter-phalanx and on digital pulp. Immunological investigations showed positive antinuclear antibodies in four patients, positive antinucleosome antibodies in three patients. The antinuclear serology was positive before treatment by anti-TNF in three patients and doubtful in one patient. The first symptoms of chilblain occurred between 3 months and 44 months of anti-TNF treatment. In all cases, the anti-TNF treatment was continued. The symptoms improved or resolved with symptomatic treatment (hydroxychloroquine and/or calcium inhibitors) but recurrences occurred when risk factors such as cold were present.

Conclusion: All four cases were non serious and can be managed without stopping anti-TNF therapy. However, the consequences on the daily life of these patients were far from negligible. It is important for pharmacovigilance purpose to standardise the codification of this unusual adverse effect.

46. ECOPHARMACOLOGY — A NEW IMPORTANT TOPIC FOR PHARMACOVIGILANCE

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Pharmaceuticals and their metabolites are excreted with urine and faeces. Unused medicaments are sometimes disposed of in drains. The unchanged drugs or (still active) metabolites end up in sewage. If they are not eliminated in sewage treatment they enter the aquatic environment. Within the last decade pharmaceuticals of different groups such as antibiotics, hormones, cytotoxics, lipid regulators, anti-depressants, spasmolytics, pain killers, and others including diagnostic agents and disinfectants have been detected in sewage, surface water, ground and drinking water in several countries around the world. This indicates that pharmaceuticals are at least not fully eliminated in sewage treatment and the aquatic environment. The drugs may eventually reach drinking water. In laboratory testing most of the pharmaceuticals have not been degraded. Risk assessment is performed for single substances and relies on the assumption that short term high dose ingestion (i.e. within therapy) is comparable to ingestion over a life time (i.e. with drinking water) at low dose. It assumes also that babies, children and elderly people have the same dose response as other people. Amongst others cytotoxins deserve

special attention because they are often mutagenic and carcinogenic. Antibiotics contribute to resistance. Hormones are known for their very low activity levels. Mixtures of all used compounds are present in the aquatic environment. Some cytotoxic compounds exert synergistic effects with some antibiotics. Additionally, type B adverse effects are dose/concentration independent. Therefore, the input of pharmaceuticals into the environment has to be reduced strongly. At least it is not only a issue of human health, it is also one of environmental hygiene and health of environmental organisms as well as of sustainable development.

47. COUNTERFEIT DRUGS AND IRON POISONING

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Objective: This paper presents the cases of 9 women that were poisoned by a counterfeit iron salt (IM administration) and discusses the role of the National Pharmacovigilance System in these situations.

Methodology: A total of 19 notifications were submitted to the National Pharmacovigilance System. The information suggested that the patients suffered from acute iron poisoning. The suspected product was an intramuscular injectable drug product, which active ingredient was sorbitex iron.

In December 2004, 9 notifications from a hospital located in Viedma, a city 800 km from Buenos Aires were received. They referred to 9 women, aged 19–39, that were diagnosed anemia due to gynecological or obstetrical disorders. In the following days, other 10 cases were notified (from different cities). Considering the new cases, the age range was broader: 19–60 yrs. All these patients had received at least one intramuscular sorbitex iron ampoule. They presented nausea, itching, edema, fever, hypotension, abdominal pain, sweating, asthenia, liver and renal insufficiency, sinus tachycardia. One of the patients died of liver failure. In most of the cases, the symptoms disappeared after 5 hours.

A sample of the suspected drug product was submitted to the Pharmacovigilance System and was analyzed in its laboratories together with the drug manufacturer. The first tests showed already that the product was counterfeit. It contained three times the iron it should, and a significant amount of iron citrate compared to the original product.

Conclusions: The National Pharmacovigilance System receives notifications referred to adverse events and quality problems of marketed drug products in Argentina, and has proved to be of use in this kind of situations.

48. COMPARISON OF PREPARATION OF INFUSION BAGS ON THE WARD OR IN THE PHARMACY

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Objective: We have previously studied errors in making up infusion bags containing acetylcysteine.[1] We now examine carboplatin. Acetylcysteine bags are made up on the ward by staff who are not specifically trained, whereas carboplatin is usually made up by trained pharmacy staff under controlled conditions. Carboplatin along with other cytotoxic drugs has a low therapeutic index and is usually used in doses close to the maximum tolerated dose.

Methods: In both experiments, the procedure used to collect samples was:

- infusion bag was made up by staff in the usual manner and mixed by agitation
- a small sample was removed by the ward nursing staff, and labelled with patient's height and weight, pre- or post-infusion sample and patient identifier, and refrigerated
- after infusion a further small sample was removed (if possible) and stored as above
- analysis was by plasma ionization mass spectrometry

Samples were collected in 1 centre between July and December 2003.

Results: We analysed 53 bags of carboplatin. The median concentration of the bags was 99.4% (97.8% – 101.9%) of the intended concentration.

Conclusion: All the carboplatin bags contained within 10% of the intended dose (compared with only one-third of samples in our acetylcysteine experiment) and over 80% were within 5% of the anticipated dose. A previous study detected a wide inter-patient variation in the maximum tolerated dose of carboplatin, and hypothesised that dose delivery errors were a potential explanation.[2] Our audit shows that the upper 95% confidence limit for the major error rate is 3/53 (6%). We conclude that careful preparation by experienced staff reduces major errors substantially in critical cases where under- or over-dosage would be serious, infusion bags should be made up by experienced pharmacy staff under controlled conditions.

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49. BENEFIT-RISK QUANTIFICATION IN PHARMACEUTICAL RISK MANAGEMENT: PREPARING METHODOLOGIES FOR A PARADIGM SHIFT

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Background: Recent guidelines on risk management (RM) state that enhanced benefit-risk (B-R) should be the primary outcome of RM interventions and other commitments. B-R assessment is complicated due to its multifactorial nature, influenced by, for example,

individual versus society risks, cultural perceptions, differing measures, changes across product life cycle and indications, absence of common aggregate measures that would allow comparisons over time and between products. Thus, traditionally, regulatory authorities assess and communicate B-R qualitatively. The availability, validation and comparison of quantitative methods to assess benefit-risk in post-marketing settings remain largely unexplored.

Objectives: (i) Compare B-R ratios obtained from quantitative methods found in the literature, using empirical effectiveness and risk data; (ii) identify advantages and limitations associated with each method; and (iii) recommend future research directions.

Methods: B-R quantification methods can be compared through, for example, Monte-Carlo simulations. An empirical framework option for the modeling is that of non-steroidal anti-inflammatory drugs (NSAIDs)-associated gastrotoxicity and hepatotoxicity, taking into account case-fatality, seriousness and morbidity. Simulation parameters are derived from absolute risk estimates in observational studies. Trade-offs between benefits and risks are obtained for various subpopulations taking into account dosage and competing risks. The population and society impacts of risk management interventions based on B-R analyses are assessed using the population attributable risk measure.

Conclusion: Moving from qualitative to quantitative benefit-risk assessments explores largely unknown terrain and must be approached cautiously and with an open mind, to avoid over-or underestimating B-R. Thus during this exploratory phase several methods need to be compared and validated, aiming towards promoting internationally acceptable guidelines and harmonisation.

50. EFFECT OF AN EDUCATIONAL INTERVENTION ON IMPROVING DRUG SAFETY AWARENESS AMONGST SELLERS OF NON-PRESCRIPTION MEDICINES IN A DEVELOPING COUNTRY

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Introduction: Non-prescription medicine sellers are the main pharmaceutical service providers in most developing countries including Ghana. In Ghana non-prescription medicine sellers known formally as Licensed Chemical Sellers (LCS) are legally permitted to supply specified over-the-counter medicines. They are over 7000 (compared to 900 pharmacies) and are widely distributed nationwide serving the needs of over 80% of the population. Innovations to improve the safe use of medicines should therefore target this group whose formal educational is minimal and who have received little or no formal training in medicine or pharmacy.

Objective: To examine the effect of formal adult-based training on the ability of LCS to understand and act on drug safety issues.

Methodology: A 4-hour training session on pharmacovigilance as part of a 32-hour training session on managing simple ailments of common occurrence. A pre- and post-training questionnaire was administered to assess knowledge gained during the training.

Results: Analysis of data following 5 separate sessions involving 220 franchised LCS (known as CAREshop Managers) indicates no knowledge and awareness of pharmacovigilance before the course. Post-test questionnaire indicated acquisition of important basic knowledge on pharmacovigilance by over 90% of participants with over 80% able to identify possible symptoms of toxicity of some commonly used medicines.

Conclusion: Training of over-the-counter suppliers of medicines in pharmacovigilance can improve drug safety and the rational use of medicines in resource-limited countries.

Credit for Funding: The training was undertaken as part of the Strategies for Enhancing Access to Medicines Initiative funded by the Bill & Melinda Gates Foundation with support from Management Sciences for Health in collaboration with GSMF International.

51. INFLIXIMAB AND PULMONARY EMBOLISM

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Infliximab is a monoclonal antibody against TNFα, used in the treatment of rheumatoid arthritis and Crohn's disease. Pulmonary embolism is not a recognised adverse reaction to infliximab.

The Uppsala Monitoring Centre (UMC) collaborates with pharmacovigilance centres in 75 countries around the world and maintains a cumulative database of summaries of case reports of suspected adverse drug reactions. These reports are heterogeneous as regards source, completeness and causality.

There are 73 case reports from 9 countries stored in the UMC database regarding pulmonary embolism as suspected adverse reaction to infliximab. The data mining method, routinely used at the UMC to highlight reports for review, showed that the number is substantially higher than expected from the background of the database. In 62 reports infliximab was the single suspected drug. In 18 reports the patients also had venous thrombosis. Six other patients had concomitant autoimmune-related events: ANF test positive (n=3; one of these patients also had SLE-like symptoms and anticardiolipin antibodies), serum sickness-like disorder (n=1), influenza-like disorder (n=1) and disseminated intravascular coagulation (n=1). 33 additional cases have been reported to the UMC of venous thrombotic episodes during the use of infliximab.

The reports to the UMC suggest that the use of infliximab may be associated with an increased risk of pulmonary embolism. Additional reported adverse events suggest that pulmonary embolism may occur in connection with venous thrombosis, intravascular coagulation and perhaps autoimmune activation.

52. POTENTIAL DRUG INTERACTIONS WITH THIORIDAZINE OF PATIENTS WITH SCHIZOPHRENIA IN TAIWAN — ANALYSIS OF NATIONAL HEALTH INSURANCE RESEARCH DATABASE

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Background: Drug-drug interactions (DDIs) is one of major concerns in clinical practice. Some antipsychotics may cause QT interval prolongation or torsade de pointes leading to sudden death. The potential cardiotoxicity of thioridazine has caught lots of attention. Health Regulatory Agencies in many countries bulletined warnings with thioridazine since July, 2000.

Objective: The objective of this study is to evaluate potential significant DDIs with thioridazine usage of patients with schizophrenia from 1997 to 2001 in Taiwan. The National Health Insurance Research Database – Psychiatric Inpatient Medical Claim Dataset (PIMC) is used.

Method: A database of 52 DDIs drug pairs regarding to thioridazine were established based on the information from MICROMEDEX® and Drug Interaction Facts. From PIMC, patients with schizophrenia and prescribed with thioridazine from 1997 to 2001 were enrolled for this study. Concomitant administration is defined when the dates of prescriptions of drug interaction pairs were overlapped.

Results: From the analysis, the most frequently appeared (incidence >3.5%) drugs with thioridazine related DDIs were haloperidol, propranolol, chlorpromazine, lithium, risperidone and trifluoperazine. About 55.4% to 59.7% of the thioridazine users from 1997 to 2001 were exposed to potential risk of thioridazine related DDIs from the prescriptions of the same medical visit, and 65.2% to 68.9% of them were exposed to thioridazine related DDIs from different medical visits. Overall, the incidence of potential DDIs with thioridazine were 75.5% to 77.4% estimated patients base.

Based on the number of thioridazine prescriptions, the incidence of potential thioridazine related DDIs were 49.2% to 55.2% from the same visit, and were 51.82% to 55.27% from different visits. Overall, the incidence of potential DDIs with thioridazine ranged from 59.26% to 65.04%.

Conclusions: It was found that polypharmacy is one of the factors that contributes to the high incidence of thioridazine related DDIs. The average daily dose of thioridazine within prescriptions with thioridazine related DDIs was lower than those without thioridazine related DDIs ($p<0.0001$). Such dosage difference is most likely due to that under antipsychotics polypharmacy condition physicians might prescribe thioridazine with a lower dose.

53. NEUTROPENIA IN ALLOGENEIC HEMATOPOIETIC-CELL TRANSPLANTS RECEIVING GANCICLOVIR FOR CYTOMEGALOVIRUS DISEASE AT A MEDICAL CENTER IN EASTERN TAIWAN

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Objective: To observe ganciclovir-related neutropenia in allogeneic hematopoietic cell transplants, patients who had been received hematopoietic cell transplants at a medical center in eastern Taiwan were studied.

