ORIGINAL RESEARCH ARTICLE

Drug Safety 2002; 25 (10): 713-724
0114-5916/02/0010-0713/$25.00/0

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Detection of Adverse Drug Reactions in a Neurological Department

Comparison Between Intensified Surveillance and a Computer-Assisted Approach

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Abstract

Objectives: Adverse drug reactions (ADRs) leading to hospitalisation or occurring during hospital stay contribute significantly to patient morbidity and mortality as well as representing an additional cost for healthcare systems. The aim of this study was to provide data about the type and incidence of ADRs in a neurological department and to compare two different methodological approaches to collecting information on ADRs.

Methods: The two methods used were intensified surveillance of neurological wards by daily ward rounds and computer-assisted screening for ADRs by means of pathological laboratory parameters.

Results: Of admissions to the neurological department, 2.7% were caused by an ADR and 18.7% of patients experienced at least one ADR during hospitalisation. The positive predictive values of pathological laboratory parameters ranged between 0% (eosinophil count) and 100% for increased drug serum concentrations and international normalised ratio, i.e. the latter were always accompanied by a clinically relevant ADR. However, only half of all ADR could be detected by pathological laboratory parameters, the sensitivity of this method came to 45.1% with a specificity of 78.9%.

Conclusion: Similar to departments of internal medicine, a high number of ADRs occur on neurological wards. The predominant ADRs were those typical of neurotropic medications such as dyskinesia and increased sedation. Due to the age of the patients involved, cardiovascular co-medication is often prescribed and represents an additional risk factor for ADRs. By measuring pathological laboratory parameters the majority of ADRs could not be detected in neurological patients.

Anticonvulsants, drugs for treatment of Parkinson's disease and most drugs used for neurological conditions have an increased propensity to cause adverse drug reactions (ADRs) affecting the central and peripheral nervous system as well as all other organ systems. Drug-related adverse events contribute to about 3 to 15% of all hospital admissions.[1-6] For hospitalised patients, ADRs represent an important risk, resulting in an increased length of stay, extra costs and increased mortality.[7-9] Reports of the incidence of ADRs in hospitalised patients differ between 6.6 and 30%, depending on clinical speciality, method of ADR detection and definition of ADR as well as a number of other factors.[1,10-13] To our knowledge, to date no data on ADRs are available for neurology departments. Recently, clopidogrel, which is widely and chronically used in neurological patients, has been associated with thrombotic thrombocytopenic purpura,[14] supporting demands for more aggressive approaches to post-marketing surveillance.[15,16]

The implementation of surveillance programmes in hospitals has been suggested by several authors;[1,16,17] however, continuous intensive surveillance programmes are time consuming whereas spontaneous, voluntary reporting schemes involving medical staff provide only limited information.[15,16,18] Only one comprehensive computer system (HELP) has been described offering the opportunity for producing alerts from pathological laboratory values or requests for certain antidotes and clinical services, indicating a potential ADR.[7,19,20]

Studies assessing the frequency and recognition of ADRs have so far only been reported for medical wards, geriatric departments, departments of surgery, intensive care units, and departments of psychiatry and paediatrics.[1,2,21,22] Considering the fact that medical advances, i.e. the implementation of stroke units and the increased age of neurological patients, are most likely to result in a polypharmacy resembling the situation on medical wards, data about drug safety in departments of neurology will provide valuable additional information.

We therefore designed a prospective study combining a computerised surveillance system for pathological laboratory data and intensified collection of ADR by daily review of patient charts in the department of neurology of a teaching hospital. Pathological laboratory values were chosen as signals for potential ADRs, since approximately 60% of all ADRs on medical wards could be detected by pathological laboratory parameters.[11,20]

Methods

Patients

All patients admitted to the department of neurology (86 beds) at the teaching hospital Wuppertal GmbH (Germany), providing five wards including a stroke unit and an intensive care unit, were included in our prospective study. The computer-assisted surveillance system (CSS) was conducted over a 3-months period between June and August 1999, whereas an intensified collection of adverse drug reactions was only feasible over 2 months, from June to July 1999, due to personal constraints.