Methodology: *Patients* — All consecutive CMV DNA positive patients undergoing allogeneic hematopoietic cell transplantation between July 2002 and June 2005 received ganciclovir for prevention or treatment of CMV disease were included in this study. *Neutropenia* — ANC decreases to <1000/mm^3 for 2 consecutive days. *Ganciclovir treatment and discontinuation* — induction dosing: 5mg/kg BID × 7 days for CMV prevention, or 14–21 days for treatment; maintenance dosing: 5mg/kg/day for at least 14 days, or at least 3–4 weeks for treatment; ganciclovir was stopped when ANCs fell to 1000/mm^3 for 2 consecutive days and shifted to foscarnet (induction dosing: 60mg/kg BID × 7 days for CMV prevention, or 90mg/kg BID × 14-21 days for treatment; maintenance dosing: 90mg/kg/day for at least 14 days, or at least 3–4 weeks for treatment).

Results: Five patients who received ganciclovir for CMV prevention or treatment after allogeneic hematopoietic cell transplantation were studied. Neutropenia of less than 1,000/mm^3 was found in one patient for two times, 10 days and 22 days separately after dosing of ganciclovir. After discontinuation of ganciclovir and shifting to foscarnet, the patient's ANC recovered to 3,021 and 1,512 on 4–5 days later, the patient completed the courses for CMV prevention and treatment. One patient shifted to foscarnet for his poor engraftment, and recovery of ANC was noticed after discontinuation of ganciclovir.

Conclusions: With the current early treatment strategy, the incidence of CMV disease has been reduced. ANC should be monitored closely and shifted to foscarnet treatment for ganciclovir-related neutropenia. Follow these guidelines, resolution of neutropenia and good control of CMV disease were observed.

54. REGISTRY OF JAPANESE RHEUMATOID ARTHRITIS PATIENTS ON BIOLOGICS FOR LONG-TERM SAFETY

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Background: Biologic agents have dramatically changed paradigm

of the treatment for rheumatoid arthritis (RA). In Japan, infliximab, anti-tumor necrosis factor-α (TNF- α) chimeric monoclonal antibody, and etanercept, soluble TNF receptor, have been launched into the market in 2003 and 2005, respectively. The approval of these biologics has enabled Japanese rheumatologists to place them in the strategy of treatment for RA. Although these TNF blockers have strong efficacy for RA, several adverse events (AE) or adverse drug reactions (ADR) including opportunistic infections and malignancies have been reported in post-marketing surveillance (PMS) of infliximab in Japan; 16 patients with tuberculosis, 19 with *Pneumocystis carinii* pneumonia (PCP), and 6 patients with malignancy among 6,360 patients (as of April, 2005). Since PMS tracks each patient for only 6 months after the institution of biologics and do not have a comparator (i.e., patients with RA on conventional therapy other than biologics), we cannot conclude whether the rate of occurrence of these AE or ADR is more frequent in patients on biologics than those on non-biologics. We also cannot obtain long-term safety information for biologics, especially on malignancies. The unexpectedly high reporting rate of PCP in the PMS indicated that some ADR could be unique to Japanese patients with RA.

Methods and Results: We have developed a new on-line registry system to collect, store and analyze the safety information of each patient with RA. Our new registry is called *REAL* from the acronym of '*Re*gistry of Japanese Rheumatoid *A*rthritis Patients on Biologics for *L*ong-term Safety', and our pharmacoepidemiological study using *REAL* is named the *REAL study*. Seventeen university hospitals have participated in the study and began to enroll their patients into the registry. Patients with RA on biologics and non-biologics will be enrolled into the registry and followed up for five years so that we will be able to compare the two groups for short-term as well as for long-term safety information.

Conclusion: *REAL* will provide safety information of biologics for Japanese patients with RA and enable us to compare the data with those from other countries. The data will help Japanese rheumatologists to improve their therapeutic strategy against RA.

55. SPREADING OUT PHARMACOVIGILANCE CONCEPT AND METHODOLOGY AMONG ARGENTINIAN PHYSICIANS

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Aim: Disseminate among physicians Pharmacovigilance concepts and methodology with the necessary adjustments to the Argentinian reality and problems in order to commit them to have active participation in drug safety activities.

Background: Pharmacovigilance is a scientific activity whose efficiency highly depends on physician's skills and attitude. University education does not give the physician useful knowledge on Pharmacovigilance: what, how and who to report — national and international Pharmacovigilance organizations, and how the decisions taken by Pharmacovigilance officers contribute to public health and to pharmacological science.

Methods: A course on basic contents about Pharmacovigilance and other drug related aspects was designed for physicians. The topics included in the course were: phases of drug development, ethical consensus for clinical investigation, Pharmacovigilance, generic drugs and bioequivalence tests, quality controls, national and international institutions for drug regulation and control.

The course is available in two formats:

- A face to face course for physicians attending the Residence Training Program of the Hospital Nacional de Clínicas, Córdoba City.
- A distance course whose aim is to reach a higher number of physicians around the country.

Conclusion: Spreading out knowledge related to the methodology and results of Pharmacovigilance and making physicians actively participate in Pharmacovigilance activities can contribute to increase reports of Adverse Drug Reactions and foster safe use of medicines.

56. WHAT CAN WE DO TO STOP COUNTERFEIT MEDICINES CIRCULATION?

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Aim: Propose the method used by IPAM in order to avoid the purchase of counterfeit medicines in public and private health centers.

Background: In June 2004, instead of an inhalant anesthetic, water was found in a sevofluorane bottle in the main municipal hospital of Córdoba, Argentina. In December 2004, one pregnant woman died from a counterfeit iron sorbitex injection administered in a provincial public hospital. Other 8 women got sick due to the administration of this counterfeit product in the same hospital. Counterfeit iron sorbitex had three times the declared amount of iron, including iron citrate. Out of 19 Yellow Cards reporting iron poisoning, 9 were for injections administered in the public hospital.

At present, there is no legislation that obliges to prove the legitimacy of the purchased medicines. In the public or private hospitals or any other health center, the purchases are often made to wholesale distributors or pharmacies and not to the manufacturing labs due to the fact that:

- the purchase is made little by little
- and to the lack of credit that the hospital or health center may have because of arrears.

This situation makes possible the circulation of eit medicines.

Method: The method currently used by IPAM is to demand its suppliers their licensure to check whether they are authorized distributors without any penalties applied by the ANMAT (National Administration of Medicines, Food and Medical Technology). If the

purchase is not made to the manufacturing lab, the drug store must present packing lists and invoices that show the legitimacy of the medicine to be bought.

Conclusion: eit medicines can cause RAM, poisoning, lack of efficacy, and even death. Simple procedures like the one described should be made obligatory by national law because they help to interrupt the corruption and negligence chain that permits the circulation of eit medicines.

57. ROSIGLITAZONE AND LOWERED HIGH DENSITY LIPOPROTEIN CHOLESTEROL

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The New Zealand Pharmacovigilance Centre received a report in late 2004 of high density lipoprotein cholesterol (HDLc) lowering with rosiglitazone. A fall in HDLc from 0.8 to 0.2 mmol/L was described in a 64 year old patient 3 weeks after starting rosiglitazone. There was rapid recovery when it was discontinued. This patient had experienced a similar reaction to bezafibrate previously.

Vigibase, the database of the WHO Collaborating Centre for International Drug Monitoring held at the Uppsala Monitoring Centre, was interrogated for further cases.

There were 14 reports from three countries of lowered serum HDLc concentrations associated with rosiglitazone. This drug/adverse reaction combination was statistically significant compared with the background data. Fibrates are known to cause a paradoxical lowering of HDLc in some patients. Nine patients were also taking a fibrate, but five were not. Two patients recovered when rosiglitazone was withdrawn and one of these patients was not taking a fibrate. Seven other patients recovered but no specific information on drug withdrawal was given and there was incomplete information for the remaining patients. Five patients had an associated hypertriglyceridaemia, two had an elevation and one a fall in total cholesterol levels.

A fall in HDLc with a combination of rosiglitazone and a fibrate was found in patients in three recently published case series; however, this occurred in only one patient taking rosiglitazone alone.

Spontaneous adverse reaction reports thus support the single published observation that rosiglitazone can lower HDLc whether or not a fibrate is prescribed. The occurrence of lowered HDLc with rosiglitazone in a patient who had experienced a similar reaction with bezafibrate suggests a common mechanism. While small changes in HDLc measurements must be interpreted with caution the New Zealand case report indicates that the fall can be profound. This study also demonstrates the potential for early detection of a signal when a key report received by a national centre is immediately linked with reports in Vigibase.

58. IS ROFECOXIB DIFFERENT AND DO COX-2 INHIBITORS HAVE ADVANTAGES OVER STANDARD NSAIDS? AN ANALYSIS OF INTERNATIONAL VOLUNTARY ADVERSE REACTION REPORTS

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Reporting profiles for cyclooxygenase-2 (COX-2) inhibitors and standard nonsteroidal anti-inflammatory drugs (NSAIDs) were created to assess if the profile for rofecoxib differed from other COX-2 inhibitors with respect to serious adverse reactions and if there was evidence for any advantage for COX-2 inhibitors compared with standard NSAIDs. Proportional reporting profiles for COX-2 inhibitors and three standard NSAIDs were derived from the WHO International Drug Monitoring database to compare the reporting of critical terms, indicating serious disorders, attributed to COX-2 inhibitors and three standard NSAIDs across a range of system organ classes commonly affected by these medicines. The number of suspected reactions in the database ranged from 38,715 to 48,375 for celecoxib, rofecoxib and the three standard NSAIDs. For valdecoxib and etoricoxib there were 5115 and 1111 reactions, respectively. The most marked differences were that 4.3% of rofecoxib reports were of cardiac failure or hypertension compared with 1.8% for the other COX-2 inhibitors and reporting of anaphylaxis (0.3% v 2.0%), bronchospasm and skin reactions (apart from valdecoxib) was less for the COX-2 inhibitors compared with the standard NSAIDs. The system organ class most often affected was gastrointestinal and proportions of reports were 3% lower for the COX-2 inhibitors compared with the standard NSAIDs (11.1% v 7.9%.). Differences between individual medicines in reporting of gastrointestinal, hepatic and skin disorders were also noted. In conclusion, voluntary adverse reaction reports suggest that rofecoxib differs from other COX-2 inhibitors with respect to hypertension and cardiac failure. They also support findings of a lower risk of serious gastrointestinal reactions with COX-2 inhibitors compared with standard NSAIDs and indicate that serious allergic reactions may occur less frequently with COX-2 inhibitors with the exception of valdecoxib.

59. ASSESSMENT OF INHALATION ANESTHETICS SAFETY ON PEDIATRIC PATIENTS FROM THE SPONTANEOUS REPORTING SYSTEM IN TAIWAN

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Objective: The National ADR Reporting System in Taiwan was established in 1998. Inhalation anesthetics, i.e., methoxyflurane, enflurane, isoflurane, desflurane, sevoflurane, have been launched in Taiwan. Among them, isoflurane and sevoflurane have been found relatively higher incidence of death event occurrence. It is important

to know the domestic safety profiles from the spontaneous reporting system in Taiwan.

Methodology: We retrospectively analyzed all the ADR cases of isoflurane and sevoflurane (other inhalation anesthetics found no cases reported) retrieved from the electronic database of the National ADR System from 1998 to June 2005 in Taiwan. ADR reports ranked as "doubtful" or from clinical trials were excluded. Each case was reviewed to ascertain the type and severity of ADR. We used Naranjo score to assess the causality of suspected drug and the ADR (score 9: certain, 5-8: probable, 1-4: possible, 0: doubtful).

Results: In the past seven years, 9 reports from the database were eligible for this study. The average age of all cases was 19 y/o at the time ADR occurred. It is observed that 55.5% (5/9) of the cases were less than 16 years old. Male gender was predominant (8/9; 88.9%). Malignant hyperthermia (MHT) was the major ADR and occurred in all cases reported. Seven out of 9 cases (77.8%) were death events and 4/5 (80%) pediatrics cases were fetal. Among all death events, hyperthermia contributed to the death with or without other ADR complications such as hyperkalemia, arrhythmia, hyperventilation, bronchospasm and ultimately, multiple organs failure. Five cases were given Dantrolene and patient's body temperature was successfully reversed in 2 cases.

Conclusions: The data indicates that pediatric patients receiving isoflurane and sevoflurane are at high risk of developing MHT. Body temperature should be carefully monitored throughout the procedure as well as post-op observation period. Oral or intravenous dantrolene prophylaxis of MHT may be considered before anticipated anesthesia. Once MHT is observed, dantrolene administration and cooling process should be implemented as soon as possible.

60. DEATHS NOTIFIED FOLLOWING THE USE OF HERBAL MEDICINES MOROCCAN PHARMACOVIGILANCE CENTER RETROSPECTIVE STUDY 2001–2004

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Introduction: The influence of religious, sociocultural and socioeconomic levels, traditions, practices and beliefs on the use of herbal medicines (HM) is evident particularly in the Chinese and African societies. Documented use of HM among western community is also high. Among consumers, there is a widespread belief that remedies from natural origin are "safe" and "harmless". Although the majority of them are (derived chemicals of many plants are the basis of conventional drug therapies), as with all medicines, HM have been shown to cause adverse events and many of them are serious enough to cause deaths.

Aim: To index all deaths notified following HM use in order to establish in perspective, a national register of deaths from health products as it is for HM.

Methods: Retrospective study of deaths cases reported to Moroccan Pharmacovigilance Center (CMPV) since the founding of pharmacovigilance of HM or "Phytovigilance" department within the CMPV on 2001 to 2004. It concerns all notified deaths that involve HM use.

Results: From January 2001–December 2004. CMPV has received 34 deaths reports. They are attributed to HM use in 32.35% (11 cases). Many HM are concerned: *Ridolfa segetum* (L.) Moris (27.28%); *Peganum harmala* L. (18.18%); *Nigella sativa* L. (9,09%); *Peganum harmala* L. in combination with *Ferula communis* L. (9.09%); *Rubia peregrina* L. (9.09%); *Salvia verbenaca* L. (9.09%) and herbal preparation (18.18%) which the nature of HM is unknown. These HM were taken as a crude material. The male/female reporting sex ratio is 0.37. Deaths have been occurred among babies (3 cases), children (2 cases) and adults (6 cases). Various symptoms were reported which often affect vital prognosis. They are mainly represented by liver damage, renal failure and hemorrhage.

Conclusion: Because HM use has caused deaths and because the problem with the imputability of HM, it is important for health professionals, consumers, and other interested parties including regulatory authorities and suppliers of HM to be aware of the seriousness of risks when herbal medicines are used. This use must take into account their safety, efficacy, consistency, and quality. These should be ensured through pharmacovigilance systems and strict regulatory control. Strength communication between patients, health professionals and authorities and the inclusion of HM as source of therapy in our academic program, will be also needed.

61. HEPATOTOXICITY ASSOCIATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN HIV/AIDS PATIENTS

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Objectives: Liver toxicity has been frequently reported to be a potential side effect of highly active antiretroviral therapy (HAART), especially associated with the use of protease inhibitors (PIs) and non nucleoside reverse transcriptase inhibitors (NNRTIs). Therefore, the purpose of this study was to assess the incidence of severe hepatotoxicity in HIV/AIDS patients using PIs or NNRTIs as a part of HAART.

Methodology: Data were obtained from patients continuously monitored for 24 months at the HIV/AIDS Center, University of Belgrade, Serbia and Montenegro. The liver parameters have been performed every 3 months after treatment started. Patients with the concurrent liver disease, current or previous IVDU, alcohol abuse, were excluded from the final analysis. Severe hepatotoxicity was defined as an increase alanine or aspartate-aminotransferase at least 5 times upper normal level.

Results: There were 114 HIV infected patients treated with PIs or

NNRTIs. 82 patients were treated with PIs: lopinavir/ritonavir—32.5%, nelfinavir—32.5%, indinavir—18.5%, indinavir/ritonavir—16.5% and 32 with NNRTIs: efarirenz—68.0%. There were 76 men and 38 women; median age 34.7 years. Persistently mild elevated aminotransferases were found in 8.77% patients before treatment. The liver parameters in normal range were present in 55.26% patients. Severe hepatotoxicity developed in 12.28% patients. Multivariate logistic regression shows an increased risk of severe hepatotoxicity in HIV infected patients treated with NNIRTs, especially with nevirapine (RR 3.92; 95% CI 1.23-6.98). In all cases, liver toxicity, as adverse event, occurred within first 3–6 months after the initiation of treatment.

Conclusions: In our patient population severe hepatotoxicity is associated with NNRTIs, especially with use of nevirapine. Our results demonstrate that the relative risk of severe hepatotoxicity is almost 4-fold higher when nevirapine is used. Besides, our results suggest that hepatotoxicity occurs most frequent in first 6 months of the treatment.

62. DYSLIPIDAEMIA IN PATIENTS RECEIVING THYMIDINE ANALOGUE BASED HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) FOR A LONG TERM

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Objective: In the poor resource settings, as Serbia and Montenegro (SCG) is, thymidine analogues are the most popular backbone of the HAART. Since prolonged treatment is more frequent, dyslipidaemia is one of the most frequent adverse effects and some studies suggest its association with thymidine analogue toxicity. Therefore, the objective of this study was to compare long term outcomes of treatment contains AZT/3TC vs D4T/3TC based HAART.

Methodology: Data were obtained from patients continuously monitored at the HIV/AIDS Center, University of Belgrade, SCG. Inclusion criteria were: ongoing treatment with regimen containing AZT/3TC or D4T/3TC lasting over one year and at least 3 TG and cholesterol measurements in 12 months follow-up period. There were 2 groups of patients. I group — 72 patients on AZT/3TC and II group — 81 patients on D4T/3TC. Mean lipid levels were analysed before start of studied regimen and during the study. Protease inhibitors were included in 66.67% regimens in AZT/3TC and 56.79% in D4T/3TC group.

Results: Mean prevalence of elevated TG increased from 38.8% before start of studied regimen to 51.03% during treatment for AZT/3TC and from 36.14% to 62.89%, respectively for D4T/3TC group. Mean prevalence of elevated cholesterol increased from 19.93% before start of studied regimen to 38.89% during treatment for AZT/3TC and from 11.46% to 44.45%, respectively for D4T/3TC group.

Conclusions: Our results show that the serum TG and cholesterol elevations were more frequent in patients treated with D4T/3TC as a part of HAART. Due to high prevalence of dyslipidaemia, HIV-infected patients with dyslipidaemia should be routinely monitored for possible consequences, especially if HAART contains D4T/3TC regimens.

63. HAART AND THE RISK FOR DEVELOPING HYPERGLYCAEMIA IN HIV INFECTED PATIENTS CO-INFECTED WITH HCV

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Objective: The objective of this study was to evaluate whether HIV-infected patients co-infected with HCV have an increased risk of hyperglycaemia while on HAART.

Methodology: Data were obtained from patients continuously monitored at the HIV/AIDS Center, University of Belgrade, Serbia and Montenegro. There were 2 groups of patients: 106 patients (HIV-infected patients without HCV co-infection — I group) and 88 patients (HIV-infected patients with HCV co-infection — II group). CD4 cell counts, HIV plasma viral load (pVL), ALT and glycaemia levels in fasting serum samples drawn before and each 3 months for 12 months period after initiating HAART. In order to asses the risk for developing hyperglycaemia Kruskal-Wallis and the chi-square tests were used.

Results: There were 194 HIV-infected patients in total. The mean age was 41 years in I group and 38 years in II group. 55% patients in I group and 66% in II group were on protease inhibitor regimens. At baseline the mean CD4 count, pVL, ALT and glycaemia levels were similar between two groups. After 12 months of follow-up 62% of patients in I group and 64% in II group had undetectable pVL. II group presented a lower mean CD4 count: 328 cells/μL (vs. 381 cells/μL in group 1, $p=0.059$) and higher mean ALT levels: 79 U/L (vs. 33 U/L, $p<0.001$). No significant differences were found in mean glycaemia levels, mean glucose level elevations from baseline between two groups of patients.

Conclusions: Our results suggest that HCV co-infection did not significantly increase the risk of HAART associated hyperglycaemia in HIV infected patients.

64. HEPATOTOXICITY DUE TO ANGIOTENSIN II RECEPTOR ANTAGONIST/HYDROCHLOROTHIAZIDE COMBINATION

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Objective: We report two cases of hepatotoxicity, the first was fatal and subfulminant induced by Hyzaar® (losartan, hydrochlorothia-

zide), the second induced by Coaprovel® (irbesartan, hydrochlorothiazide).

Case n° 1: A 42-year-old man took since August 2001 atenolol for hypertension. In March 2003 he had been taking 200 mg/d flecainide for extrasystole and 65,5 mg/d Hyzaar® after stopping atenolol. Thirty-five days after beginning this new treatment, he presented weakness, dark urine, and jaundice. The transaminase levels were: alanine aminotransferase (ALAT) = 27 N (N = normal value), aspartate aminotransferase (ASAT) = 34 N. Thirteen days after stopping Hyzaar® and flecainide, laboratory tests were: ALAT = 48 N, ASAT = 50 N, alkaline phosphatase (PAL) = 3 N, γglutamyltransferase (GGT) = 2 N, total bilirubin = 23 N and prothrombin activity 45 %. Etiologic investigation was negative.

Case n° 2: A 74-year-old woman with a history of hypothyroidism, uraemia and dyslipemia was treated respectively by levothyroxine, allopurinol and fluvastatin. She had been hypertensive for 4 years and took Hypoten® (atenolol), Tenordate® (nifedipine, atenolol). Since December 2003, amlodipine and Coaprovel® have been introduced. On November 29, 2004 biologic hepatic tests showed an increase of transaminase level at 7 N. All medicines were continued. On December 16, 2004, in front of the aggravation of the liver function tests: ALAT = 14 N, ASAT = 12 N, GGT = 4 N and PAL = 2 N, Coaprovel® was stopped. Etiologic tests were negative. One week after the Coaprovel® was withdrawn, the transaminase decreased to the normal level.

Discussion: Hyzaar® responsibility is probable because of normal liver tests before drug initialization, a delay of 35 days from first drug intake to the apparent onset of the reaction suggestive with drug hepatotoxicity, the absence of other hepatic disorder, the exceptional flecainide-induced hepatotoxicity. Coaprovel® responsibility was retained in front of: a compatible delay (eleven months), a favourable evolution of the hepatic injury and a no evidence of other hepatic disorders.

65. BIRTH OUTCOMES IN WOMEN EXPOSED TO ANTICONVULSANT DRUGS

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Objective: Our objective is to assess birth outcomes after intake of anticonvulsant drugs during pregnancy.

Patients and methods: We led a retrospective study involving 62 women having taken anticonvulsant drugs during pregnancy. All our cases had consulted at the National Centre of Pharmacovigilance between November 1993 and March 2004. Data about birth outcomes has been obtained in 30 cases (by telephone call and by post). For 32 cases we didn't obtained data. Thus only the outcomes of 30 pregnant women were analyzed.

Results: The mean age of the pregnant women was 30.5 years. Women were exposed, during all the period of pregnancy, to only one anticonvulsant drug in 24 cases and to two drugs in 6 cases. Phenobarbital was taken in 13 cases, valproate in 10 cases, carbamazepine in 10 cases and benzodiazepine in 4 cases. The gestational age was ≥ 37 weeks in 33 cases and < 37 weeks in one case. The total of outcomes was 34 newborns, 3 lost pregnancies and 2 pregnancies were interrupted for medical reasons. The mean birth weight was 3280 ± 427 g. One case had low birth weight. We found two cases of malformation: convergent strabismus and frenum linguae.

Discussion: In our study we didn't find serious malformation (neural tube defect, heart malformation, failure of face development). It may be due to the fact that most pregnant women were exposed to only one anticonvulsant drug. In literature, the available epidemiological data support the hypothesis that anticonvulsants increase the risk of major malformations by an order of 2- to 3-fold especially with polymedication.

Women in treatment should be informed about the risk of malformations and the possibility of prenatal diagnosis of the most severe birth defects. A plasmatic monitoring of anticonvulsant drugs is necessary during pregnancy in order to keep the minimal and efficient doses.

66. MALIGNANT HYPERTHERMIA INDUCED BY ANAESTHETIC DRUGS

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Introduction: Malignant hyperthermia (MH) during general anaesthesia is due to dominantly inherited skeletal muscle disorder that predisposes susceptible individuals to potential fatal reaction. We report two cases of MH triggered by halogen agents and succinylcholine.

Case n° 1: A 13-year-old girl, who had antecedent of facial dysmorphia, scoliosis and Recklinghausen's neurofibromatosis, was admitted for surgical correction of her spinal deviation. Anesthesia was induced with cisatracurium, fentanyl and thiopental then maintained with isoflurane, cisatracurium and remifentanyl. One hour after the induction of anaesthesia, expired CO_2 was over 70 mmHg despite hyperventilation. The patient developed gradual increase in fever (40 °C), tachycardia, hypotension, skeletal muscle rigidity and rhabdomyolysis. Creatine phosphokinase (CK) level was 5500 U/l. MH was diagnosed and dantrolene was administered. One month later, the patient underwent a second surgery using the following anaesthetised drugs: cisatracurium, remifentanyl, and propofol, without recurrence of MH.

Case n° 2: A 12-year-old boy with no neurological deficit and no evidence of myopathy or dystrophy was admitted for tonsillectomy. Few minutes following inhalation induction anaesthesia with halothane and intubation with succinylcholine, he developed spasticity, tachycardia and elevated expired CO_2. CK level was 5703 U/l. MH was diagnosed and dantrolene was administered. The course was rapidly favourable.

Discussion: In the 2 cases, the responsibility of anaesthetic drugs was suspected in front of the occurrence of MH during anaesthesia. In the first case, the role of cisatracurium and morphinic agents was excluded because of a negative rechallenge. The responsibility of isoflurane was retained because the MH has been reported with isoflurane but not with thiopental. In case n° 2, we couldn't decide between halothane and succinylcholine imputability because of the same chronological administration. In addition, these 2 drugs may induce MH.

67. BICYTOPENIA INDUCED BY LOCAL INFILTRATION WITH CORTIVAZOL

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Introduction: Hematological disorders induced by cortivazol seem not to be described in the literature. We report a case of bicytopenia induced by cortivazol.

Case report: A 19 year-old girl has since the age of 4 years, idiopathic juvenile arthritis. She has been treated since July 2001 by paracetamol (2 g/j), indometacine (100 mg/j) and methotrexate (7,5 mg/semaine). She received 3 local infiltrations with cortivazol (2 into elbows and one into the left knee) at the same time (on 2001). On 19 July 2004, she received another local infiltration into the left elbow with cortivazol. Fifteen minutes later, she had uneasiness, with important lombalgia radiating toward the lower limb. The patient was asthenic, plaintive, febrile in 38,2 °C with an abdominal sensitivity. The biologic tests showed a bicytopenia: a thrombopenia to 66.103 /mm3 and an haemolytic anemia with 6,5 g/dl of Hb and elevation of the non conjugated bilirubin (30 µmol/l). All medications were discontinued and prednisolone was initiated at 1mg/kg/d dose. Normalization of the blood-platelet rate was within 8 days, whereas the Hb rate was returned to its initial value one month later. The etiologic investigations were negative. No incident has been noted after the rechallenge test with indometacine, paracetamol and methotrexate.

Discussion: The responsibility of cortivazol in genesis of the bicytopenia has been retained in front of: suggestive delay of an iatrogenic origin, previous intake of cortivazol (in 2001) that could be pre-sensitizing, favorable course after cortivazol withdrawal, negative rechallenge test to paracetamol, indometacine and methotrexate, negative etiologic investigations and the absence of a history of hematological disorder. In the literature, cortivazol has never been described to be responsible for hematological disorder.

68. PNEUMONITIS COMPLICATING LOW DOSE METHOTREXATE TREATMENT

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Introduction: Pneumonitis is a serious and unpredictable side effect of treatment with methotrexate (MTX) that may be life-threatening. We report three cases of pneumonitis complicating low-dose MTX for rheumatoid arthritis (RA).

Case n° 1: A 72-year-old woman with RA since 1992, had been taking 10 mg MTX weekly since 1998. On 2004, she developed progressive dyspnea. Chest radiography showed bilateral interstitial infiltrate. All microbiological investigations were negative. Computed tomography scan of the thorax revealed a non specific bilateral interstitial infiltrate. Pulmonary function tests (PFT) showed a moderate restrictive defect.

Case n° 2: A 39-year-old woman with RA since 17 years had been treated with MTX weekly for 11 years. She developed whistling dyspnoea and bronchorrhoea. MTX was stopped. Chest X-ray revealed a bilateral interstitial infiltrate. PFT showed a restrictive defect with a decrease of a vital capacity. The microbiological investigations were negative. Computed tomography scan of the thorax was normal. MTX was reintroduced and a reoccurrence of pneumonitis was noted within 3 weeks. MTX was stopped definitively. The patient had no reoccurrence of respiratory symptoms following discontinuation of MTX.

Case n° 3: A 60-year-old woman with RA had been taking 7,5 mg of MTX weekly since 1992. Five years later (on 1997), she developed dyspnea, chest pain and dry cough. Chest X-ray showed diffuse and lower lobe-dominant infiltrates. Computed tomography scan of the thorax revealed a diffuse interstitial infiltration. BAL fluid cell analysis showed hypercellularity and lymphocytosis. All microbiological investigations were negative. MTX was stopped.

Discussion: Criteria for diagnosis of MTX induced lung toxicity were: appropriate history of exposure, pulmonary infiltrates on chest radiography and exclusion of other pulmonary diseases, especially infections. The pathogenesis of MTX-induced lung disease is not known. A variety of theories have been proposed. Early respiratory symptoms even in patients on low-dose MTX treatment should be appropriately investigated.

69. ANAPHYLACTIC SHOCK INDUCED BY ALUSTAL® (STALLERGEN)

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Objective: Allergen immunotherapy is a subcutaneous injection of gradual increasing quantities of specific allergen to patient with IgE mediated disease until reaching a maintenance dose. This therapy could be associated with anaphylaxis. We report a case of anaphylactic shock induced by Alustal®, an allergenic extract, notified in the Tunisian National Centre of Pharmacovigilance and analyzed with the method developed by Begaud et al.

Case report: An asthmatic 13 year-old girl had a skin prick test positive to house dust mites DPTE/DF. A specified hyposensitization by Alustal® was initiated on 28/6/04. The immunotherapy was

given during 6 months by weekly subcutaneous injections. The amount of allergenic extract was increased at each injection. All injections were well tolerated. On 29/1/05, the patient received 0.45 ml from vial N°3 (10 IR). Then she was observed for at least 30 minutes. Two hours later, she developed an erythematic eruption, tachycardia, hypotension, rapid pulse, dyspnea and pulmonary sounding notified whistling rale (respiratory examination before injection was normal). The patient received parenteral adrenaline and bronchodilator. Brochospasm signs disappeared within 24 hours. The cutaneous lesion disappeared 24 h later. The immunotherapy was discontinued. The intrinsic score of imputability attributed to Alustal® was plausible (I2).

Discussion: No evidence-based guidelines for dose adjustments following serious systemic reactions such as anaphylactic shock are available. In our case, a systemic reaction occurred although no risk factor was identified. The patient was compliant to the protocol and no extended time interval between injections was noted. The analysis of health status before the injection did not show fever, acutely ill or respiratory difficulties. In addition, the anaphylactic shock was noted 2 hours after the injection, while most systemic reaction occurs within 30 minutes. Thus, even without any risk factor, patients should be carefully observed throughout the protocol.

70. HEPATOTOXICITY RELATED TO ANTICONVULSANT DRUGS: ABOUT 50 CASES NOTIFIED TO THE CENTRE NATIONAL DE PHARMACOVIGILANCE (CNPV)

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Introduction: Anticonvulsant drugs can be responsible of hepatotoxic events. The incidence of this adverse drug effect is controversial.

We determined the rates of hepatotoxic events related to anticonvulsant drugs, and we identified the most involved agents in hepatotoxicity cases notified to CNPV.

Methods: We performed a retrospective analysis of 607 cases of hepatotoxicity notified to the CNPV between 1991 and 2003 and validated according to Begaud's method of imputation. We included in our study the 50 cases in which anticonvulsant drugs were taken before hepatotoxicity. We studied the sex, the age, the type and the seriousness of hepatotoxicity, the number of drugs, the imputation, and the decision of the CNPV.

Results: There were 21 women (42%) and 29 men (58%). The age varied from 2 to 87 years (median = 32 years). Hepatotoxicity types were cytolysis (16 cases), cholestasis (22 cases), mixed acute injury (3 cases), isolated elevation of gamma-glutamyl transferase (2 cases) and non identified type (7 cases). The hepatotoxic event was severe in 5 cases (10%). Valproic acid and valpromide were taken in 26 cases, phenobarbital in 24 cases, carbamazepine in 17 cases, clonazepam in 3 cases, diazepam in 2 cases and vigabatrin in 1 case. In 22 cases, the patients were taken more than one anticonvulsant.

In 17 cases, all the drugs were excluded (anticonvulsants and others). In 4 cases, other drugs than anticonvulsants were retained. In 6 cases, more than 1 anticonvulsant, were suspected. In 23 cases, 1 anticonvulsant drug was suspected.

Discussion: In our study, the 3 most involved agents were carbamazepine, valproic acid and phenobarbital. In literature, the 3 most commonly involved agents in hepatotoxicity are phenytoin, carbamazepine and valproic acid. This difference can be explained by the youth of our population in which such anticonvulsant drug are prescribed more frequently.

71. BIRTH OUTCOMES AFTER IN-UTERO EXPOSURE TO ORAL HYPOGLYCAEMIC DRUGS

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Objective: Oral hypoglycaemic agents are not recommended for pregnant women. We have collected cases of fetal exposure to oral hypoglycaemic drugs to assess birth outcomes.

Subjects and methods: Thirty-nine women with pregnant exposure to oral hypoglycaemic agents were followed in the Tunisian National Centre of Pharmacovigilance between 1993 and 2004. Data about birth outcomes were obtained retrospectively by telephone contact or using an information sheet sent to patients by postal way. No information was available among 13 cases. Thus 26 cases (66 %) were analysed with 27 fetal exposures (1 woman was exposed twice).

Results: The Mean age of the pregnant women was 36.5 years. Fetal exposure occurred before 12 weeks in 14 cases and later in 13 cases. Oral hypoglycaemic agents were switched to insulin in 23 cases. We noted a miscarriage rate of 22 %. Twenty-one pregnancies resulted in live births. Sixteen were term deliveries. Six babies were normal neonates with appropriate size for gestational age, 4 had macrosomia and 5 birth weights were unknown. Affected babies among those exposed during the first trimester were: 1 case with jaundice, and 1 with cleft palate. For those exposed later, we noted 1 baby with a ventricular septal defect, another with a respiratory depress and 1 case with renal hydronephrosis. One infant, exposed to glibenclamide and metformin for 30 wk, had an oral cleft, a shortening of the left leg, an inguinal hernia, a cardiac malformation and an anal anomaly. The prevalence of affected infants was 22%.

Conclusion: The association of oral hypoglycaemic drugs with fetal embryopathies and neonatal metabolic abnormalities in the small number of infants described in this study does not establish causality but justifies caution with the use of these drugs during pregnancy. A large prospective study is needed to exclude the confounding effect of maternal metabolic derangement secondary to diabetes.

72. OSTEONECROSIS OF THE JAW IN A PATIENT WITH BISPHOSPHONATES THERAPY

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Bisphosphonates are commonly used to prevent and treat osteoporosis in post-menopausal women. They are also widely used in management of advanced cancers with hypocalcaemia of malignancy and bone metastasis.

Objectives: Alert about this potential side effect of bisphosphonate treatment.

Methods: We report a case of osteonecrosis of the jaw (ONJ) after zoledronate treatment. A 57-year-old woman was addressed to the odontologist because of an exposed jaw bone 7 months after a non-healing parodontal curettage in May 2003. She had a breast adenocarcinoma in 1993 with bone then hepatic metastases in 1998, treated by radiotherapy then chemotherapy. She received intravenous zoledronate since May 2003. Examination of the buccal cavity on January 2004 showed a non-painful exposed bone involving the maxillary and osteomyelitis. A sequestrectomy was performed with prescription of antibiotics. Histology of the sequestrum confirmed the bone necrosis and didn't show bone metastasis. Two weeks later, a new area of bone was exposed. It was protected by biological adhesive with continuing antibiotics. The bad outcome led to cessation of zoledronate therapy. In September, expansion of the osteonecrosis was noted, with spontaneous loss of three teeth. Her condition deteriorated, with progression of metastases, she died 2 months later after a hepatic decompensation.

Results: ONJ was first reported in 2003, in USA. Since, about 200 cases are reported in the literature, most often with pamidronate or zoledronate in IV route. Associated risk factors are: cancer, chemotherapy, corticosteroids, co-morbid conditions, dental procedures. The physiopathology is still unclear.

Conclusion: Patient receiving bisphosphonates should avoid invasive dental procedures and should be followed up regularly to avoid the occurrence of ONJ which should be diagnosed early and treated adequately. The SPC of pamidronate and zoledronate are being updated to include ONJ in precautions and as a possible adverse effect.

73. A PROSPECTIVE STUDY OF ADVERSE DRUG REACTIONS IN CHILDREN: PRELIMINARY RESULTS

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Objectives: The aim of this study was to systematically evaluate adverse drug reactions (ADRs) in children for a 6-month period.

Methodology: A prospective study was carried out in 3 paediatric (emergency, nephrology and gastroenterology) wards of Lyon general hospitals in cooperation with the regional pharmacovigilance centre (CRPV). All potential ADRs among in- and out-patients younger than 18 years of age reported by clinicians were systematically recorded by a pharmacologist who attended the daily or weekly staff meetings in paediatric wards. All reported cases were then screened by the CRPV and the clinical pharmacology unit. For validated cases, the preventability, the seriousness and whether the prescribed drug had a paediatric license or label were evaluated. We report the results obtained from March 1 to April 30, 2005.

Results and conclusions: Thirty-five children presented with potential adverse drug events among 4690 who had been admitted during the study period. ADRs were validated in 20 (0.4 %) patients, 9 females and 11 males. Sixteen patients were under 5 years of age. According to the criteria of the French Pharmacovigilance System, 7 patients (35 %) had serious ADRs and ADRs were probably avoidable in 2 patients (a haemorrhagic syndrome by a non-steroidal anti-inflammatory drug (NSAID) and worsening of acute gastro-enteritis by anti-diarrhoeal, antiemetic, anti-spasmodic and a NSAID). Antibiotics and vaccines were the possible cause of ADRs in 14 patients. Skin reactions (n=12), gastric disorders (n=3) and fever (n=3) were the most common clinical manifestations. Because ADRs were reported by clinicians on a voluntary basis, serious ADRs were probably reported more systematically. Our preliminary results show, however, that children under 5 years of age seem more vulnerable to ADRs and a high proportion (15 cases) of reported adverse drug events were not related to drugs.

74. INFLUENCE OF SELF-REPORTING OF ADVERSE EVENTS ON THE SAFETY PROFILE OF A VIROSOME HEPATITIS A VACCINE (EPAXAL®): EXPERIENCE IN OVER 2500 SWISS TRAVELLERS

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Objective: To assess the safety profile of an aluminium-free, virosome-formulated hepatitis A vaccine (Epaxal®, 24 IU/0.5 mL) with solicited versus unsolicited questions.

Method: In an open, comparative multi-centre post-marketing safety study, over 2500 travellers eligible for hepatitis A vaccination were enrolled at four travel clinics in Switzerland. After written consent was obtained a single dose of vaccine was administered and the vaccines were openly randomised to record the AEs on diary cards using either solicited (Group A) or unsolicited (Group B) questions. All participants were carefully instructed on how to document the safety parameters during a four day observation period and asked to send the diary back after completion.

Results: The diary cards from 2541 participants (52.3% female, 47.7% male) could be evaluated (return rate > 90%). The mean age was 37.5 years (range (2–70), with 2.9% being < 18 years and 8.0% > 60 years of age). 69.9% of the subjects received 1–5 different vaccines concomitantly. 50.9% of travellers in Group A using solicited questions for safety reporting and 38.1% of travellers in Group B using unsolicited questions reported ≥ 1 local and/or systemic AEs

($p<0.001$). The type of questioning had striking effects on the overall AE reporting rate as well as on the pattern and the severity of the reported symptoms. Headache was reported in 15.5% in Group A vs 4.4% in Group B, dizziness in 8.2% vs 1.6%, and anorexia in 6.4% vs 0.08%. For the reporting of solicited and unsolicited AEs sex and age of the vaccines as well as the travel centre administering the vaccine had a significant influence on the reporting frequency of local AEs whereas the vaccination type (first, booster vaccination) had no influence. For systemic AEs sex, age and travel centre had no significant influence, whereas the vaccination type and concomitant vaccination played a significant role.

Conclusion: The solicited questions resulted in significantly more and qualitatively different AE reporting compared to the unsolicited questions. Furthermore, the reporting rate for local AEs was significantly influenced by the age and sex of the vaccine and by the travel centre administering the vaccine whereas the reporting rate for systemic AEs was significantly influenced by the type of vaccination (first, booster, and by concomitant vaccination).

75. NSAID USAGE IN CANADA, 1999–2005

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Objective: To investigate the usage of non-steroidal anti-inflammatory drugs in Canada during 1999–2005, including the effects of the introduction of COX-2 inhibitors and the subsequent withdrawal of rofecoxib and suspension from marketing of valdecoxib.

Method: Examination of prescription and sales databases obtained from IMS Health Canada.

Results: From March 1999 to March 2001, a period corresponding to the introduction of celecoxib and rofecoxib onto the Canadian market, the use of traditional NSAIDs such as diclofenac and ibuprofen fell by 29%; however, the use of all prescription NSAIDs, including COX-2 inhibitors, increased by 65%, from 775 to 1281 thousand DDDs/day. Following the withdrawal of rofecoxib in September 2004, and the subsequent suspension from marketing of valdecoxib, the total use of prescription NSAIDs, including COX-2 inhibitors, up until May 2005, fell by 32% to 1010 thousand DDDs/day, with a 72% fall in the use of COX-2 inhibitors and a 20% increase in the use of other NSAIDs. During this time, the usage of celecoxib fell by 42%. There does not seem to have been a significant increase in the use of over-the-counter NSAIDs.

Conclusion: The total use of prescription NSAIDs in Canada rose substantially following the introduction of the COX-2 inhibitors in 1999, indicating that there were many patients newly starting NSAIDs rather than a switch from older to newer products. Following the withdrawal from market of rofecoxib, and the subsequent marketing suspension of valdecoxib, there appears to have been a return to the use of the older NSAIDs, particularly diclofenac and naproxen, along with a substantial fall in the use of the remaining COX-2 inhibitor, celecoxib.

76. HOSPITAL ADMISSIONS TO INTERNAL MEDICINE AND EMERGENCY DEPARTMENTS CAUSED BY ADR: RESULTS OF A PROSPECTIVE POPULATION BASED STUDY

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Aims: To identify ADRs leading to hospital admission and to estimate incidence rates.

Methods: Since 1997 four Pharmacovigilance Centers screened all hospital admissions to determine if the admission had been caused by an ADR. Causality was assessed using Begaud's algorithm. For the estimation of incidence rates we used the quarterly drug prescription data of the hospital service areas.

Results: 5468 ADR related hospital admissions were identified and evaluated (type A: 83%, type B: 11%). About 3% of all non elective hospital admissions were due to ADRs. Most often the GI tract was afflicted. The five drug groups most frequently assessed to be causally related were: B01 antithrombotic agents (17%), A10 drugs used in diabetes (12%), C01 cardiac therapy (8%), M01 antiinflammatory and antirheumatic products (8%) and C03 diuretics (7%). Quarterly incidence rates were highest for antithrombotics and insulins. Detailed analyses including differences between drugs of the same drug group, e.g. beta blockers, and the use of proportional reporting ratios for signal generation will be presented.

Discussion and conclusions: The combination of hospital based Pharmacovigilance and the use of population based drug prescription data allows for very detailed analyses of ADR related hospital admissions and its potential for prevention.

77. ANALYSIS OF CLINICAL TRIAL OF ANTIMALARIAL DRUGS IN PAEDIATRICS IN SUB-SAHARAN OF AFRICA

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Background: The emergence and the propagation of chemoresistence imply an effective and well tolerated rigorous evaluation of antimalarial drugs. Malaria constitutes an issue of public health in sub-Saharan Africa area with a very high infant mortality. Whereas few tests are carried out in children. The aim of this study was to identify the methods used in the trials on the antimalarial drugs in the children.

Material and methods: A bibliographical study was conducted to select therapeutic trials of antimalarial drugs published in French and English language, between 2000 to 2003 in the sub-Saharan Africa area. These trials were analyzed according to methodological principles of the clinical trials.

Results: 42 therapeutic trials out of 55 were retained. In the meth-

odological plan, 39 trials were comparative including 32 with randomization. Half of these trials were a blind study. These trials were mostly monocentric (74%). The period of study was in general two years. The children under 5 years represented 76.3%. The efficacy and harmlessness were evaluated in simple and serious malaria, generally at D14 and D28. The therapeutic combinations were evaluated in 19 trials (45.2%). The adverse drug reactions were reported in 69% of the trials.

Conclusion: The pediatric therapeutic trials of antimalarial drugs have respected the methodological principles of classic clinical trials. However, we do not have hindsight to compare the therapeutic combinations concerning pharmacoresistence and tolerance.

78. PRODUCT LIABILITY: AN INDUSTRY PERSPECTIVE

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A great deal of time and effort in substantiating product quality, efficacy, purity and safety goes into preparing a pharmaceutical product for commercial distribution. The primary regulatory agency that monitors drug quality and safety in the Philippines, the Bureau of Food and Drugs (BFAD), evaluates all drug registration materials against strict quality standards as a way for the State to protect its people against hazards to health and safety.

Philippine laws hold manufacturers and processors of drug products liable (i) for death or injuries caused by any noxious or harmful substances used,[1] (ii) for damages caused to consumers by defects resulting from the manufacture, formulas, handling, presentation or packing of their products as well as for the insufficient or inadequate information on the use and hazards thereof,[2] and (iii) when their drug products are injurious, unsafe or dangerous, although a complainant's contributory negligence reduces the compensation that he may recover.[3]

However, liability will be enforced only when there is sufficient proof of (i) the product defect, (ii) the injury suffered, and (iii) the causal connection between the defect and the injury. From a drug company's perspective, it is essential that a claimant initially prove that the drug product complained of (i) is an authentic product of the manufacturer, and (ii) suffers from a defect arising before the product left the manufacturer's hands. The evidence should be weighed with caution and discernment in every case because not all evidence of product defect is credible based on human — or industry — experience.

Along with the required proof of facts, one must consider the claimant's credibility and motive, especially where threats of negative media exposure precede, or accompany, a claim for compensation. At the other end of this responsibility spectrum is the challenge for each drug company to exercise its moral judgment (or business decision) to readily compensate an individual injured by its defective product, where evidence of such injury and defect is clear to the company.

The discipline of requiring the consumer or patient (or his legal representative) to present acceptable evidentiary support for a product liability claim serves not only to provide to the drug manufacturer an objective basis for (i) rectifying the defect, (ii) improving product and process standards, and (iii) monitoring the quality of its own products, but also to (i) prevent unfounded and malicious claims against it by not supplying a motive for unjust gain, and thereby (ii) protect the public from the harmful consequences of product tampering, including unnecessary confusion as to the safety record of a product.

References

1. New Civil Code (NCC) of the Philippines, Article 2187
2. Consumer Act (RA 7394), Article 97
3. NCC, Article 2214

79. EFFECTIVENESS OF A SIMPLIFIED SPONTANEOUS REPORTING FORM FOR INTENSIVE MONITORING OF ADVERSE EVENTS DURING INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANT WOMEN WITH SULPHADOXINE-PYRIMETHAMINE

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Introduction: Malaria causes huge morbidity and mortality in pregnant women in hyper-endemic countries including Ghana. As part of the Roll Back Malaria Programme, Ghana has embarked on a policy change replacing weekly administration of 300mg chloroquine with 3 courses of sulphadoxine-pyrimethamine (SP) given intermittently at, at least four weekly intervals between 16 and 36 weeks gestation. IPT with SP has been shown to be effective and tolerable in several countries. Deployment in Ghana started on a pilot basis in 20 administrative districts.

Objective: To develop a simplified spontaneous reporting form for monitoring SP in IPT.

Methodology: Design of simplified spontaneous reporting forms in collaboration with district health workers followed by training on use of the forms. Filled forms are submitted to the District Directors and to the National Centre for Pharmacovigilance and/or National Malaria Control Programme.

Results: The simplified forms were included in the folders (medical records) of all women administered SP for IPT. After 12 months of monitoring, 36430 women had been put on SP for IPT and 62 adverse events reported. Whilst the level of reporting appears very low, the quality of reports was high. In addition to two serious adverse events reported, this simplified pharmacovigilance tool permitted the identification of a potentially serious drug quality problem due to contamination of a batch of SP.

Conclusion: Simplified ADR forms can help in safety monitoring of public health programmes in resource-constrained environments. Low reporting can be improved with increased education.

Credit for Funding: National Malaria Control Programme, Ghana. Global Fund for HIV/AIDS, Malaria and TB.

80. INTEREST OF SPECIFIC REPORT SYSTEM OF ADVERSE DRUG REACTION DUE TO ANTIMALARIAL DRUGS IN CÔTE D'IVOIRE

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Introduction: In Côte d'Ivoire, malaria is a public health problem. The use of antimalarial drugs is relatively important and could cause serious adverse drug reactions. The self medication could also increase pharmacoresistence and limited therapeutic arsenal.

Objective: The objective of this study was to assess adverse drug reactions of antimalarial drugs.

Material and Methods: Our study reported on 10 years period 249 cases of adverse drug reactions of antimalarial drugs. These cases were selected among 520 global adverse drug reactions in data base of clinical pharmacology department in Abidjan. The French imputability method was used to establish the causal relation.

Results: The antimalarial adverse effects concerned mostly male adults between 20 and 39 years old.

The principal adverse reactions were represented by damages of haematology (26%), skin (20%), liver (18%) and nervous system (17%). Serious Adverse drug reactions (57% of cases) were mainly constituted by black fever (22%), hepatitis (18%) and oro-facial dyskinesia (11%). The active principles incriminated were respectively Quinine (49 cases), halofantrine (8 cases), sulfadoxine-pyrimethamine (10 cases), and Amodiaquine (27 cases).

The causal relation was judge doubtful in 91% of cases; it concerned 19 drugs with one active principle and 5 drugs with associated active principle.

Conclusion: Evaluation of adverse drug reactions of antimalarial drugs answer to health public need.

It's implying to organise a specific pharmacovigilance or "Paludovigilance" in order to analyse issue of under notification and adapt French imputability method to our medical activities. This would permit to take decision in case of serious and/or unexpected adverse drug reactions.

81. ADVERSE DRUG REACTIONS RELATED TO AMODIAQUINE REPORTED AND HEALTH AUTHORITIES DECISION

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Background: Today, WHO recommends the therapeutic combinations against pharmaco-resistance. The combination Amodiaquine-Artesunate was adopted by Côte d'Ivoire in her new policy. However, the use of Amodiaquine was restricted in 1986 because of the increase of cases of hematotoxicity and hepatotoxicity. The aim was to analyze the harmlessness of Amodiaquine.

Material and methods: From the data base of the clinical pharmacology department in Abidjan, we have selected report cases about adverse drug reactions implying Amodiaquine since 1994. The French imputability method was used.

Results: Among 249 of adverse drug reactions related to the use of antimalarial drugs, 45 (18.1%) were due to Amodiaquine. These adverse drug reactions were all serious. It was about 27 cases of dyskinesia and neurological signs, six pruritus, five cytolytic hepatitis, four agranulocytosis, two emesis and one black fever. The causal relation was mostly doubtful because of the absence of reliable or specific paraclinic exams.

Conclusion: The difficulties of notification and evaluation of causal relation by the French causality assessment method in the developing countries are not very likely to influence the decision-making by Health authorities. However, in the face of increasing self medication and recrudescence of adverse drug reactions related to Amodiaquine, a reflexion about simplified and adapted method of imputability should be led in our countries.

82. COMPARATIVE CARDIOVASCULAR SAFETY OF IODINATED CONTRAST AGENTS: RESULTS OF A DISPROPORTIONALITY ANALYSIS

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Background: Data mining algorithms (DMAs) can be used as a binary classifier (signal/no signal) or a ranking classifier. Some have advocated use as a ranking classifier for exploratory disproportionality analysis (DA) of potential toxicity gradients within a therapeutic class. DA using a hierarchical empirical Bayesian method (i.e. Multi-item Gamma-Poisson Shrinker [MGPS]) is theoretically appealing as a ranking classifier since the empirical Bayesian shrinker paradigm results in substantial data compression and smoothing.

Objectives: To test the ranking classifier performance of MGPS by using iodinated contrast agents as positive control since for these agents correlations between toxicity, ionicity, osmolality, viscosity, intrinsic chemotoxicity, and presence/absence of calcium binding additives have been identified.

Methods: MGPS was applied to the FDA-AERS database to rank the following contrast agents with regards to cardiovascular events: diatrizoate, iodixanol, iohexol, iopamidol, iopromide, ioversol, and ioxaglate. Ranks were examined for consistency of the rankings.

Results: No clear correlation could be revealed between the rank and the physico-chemical characteristics of the agents. These results were unlike the physicochemical-toxicity gradients observed in studies.

Conclusions: Given the abundant pharmacological, clinical, and investigational data in support of a more favorable cardiovascular

safety profile of non-ionic agents the results of this study were very surprising and probably reflect some form of channeling bias, differential reporting or differential use by procedures. The variation in rank according to the MedDRA term used, suggests that different coding practices have impinged upon the results. Further research is needed on the reliability of DA as ranking classifiers including potential effects of channeling bias and other reporting artifacts.

83. DIRECT REPORTING OF VACCINE ADVERSE EVENTS IN THE NETHERLANDS

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Information regarding vaccine safety is derived from epidemiological studies and professional vaccine adverse event (VAE) reporting schemes. The Stichting Vaccinatieschade (Vaccine Injury Foundation) in the Netherlands has asked the Science Shop for Medicines (SSM) of the University of Utrecht to provide in addition information directly originating from patients and their parents.

A special VAE reporting form was added to the SSM Web-based system for the reporting by patients of drug experiences.

In the period 14 January 2004 – 2 February 2005, 186 direct VAE reports were submitted the SSM. 161 were considered valid; 150 concerned the national childhood vaccination program (RVP). The pattern of direct VAEs reports was roughly similar as that of the professional RVP VAEs reporting scheme. Many of the serious reports concerned established vaccine complications such as collapse and febrile fits. In addition, a variety of serious disorders were reported that had become manifest in the period following vaccination but were likely to have been coincidental, e.g. epilepsy or autism. A substantial number of reports suggested that the treatment of the patients and/or the provision of information to their parents had to some extent been inappropriate or ambiguous and caused or worsened anxiety, uncertainty, erroneous suspicions and sometimes anti-vaccination feelings. This may have been influenced by the situation in the Netherlands that childhood vaccines and paediatric care are often given by different persons and institutions.

Direct reporting to the SSM revealed a similar pattern as the professional VAEs reporting system. A sudden or progressive disease in a previously healthy child is a sad and serious experience. When occurring in a temporal association with a vaccination and without an obvious cause or explanation, substandard treatment or failing communication may lead to anxiety, distrust and erroneous conclusions. Prompt good care, on the other hand, may ensure, improve or restore confidence in childhood vaccination.

84. HOW TO EVALUATE SAFETY OF OTC DRUG USE

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Background: Potent modern drugs, e.g. proton pump inhibitors and statins are approved for over the counter use. In addition in many developing countries prescription-only medications can be bought without prescriptions. Thus, it is relevant to assess whether these drugs are used according to the directions for use.

Methodology: The concept of safety in the OTC area has got two dimensions: appropriateness of use and the occurrence of adverse drug reactions. Appropriateness of use is evaluated by checking whether the approved indications, contraindications and precautions, the recommended dosages and duration of treatment have been adhered to. Occurrence of adverse drug reactions can be identified by asking to physician visits and hospital admissions. The design of choice is the pharmacy based cohort study. The enrollment of participants, informed consent and the recording of baseline variables takes place in the pharmacy once the customer has bought the drug under investigation. Follow up observation uses mail questionnaires or telephone. Thus lost to follow up cases can be kept very low.

Results: Experiences with three pharmacy based cohort studies will be presented and discussed, enriched by published reports.

Conclusions: Pharmacy based cohort studies provide a methodologically sound design to evaluate safety of OTC drug use. Due to the follow up observation by mailed questionnaires and /or telephone it is a comparatively low cost approach too.

85. STATINS AND HEPATIC REACTIONS: DATA FROM SPONTANEOUS REPORTING IN ITALY

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Statins are generally well tolerated but they can occasionally lead to muscle and liver toxicity. As a matter of fact hepatotoxicity, including elevated liver enzymes and hepatitis is known to be related to statins therapy even if with a rare incidence. However, to our knowledge, studies that evaluate the risk of hepatotoxicity from statins, and particularly the risk differences between the different statins, are lacking. The main objective of this study is to evaluate the hepatic adverse drug reactions by statins in the database of the Italian Interregional Group of Pharmacovigilance (GIF) coordinated by the Verona Centre.

GIF database contains reports of suspected adverse reactions sent to six Regional Pharmacovigilance Centres in Italy (Veneto, Lombardia, Emilia Romagna, Friuli Venezia Giulia, Sicilia and Provincia Autonoma di Trento). Up today The GIF database has 35,757 reports, 37% of which are serious. The 2004 GIF reports were 4,105 report (corresponding to an annual spontaneous reporting rate of 170 reports/million inhabitants), more than 60 percent

of total Italian reports. Twice in a year the database is analyzed for potentialsignals.

In the GIF database there are in total 1512 reports related to statins actually available in the Italian market: simvastatin (444 reports), atorvastatin (385), fluvastatin (194) pravastatin (176) and rosuvastatin (61). Fluvastatin has the highest percentage of reports containing hepatic reactions (69 reports, 36% of total reports), followed by simvastatin (50 reports, 11%), atorvastatin (32 reports, 10%), pravastatin (16 reports, 9%) and rosuvastatin (6 reports, 10%). Fifty per cent of reports with hepatic reactions related to fluvastatin were serious, compared to a percentage of less than 25% for the other statins. The hepatic reactions associated to fluvastatin include 26 hepatitis, and 5 cholestatic hepatitis. The relative risk to develop hepatic reactions, calculated within the GIF database is higher for fluvastatin (8.99 CI 95% 7.39-10.96) compared to atorvastatin (2.36 CI 95% 1.73-3.21), simvastatin (2.78 CI95% 2.13-3.63), pravastatin (2.21 CI95% 1.38-3.53) and rosuvastatin (2.38 CI95% 1.11-5.09).

86. ADVERSE DRUG REACTIONS BY SYSTEMIC ANTIBACTERIALS: SIGNALS FROM SPONTANEOUS REPORTING IN ITALY

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Adverse drug reactions are often related to systemic antibacterials. The most frequent are cutaneous reactions (from mild rash or erythema to serious toxic epidermal necrolysis or Stevens-Johnson syndrome) and gastrointestinal reactions (generally mild reactions like nausea, vomiting or abdominal pain). However, many adverse reactions by antibacterials are related to individual agents and not class side effects. Aim of this study is to analyze the spontaneous adverse reactions by systemic antimicrobials in the database of the Italian Interregional Group of Pharmacovigilance (GIF) looking for signals, i.e. reactions not previously reported or different toxicity profile among drugs of the same group.

Methodology: GIF database contains reports of suspected adverse reactions submitted to six Regional Pharmacovigilance Centres in Italy (Veneto, Lombardia, Emilia Romagna, Friuli Venezia Giulia, Sicilia and Provincia Autonoma di Trento). Up today The GIF database contains 35,757 reports, 37% of which are serious. In 2004 GIF database contains 4,105 report (corresponding to an annual spontaneous reporting rate of 170 reports/million inhabitants), more than 60 percent of total Italian reports.

Results: The database include 7,446 reports related to systemic antimicrobials, with 103 drug associated to at least one report. The most frequent are cutaneous reactions (47%) followed by gastrointestinal (12%), general (9%) and CNS (6%) reactions.

The following association are discussed: higher incidence of anaphylactic shock by parenteral administration of ceftriaxone related to other beta-lactams, increased incidence of Stevens-Johnson syndrome and hepatic reactions (including hepatitis) related to amoxicillin compared to the association amoxicillin and clavulanic acid, hematological reactions associated to cotrimoxazole, macrolides (azithromycin and clarithromycin) and agranulocytosis.

87. MUSCULOSKELETAL ADVERSE DRUG REACTIONS: DATA FROM SPONTANEOUS REPORTING DATABASE IN ITALY

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The musculoskeletal system can be a target organ for adverse drug reactions (ADRs). Drug-induced muscle, bone or connective tissue injuries may be due to a primary direct drug action, or to an indirect consequence of generalized drug-induced disease (e.g. drug-induced polyneuropathy). Musculoskeletal ADRs may be sometimes only temporarily disabling, such as muscle cramps, as well as in other cases may be serious and life threatening, such as rhabdomyolysis. Aim of this study is to analyze the data in the database of the Italian Interregional Group of Pharmacovigilance (GIF).

GIF database contains reports of suspected adverse reactions submitted to six Regional Pharmacovigilance Centres in Italy (Veneto, Lombardia, Emilia Romagna, Friuli Venezia Giulia, Sicilia and Provincia Autonoma di Trento). Up today GIF database contains 35,757 reports, 37% of which are serious. In 2004 GIF database contains 4105 report (corresponding to an annual spontaneous reporting rate of 170 reports/million inhabitants), more than 60 percent of total Italian reports.

Reports with musculoskeletal ADRs are 1,706 and account for about 5% of all reports. The more frequent reported reactions are myalgia (846 reports), arthralgia (402), tendon disorders (222) and rhabdomyolysis (164), mostly induced by HMG-CoA reductase inhibitors (simvastatin 185 reports, cerivastatin 164, atorvastatin 160, pravastatin 61, fluvastatin 49) and fluoroquinolones drugs (levofloxacin 148 reports, ciprofloxacin 56, pefloxacin 27).

However, high differences within the single drugs of the same class can be observed. The higher percentage of rhabdomyolysis caused by cerivastatin lead to the withdrawal of this drug in 2001.

If we consider tendon disorders by fluoroquinolones 35 cases related to ciprofloxacin, 79 to levofloxacin and 19 to pefloxacin are present in the database. However, looking at the more serious tendon rupture 24 cases related to levofloxacin compared to 3 cases related to ciprofloxacin and 1 case related to moxifloxacin and lomefloxacin are present.

Finally musculoskeletal ADRs not previously reported to some drugs are present: among these tendon rupture by atorvastatin and osteonecrosis of the jaw by bisphosphonates.

88. FROM PHARMACOVIGILANCE TO VIGILANCE PLANNING — THE SYSTEM BUILDING FOR DRUG SAFETY IN TAIWAN

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Pharmacovigilance is not just an issue of the pre- or post marketing surveillance of pharmaceutical products but also the risk management on medication behavior of the consumers. Medicines are in general over used in oriental society as a culture that ordinary people believe that drugs are by any means beneficial. Accordingly, risk management of medication needs to be implemented by system building and the operation of pharmacovigilance planning (PVP) has to be extended from Good Dispensing Practice (GDP) of professionals to Good Dispensing and Delivery Practice (GDDP) of the society. The national Network of Adverse Drug Reaction Reporting System was established, basically for professional communication. The *In-Telligent Mommy's Program* is a public education delivered to the general public in over 50 community colleges, with silver-hair generation as the majority of the audience, on rational drug use. As drug abuse becomes a social problem, the *Drug-Free Teenagers' Program* was initiated as pilot runs in 2004 via school teaching in 378 elementary schools. Pharmacy students join the program as part of the professional training on social pharmacy. Strong demand was requested from other elementary schools all over the nation. Statistics indicated that these educational programs fulfill the unmet need of the civilians on knowledge building of rational medication. The educational programs also facilitate the confidence building between the pharmacists and the consumers. The *Community Mommy's Eye Program* monitors illegal advertisement of pharmaceuticals, neutraceuticals, herbal medicines and cosmetics by community pharmacists from 21 counties of the nation. The illegal rates dropped from 90% to 53% after 5 month of monitoring and consequent litigation. The pharmacists who participated in such programs showed their confidence and the potential as the role model of public health activators.

89. DIFFERENTIAL USE OF NSAIDS IN THE FRENCH POPULATION

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Most adverse reactions to NSAIDs are dose- and duration-dependent. Different usage patterns, indications and patient populations can result in widely different risks.

Objective: To describe NSAIDs user populations.

Methods: CADEUS, a country-wide cohort of NSAIDs users randomly selected from national prescriptions database over one year. Data were obtained from 13 553 conventional NSAIDs users including medical data on indication, drug prescription pattern, previous medical history, concomitant prescription of gastroprotective agents [mostly proton pump inhibitors (PPIs)].

Results: There were wide variations in the use of different NSAIDs: for ibuprofen (I, 3698 users) mean age was 45.3 years, compared to piroxicam (P, 1765 users), ketoprofen (K, 1706 users), diclofenac (D, 1498 users), or naproxen (N, 1087 users), whose means ages were respectively 54.4, 49.7, 56.5, 50.8 years. Major indications for I were fever and flu (32.3%), headache (14.7%), back (14.5%), or dental pain (13.3%). P, K, D, N were used mainly for back pain (47.7, 40.9, 44.6, 35.1 % respectively for P, K, D, N), musculoskeletal pain (23.2, 17.8, 18.7, 22.2%, respectively), and arthrosis (OA) (19.5, 11.1, 23.7, 15.1%). Concomitant PPIs were found in 6.1% of I users compared to 33%, 38%, 37%, and 31% for P, K, D and N. Even within the same indication, for instance OA, there were clear differences between I and P, K, D, N. Even though the mean patient age (65) and gender distribution was the same (65–70% female), as were previous cardiovascular (Coronary history in 6.1–5.8%) and GI history (history of ulcers in 2.5 – 3.3%), 66 % of I users were on low doses, vs 9% of the other NSAIDs, 61 vs 43% were on demand users, 23 vs 45% had concomitant PPI, 68% vs 83% of which were given for systematic prevention.

Conclusion: Different NSAIDs have very different usage patterns, even within the same indication and should not be pooled. Database or even field studies that do not include indications and usage patterns may yield erroneous risk assessments

90. DETECTING INTERACTIONS IN WHO DATABASE-USING CYP INFORMATION

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Objective: To study if potential interactions are reported as such in Vigibase, and if CYP enzyme information is useful in identifying new possible interactions, enhancing the UMC signal detection process.

Methodology: The WHO Adverse Drug Reaction (ADR) database, Vigibase, contains over 3.3 million reports of suspected ADRs. The drug substance information in Vigibase was linked to information in a Cytochrome P450 Drug Interaction table.[1]

The proportion of reports listing 'interacting' drugs for Vigibase was calculated.

All reports from year 2000 were retrieved for detailed analysis, calculating:

1. Number of reports with unique drug-ADR combinations listing an 'interacting' drug, compared to total number of reports.

2. Reporting Odds Ratio (ROR) for terfenadine/substrates of CYP and QTp/TdP, serious arrhythmias and rash.

3. Number of reports for combinations, from all reported drug-drug-ADR combinations with drugs acting as substrates and/or inhibitors on the same CYP isoform, with one CYP drug reported as 'suspected' and another irrespective of reported 'drug role'.

Result: Only 0.7% of the reports in Vigibase list 'interacting' drugs.

Drug-ADR combinations often reported as interacting included e.g. theophylline and moclobemide, both with known CYP activity.

For CYP substrate drugs, ROR for ADRs of dose related/CYP induced type was greater than for non dose related/non-CYP induced.

Most reported drug-drug combinations involving CYP inhibitor and substrates are generally accepted, or listed as interactions in the literature.[2] However, none of the drugs were reported as 'interacting'.

Conclusion: Many dose-related ADRs are not recognised as the result of an interaction.

Possible interactions should always be considered if two drugs act on the same CYP isoform. CYP information linked to ADR reports will increase the chance of finding interactions at an early stage.

Potential drug safety problems and interactions can be detected in our signalling process if screening the complete database, and not only on 'interacting' drugs.

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91. COX-2 INHIBITORS MAY CAUSE DYSRRHYTHMIAS. A SIGNAL FROM THE NEW ZEALAND INTENSIVE MEDICINES MONITORING PROGRAMME

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The Intensive Medicines Monitoring Programme (IMMP) performs post-marketing prospective cohort studies using Prescription Event Monitoring (PEM) methodology. The IMMP collected prescription and event data for rofecoxib and celecoxib from 2000 to 2004. Voluntary reports of suspected adverse reactions were also received. Cardiac dysrrhythmic events recorded (total 63) included palpitations, tachycardia, atrial fibrillation, heart block, bradycardia, ventricular tachycardia and fibrillation and cardiac arrest. Amongst these thirty six of palpitations, tachycardia, atrial fibrillation or ventricular tachycardia were considered to be suspected reactions in that they were categorized as possibly (20), probably (12), or definitely (4) associated with COX-2 inhibitor use. Three patients with atrial fibrillation recovered when the COX-2 inhibitor (celecoxib 2, rofecoxib 1) was discontinued. One was stated to have ischaemic heart disease. However, none of these occurred in the context of myocardial infarction. Two patients with palpitations and two with tachycardia relapsed when the COX-2 inhibitor was re-administered. One report of ventricular tachycardia was considered possibly related to COX-2 inhibitor use. A further patient with an irregular pulse but no electrocardiographic confirmation also relapsed on rechallenge. Two patients, one with atrial fibrillation and one with tachycardia, experienced paroxysmal events over a period of weeks or months that resolved when the COX-2 inhibitor was withdrawn. Onset was in some cases rapid, occurring in less than 24 hours. The mean age of the patients was 72.5 years. The Physicians Desk Reference lists palpitations as an adverse effect of several standard non-steroidal anti-inflammatory medicines as well as tachycardia and bradycardia with ibuprofen. For Celebrex (celecoxib) the PDR indicates that ventricular fibrillation has been reported in <0.1% of patients.

The IMMP data suggests that both rofecoxib and celecoxib may have dysrrhythmogenic potential. This is likely to be rare and requires further confirmation.

92. VACCINE ADVERSE EVENTS IN CANADA: RESULTS OF SURVEILLANCE (JAN 1997 – DEC 2003)

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Objective: To summarize the most frequent and serious adverse events (AEs) reported following vaccination and to present the most common vaccines concerned in these adverse events from 1997 to 2003.

Methodology: The Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) database was searched for any AEs reported to the Public Health Agency of Canada (PHAC) temporally associated with all vaccines administered from January 1, 1997 to December 31, 2003.

Results: A total of 31,145 AEs case reports were identified in the database. Females accounted for 60.4% of all reports, and about 57.8% (17,992) were children aged 14 years and younger. The most frequently reported AEs for all vaccines over the seven years were fever 23.8 % (7,552), severe pain and or swelling 20.6% (6,561), allergic reactions 13.4% (4,255), rashes 7.4 % (2,341) and severe vomiting and/ or diarrhea 6.9% (2,206).

The most frequent adverse events following the influenza vaccine alone were ORS (oculo-respiratory syndrome) 23.6% (1,540), allergic reaction 7.6 % (1,147), fever 13.8% (907), severe pain and/ or swelling 12.4% (815), ORS time to onset > 24 hrs 6.2% (450).

The most suspected vaccine types records of adverse events were Hib18.9% (8,379), Influenza 18.4% (8,150), DaPT-IPV (Diphtheria, acellular Pertussis, Tetanus, Polio) 14.4 % (6,403) and MMR (Measles, Mumps, Rubella) 10.6% (4,725).

As outcomes, 90.9% (21,883) of the reported cases recovered completely. Among the cases considered as serious 4.5% (1,399), 57.8% (808) were cases hospitalized 3 or more days and 4.2% (58) were deaths cases.

Conclusion: The profile of the AEs based on the CAEFI database

reflects the safety of vaccine and the quality of the surveillance system in Canada. Most of AES are either local reactions or less serious systemic reactions.

93. NEURO-PSYCHIATRIC DISORDER INDUCED BY AMIODARONE

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Introduction: Neuro-psychiatric side effects due to amiodarone are rare and the most reported are: trembling, myopathy, ataxia, peripheral neuropathy and nightmare. We report a case of a neuro-psychiatric disorder induced by amiodarone.

Case report: A 71 year-old woman was hypertensive since 20 years treated with metoprolol. On June 12, 2003 (= day 1), for arrhythmia she was treated with amiodarone, acenocoumarol, hydroxyzine, sulpiride and the metoprolol was stopped. On day 5 she received amiodarone by parenteral route for three days. Seven days later, she had trembling of the limb extremity associated with asthenia. On day 26 she had the first episode of agitation, anguish and obnubilation. The doctor prescribed her the fluoxetine without disappearance of these signs. In front of the aggravation of the clinical symptomatology (auditive hallucination, nightmare, anguish and insomnia) fluoxetine was stopped and sertraline was started on day 41. Sulpiride and sertraline were stopped on day 52. In front of the persistence the neuro-psychiatric signs, amiodarone and hydroxyzine were withdrawn on day 61. Seven days later, the patient was addressed to the "Centre National de Pharmacovigilance" and a monitoring of the amiodarone plasmatic level was performed (C° = 2.46 µg/ml). Disappearance of nightmare and hallucination, and a decrease of the trembling intensity were happened on day 76, with a C° = 0.96 µg/ml. On day 100 she was asymptomatic and the C° = 0.63 µg/ml. Electro encephalogram and cerebral tomodensitometry were negative.

Discussion: The responsibility of the amiodarone in the genesis of the neuro-psychiatric disorder was retained in front of: a compatible delay (13 days) with an iatrogenic origin, a favourable course after stopping amiodarone that was sustained by the decrease of the amiodarone plasmatic levels, a negative etiologic investigation and the no recurrence after amiodarone withdraw. Neuropsychiatric disorders induced by amiodarone are rare, but the clinician must evoke them when this drug was taken.

94. ADVERSE DRUG EFFECTS OF CICLOSPORIN IN PATIENT WITH IDIOPATHIC NEPHROTIC SYNDROME

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Introduction: Ciclosporin, an immunosuppressant agent, is used in idiopathic nephrotic syndrome (INS). This immunosuppressant drug has many adverse drug effects (ADE) and the ciclosporin monitoring should be performed because of inter-individual pharmacokinetic variability. We studied the ciclosporin ADE related to ciclosporin whole blood concentration in patients with INS.

Methods: We performed a retrospective study from January 1996 to October 2004 about ciclosporin therapeutic monitoring. It concerned 213 patients having INS and in which we performed 782 ciclosporin monitoring.

We studied in each patient the ciclosporin concentration, the creatinine, the kaliemia, the blood pressure, the liver enzymes and any other ADE.

Results: In 68% of the whole 782 ciclosporin monitoring, we found ADE. Arterial hypertension was found in 209 (26%) with an average of ciclosporin concentration of 138.67 ng/ml. In normotensive patient, the average of ciclosporin concentration was 78,30 ng/ml (epsilon 2.89 < 1.96). Nephrotoxicity was found in 28% of the cases with an average of ciclosporin concentration of 127.21 ng/ml. Gingival hypertrophy was observed in 25% of the population. Neurological side effects were also observed: tremors were notified in 25 cases. The other ADE were nauseas and vomiting, hypertrichose and face oedema.

Discussion: Arterial hypertension was the most reported ADE in our study. This high level of ADE is explained partly by the concomitant use of corticoids. Chronic or acute nephrotoxicity are reported through literature with ciclosporin use. The rates of this ADE are more important in these reports than in our study and exceed 50%. This undervaluation is explained by the evaluation of nephrotoxicity in our study by only biological parameters. The other studies used histological parameters in addition to biological ones.

Conclusion: Because of its potential frequent ADE, ciclosporin should be monitored in order to avoid these effects and to benefit of its immunosuppressant effects.

95. TACROLIMUS AND SIDE EFFECTS

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Introduction: Tacrolimus has a narrow therapeutic index, making its therapeutic drug monitoring (TDM) essential. Several studies have reported that the side effects of tacrolimus are more closely correlated with tacrolimus blood concentration rather than the dose. The aim of this study was to find a correlation between tacrolimus blood concentration and side effects.

Material and method: It consists on a retrospective study (2001–2005), 175 TDM was carrying out. A total of 55 subjects (51 renal and 4 hepatic transplantations) were evaluated. The average age was 31 years and the sex ratio was 1.1. In addition to trough tacrolimus blood concentrations, ALAT, ASAT, total bilirubin, serum creatinine, serum potassium, blood glucose, were also measured.

Results: Our results showed an average concentration (Cm) with 10.65 ng/ml (therapeutic interval range 5–20 ng/ml); 77% of cases have a concentration in therapeutic interval. Results show too, failure

renal function in 51% of cases (Cm of tacrolimus 12.35 ng/ml). Hyperkaliemia was observed in 3% of patients (Cm = 13.35 ng/ml). ASAT increasing was obtained in 27% of cases (Cm = 10 ng/ml) and an increase in ALAT in 19% (Cm = 11.42 ng/ml). A total hyperbilirubinemia was occurred in 12% of cases (Cm = 10.17 ng/ml). 8 cases of gingival hypertrophy were observed (Cm = 15.6 ng/ml). Statistical analysis did not find a correlation between these side effects and tacrolimus concentration. Hyperglycemia was found in 16% (Cm = 15.8 ng/ml). The difference was statistically significant between tacrolimus concentration and occurrence of this side effect (epsilon = 4.015, p = 0.0001).

Discussion: Different studies demonstrate that tacrolimus alters glucose metabolism, they demonstrate also that hyperglycemia is a dose dependent.

For that, monitoring of tacrolimus is recommended in all patients to permit dosage adjustments on an individual basis. In addition, renal and hepatic function, serum glucose and electrolyte should be monitored.

96. BRAZILIAN PHARMACOVIGILANCE SYSTEM AND REGULATORY MATTERS

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Introduction: Brazil, an important Latin American federative country, has 178 million inhabitants in over 5,500 municipalities, is among the 10 largest pharmaceutical markets in the world with: 4,700 drug registration holders, 52,000 drug forms, 10,000 pharmaceutical products. In addition, Brazil has a social and cultural diversity that makes drug market regulation a more complex issue. In 1999, the Brazilian National Health Surveillance Agency (ANVISA) started the consolidation process for the National Pharmacovigilance System after establishing the National Centre for Drug Monitoring (CNMM), headquartered at ANVISA's Pharmacovigilance Unit, created by Ministerial Decree MS no. 696, of 7 May 2001. In August of the same year, Brazil was included in the International Drug Monitoring Programme co-ordinated by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. One of the difficulties to face is the lack of tradition among health professionals and service directors of notifying the occurrence of drug adverse events.

Objective: This work aims to assess the importance of Pharmacovigilance for guiding the decision making process based on all information from the notifications of ADR.

Methods: A standard form was established and made available on ANVISA website, as well as a specific system for "sentinel hospitals", which would be the communication channel between health professionals and the Brazilian Pharmacovigilance System. The notifications received at CNMM were assessed and gave origin to regulation measures in accordance with the seriousness and relevance of notifications.

Results: By June 2005, had received 4,876 notifications, which provided important information for the decision making process concerning pharmaceutical market regulation. Risks were identified, and thus were the basis of more than ten health actions.

Conclusions: Through the analysis of ADR notifications, it is possible to detect signs, assess the post-market benefit/risk ratio of drugs, favouring the development of Pharmacovigilance at regulatory level.

97. BRAZIL — PHARMACOVIGILANCE: A NEW EXPERIENCE WITH A NET OF SENTINEL HOSPITALS

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Introduction: Brazil is one of the 10 largest pharmaceutical markets in the world, with annual sales estimated at around US$4.8 billion in 2003. In addition, Brazil has a social and cultural diversity that makes the regulation of pharmaceutical market very complex. The creation of the Brazilian Health Surveillance Agency (ANVISA), in 1999, provided the initial steps to the consolidation of the National System of Pharmacovigilance (NSP). After establishing the National Center of Monitoring of Medicines, headquartered at ANVISA's Unit of Pharmacovigilance and was included as the 62nd member of the International Drug Monitoring Programme, co-ordinated by the Upssala Monitoring Centre, Sweden, as a collaborator to the World Health Organization. One of the difficulties to be faced was the lack of tradition among health professionals and service directors in notifying the occurrence of drug adverse effects. One of the strategies used to motivate this notification practice was the creation of a wide chain of hospitals called Sentinel Hospitals.

Objective: To assess the contribution of Sentinel Hospitals towards building this new practice of notification of drug adverse effects.

Methodology: A risk manager was assigned to each hospital, who would be the communication channel between the hospital and the NSP, thus allowing the exchange of information.

Results: In 2002, after establishing the project Sentinel Hospitals, there was a considerable increase in the corresponding number of notifications; 643 notifications compared to 178 in 2001, before the project Sentinel Hospitals was established. Of the 643 notifications received in 2002, 36% were from the sentinel hospitals. By mid 2005, the percentage of notifications from sentinel hospitals accounted for 51% of the total.

Conclusions: The project Sentinel Hospitals constitutes an important nucleus of notification, because it allows the clinical observation of drug-related risks, thus feeding the monitoring system in Brazil.

98. PHARMACOVIGILANCE AND RATIONAL USE OF DRUGS

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Introduction: Since the creation of the National Centre for Drug Monitoring in 2001, Brazil developed actions of safety and promotion of the rational use of drugs, according to the Brazilian National Drug Policy.

Objective: To promote the rational use of drugs by reorientation of irrational practices of drug use, continued education for the population and, specially, to qualify health professionals on the rational use of drugs.

Methods: Developing a program of continued education for health professionals and undergraduated students seeking the rational use of drugs through a benefit-risk analysis of marketed drugs; modifying the package patient insert information for both patients and health staff; preventing self-medication, and producing safety alerts. A specific workshop on Rational Use of Drugs at national level took place last May with the presence of 38 university professors from several medical areas. Other six regional workshops will occur, at the end of which up to 300 medical professors will be ready to spread this information at their Universities, thus establishing a net of continued education.

Results: During the first year, two workshops on Safety and Surveillance were carried out and up to 300 health professionals from a hundred hospitals, called "Sentinal Hospitals". Until last year, 291 safety alerts had been issued. A National Drug Compendium of Package Patient Insert is being created and will be divided in two: one for the patients for a better understanding and the other for health staff with more technical information.

Conclusion: Pharmacovigilance actions in Brazil are expected not only to be associated with monitoring of Adverse Drug Reactions but also to ensure the rational use of drugs. New studies, analyses and assessments ought to be developed in order to create further information and improve those actions.

99. AMOXICILLIN AND CO-AMOXICLAV (AMOXICILLIN + CLAVULANIC ACID): DIFFERENCES IN ADVERSE DRUG REACTIONS TYPE AND SERIOUSNESS EXTRAPOLATED FROM AN ITALIAN INTER-REGIONAL DATABASE

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Objectives: Amoxicillin and co-amoxiclav are antibiotic drugs largely prescribed for the same indications in Italian medical practice (year 2003). The co-amoxiclav is also the fifth drug for public health spending and alone represents the 71% on the total amount of expenses for penicillin class. Aim of the present study was to investigate adverse events caused by them and reported through the Italian spontaneous reporting system.

Methods: The Pharmacovigilance Inter-regional Group (GIF) database contains 31,000 reports of adverse drug reactions (ADRs), related to 25,000,000 inhabitants (43% of Italian population), collected from 1988 to now. From this database, amoxicillin and co-amoxiclav reports were extrapolated. Particularly, ADRs seriousness was estimated, comparing adverse reactions reported for both antibiotics.

Results: The number of reports relating to amoxicillin and co-amoxiclav is almost the same (1062 vs 1024, respectively). In the ADRs reported, the mean age of patients is similar (amoxicillin: 41.9 ± 22.8; co-amoxiclav: 43.1 ± 23.8). Co-amoxiclav is associated with a significantly higher proportion of serious ADRs (37.8% vs 31.8%; p=0.004) compared to amoxicillin. Moreover, co-amoxiclav caused hematological, hepatic and gastroenteric ADRs more often ($p<0.05$) than amoxicillin (2.2% vs 0.8%, 3.8% vs 0.6%, 12.7% vs 7.6%, respectively).

Further examples of disproportionalities between co-amoxiclav and amoxicillin were the following: hepatitis (15:1), cholestatic hepatitis (7:2), jaundice (4:10), purpura (13:5) and Stevens-Johnson Syndrome (10:2).

Conclusion: These data indicate a different safety profile between amoxicillin and co-amoxiclav. The latter was responsible for more serious adverse reactions. Thus, in therapeutic choice, this difference should be borne in mind.

100. ANAPHYLAXIS AND STEVENS-JOHNSON SYNDROME FOLLOWING TOPICAL DRUG APPLICATION IN SPONTANEOUS ADR REPORTS: CAUSALITY AND INCREASED DRUG RESORPTION AS RISK FACTOR

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Objective: Drug-induced anaphylaxis and Stevens-Johnson syndrome (SJS), either immediate or delayed-type reactions, are maximal ADR variants. Occurrence of such reactions following topical application of drugs, e.g. ointments, has only rarely been described in the literature. The objective of the present study was to analyse all such cases contained in the BfArM spontaneous ADR database.

Methodology: All case reports of drug-associated anaphylaxis and SJS following topical drug application reported to BfArM from 1989 to 2004 were identified and assessed with regard to correctness of diagnosis, causal relationship with the drug and relevant additional information provided.

Results and conclusions: 47 cases of anaphylaxis and 21 cases of SJS after topical drug application were reported to the BfArM in the review period. In 34 of 47 anaphylaxis-cases correctness of diagnosis and causal relationship was assessed at least as possible, in 9 cases at least as probable. In 24 of 34 possible anaphylaxis-cases, and in 7 of 9 probable anaphylaxis-cases, the drug was applied to inflamed skin or mucous membranes. Among the 21 SJS-cases correctness of diagnosis and causal relationship was assessed at least as possible in 4 cases. However, in these 4 cases causal relationship with other

drugs administered systemically was also considered as possible, i.e. contributing to the event.

An at least possible causal relation with topical drug application was found in a relevant number of anaphylaxis-cases and in some single SJS-cases. A possibly increased drug resorption via inflamed skin or mucous membranes could pose a potential risk factor for the occurrence of anaphylaxis following topical drug application.

101. QUANTIFYING ALERTS: THE BURDEN OF ADRS TO THE INDIVIDUAL AND TO THE SOCIETY

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It is essential that any assessment of the burden created by adverse drug effects is not made in isolation from the efficacy of the treatment. For an individual, the overall effect a drug depends on the baseline risk posed by the disease itself, the estimated probability and magnitude of the benefits and harms of the medicine. These estimates are typically derived from clinical trials and formal pharmaco-epidemiological studies. Treatments will be introduced widely if the untreated medical condition is sufficiently serious and the *average* benefits of treatment outweigh the *average* harms and costs. However, applying such data to individuals is challenging as both beneficial and harmful treatment effects may be modified by genetic, health system, economic factors, disease severity and the presence of co-morbidity. The values of individual patients also need to be considered as these may weigh disproportionately in some circumstances. These factors are also important when evaluating and comparing the burden of adverse drug effects in high and low income countries. In the latter, the burden of untreated disease and the potential benefits from treatment may be very large. This can shift the overall balance of benefit and harm and may make a case for being less 'risk averse' than in high income countries. In this presentation these arguments will be supported using a range of examples including anticoagulants, anti-inflammatory, antiretroviral and anti-malarial treatments.

102. SIGNAL GENERATION IN PHARMACOVIGILANCE — MORE THAN NUMBERS

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Several methods have been used for signal generation since the emergence of modern pharmacovigilance after the thalidomide disaster in the early 1960's, including:

- recognition by clinicians of possible adverse drug reactions (ADRs) in individual or a series of patients
- reporting by clinicians of suspected ADRs in the medical literature or to spontaneous reporting systems of suspected ADRs
- qualitative analysis of spontaneous ADR reports and published case reports
- methods to examine the disproportionality of ADR profiles of drugs compared to other drugs in pharmacovigilance databases
- qualitative and quantitative studies from drug utilisation and pharmacepidemiological databases
- signals from clinical trials.

Signals generated by any method must be evaluated in respect of their internal quality and in relation to the drug, the underlying disease, concurrent diseases, concomitant medications the patient(s) characteristics.

Information technology techniques and statistical methods are complementary to scientific, clinical and epidemiological evaluation. The strength of evidence is likely to increase when several methods of signal generation are evaluated collectively.

103. RISK MANAGEMENT IN PHARMACOVIGILANCE — SOME OF THE REALITIES OF THE PRACTICE

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Risk management in pharmacovigilance includes the identification, description and quantification (to the best possible standards) of the risk(s) associated with the use of medicines; followed by risk/benefit evaluation (including comparisons with the risk/benefit profiles of the other therapies used to treat the underlying condition or the prognosis of the untreated condition). Then, plans need to be set and implemented for risk management/mitigation and monitoring their effective implementation.

All steps in the risk management process must be based on the best possible evidence. However, frequently there is paucity of data regarding important points such as the background incidence of suspected adverse drug reactions in the underlying population. Other difficulties in risk/benefit evaluation include the limitations of premarketing studies to adequately define the safety profiles of medicines and the problems of postmarketing observational pharmacoepidemiological studies, such as bias, confounding, misclassification and under-reporting. With regard to clinical trials, there are problems with conducting good quality large scale postmarketing safety clinical trials, such as the logistical difficulties of conducting postmarketing clinical trials to answer safety questions and possible limited generalisability of the results from such trials. All these difficulties can be serious and may lead to misleading results and inappropriate decisions.

Approaches to reduce the limitations include conducting proactive studies to understand the underlying disease and the characteristics of the treated population and studies to examine the risks and the safety profiles of medicines. There is a need to use a range of study designs (both clinical trials and observational studies) in different healthcare systems to answer the safety questions. The collective results of such studies have a better chance of reducing bias and providing better evidence of the safety of medicines. However, problems remain even with careful design and multiple studies. Methodological research continues to be necessary to improve the research methods in this field.