Computer-Assisted Surveillance System of Adverse Drug Reaction (ADR) Detection

In addition to the hospital routine laboratory computer program, software was installed to filter and extract all pathological laboratory values as 'laboratory filter signals' (LFS) within predefined boundaries (tables I and II) from each routine laboratory testing (at admission and for hospitalised patients). Daily checks of these LFS (apart from weekends) were performed by the department of clinical pharmacology. The cause of each LFS value was evaluated by immediate contacts with the attending neurologist and/or by screening the patients' charts. Demographic data of patients with suspected ADRs as well as other relevant information (date of admission, diagnoses) were entered, omitting patients names, into a relational database (Microsoft Access® under Windows NT). The same abnormal laboratory parameter, e.g. low white

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Table I. Pathological laboratory values giving rise to a laboratory filter signal (LFS)

Parameter	Normal range	LFS
White blood cell count	4300-10 000/μl	<25000/μl
Platelet count	150 000-350 000/μl	<100 000/μl >500 000/μl
Haemoglobin level	14-18 g/dl	<11 g/dl or decrease of >3 g/dl
Eosinophil count	<5%	>6%
Creatine kinase level	<80 U/L	>200 U/L
AST level	18 U/L	>36U/L
ALT level	<22 U/L	>44 U/L
Alkaline phosphatase	<180 U/L	>240 U/L
Total bilirubin level	<1.1 mg/dl	>2.0 mg/dl
Glucose level	60-100 mg/dl	<60 mg/dl
Sodium level	135-145 mmol/L	<130 mmol/L
Potassium level	3.5-5.1 mmol/L	<3.0 mmol/L >5.5 mmol/L
Creatinine level	0.6-1.3 mg/dl	>1.5 mg/dl
PTT	1.5-2.5-fold above baseline	>90 sec
International normalised ratio	According to indication	>3.5

PTT = partial thromboplastin time.

blood cell count measured twice in the same patient, was included only once in the database, further changes in that parameter were documented as follow-up.

Once the suspicion of an ADR was strengthened, information about the suspected causative drug (using a brand and generic name) such as dose, route of administration, duration of treatment, up to three concomitant drugs and doses and the total number of drugs administered were entered. The time of the occurrence of the ADR, the course and outcome were documented. Subsequent medical decisions, resulting from the LFS value with or without recognition of the attending physician prior to the alert were noticed.

The conduct of the study and the documentation was in compliance with the Declaration of Helsinki and the German data protection law.

Definition of an ADR and Causality Assessment

The definition of an ADR was concordant with the classification of the WHO, thereby excluding toxic reactions after intended administration of a drug overdose; however, involuntary overdosing due to inadequate dose-adjustment in elderly patients or those with renal failure was defined as

Table II. Drug levels regarded as outside the therapeutic range giving rise to a laboratory filter signal (LFS)

Parameter	Therapeutic range	LFS
Digoxin	0.8-2.0 μg/L	>2.2 μg/L
Digitoxin	10-25 μg/L	>25 μg/L
Gentamicin	6-10 mg/L[a]	>12 mg/L
Vancomycin	20-40 mg/L[a]	>40 mg/L
Theophylline	8-20 mg/L	>20 mg/L
Carbamazepine	4-10 mg/L	>15 mg/L
Phenobarbital (phenobarbitone)	10-40 mg/L	>45 mg/L
Primidone	5-15 mg/L	>15 mg/L
Ethosuximide	40-100 mg/L	>100 mg/L
Phenytoin	10-20 mg/L	>30 mg/L
Valproic acid (sodium valproate)	50-100 mg/L	>150 mg/L
Lithium	0.3-1.3 mmol/L	>1.3 mmol/L

a Peak serum concentration.

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an ADR.[23,24] Prescribing and dispensing errors were not documented. Sources for information about potential drug adverse effects were the summary of product characteristics sheet (German 'Fachinformation') and the most recent edition of the quarterly updated Micromedex© database (Micromedex© Inc., Thomsom Healthcare, USA). The causality assessment was performed also according to the WHO classification scheme[23] with the attributes: 'definite'; 'probable'; 'possible'; 'unlikely'; and 'ruled out'. The severity of the ADR was characterised by a score ranging from 1 to 5 depending on the impairment of the patient and the extent of necessary therapeutic interventions, where: 1 denotes an ADR without physical or psychological impairment; 2 denotes an ADR with slight physical or psychological impairment; 3 denotes an ADR with moderate physical or psychological impairment (therapeutic intervention needed); 4 denotes an ADR with severe physical or psychological impairment (therapeutic intervention and intensive care needed); and 5 denotes an ADR with lethal outcome.

Finally, all cases were reviewed to classify the ADR according to Rawlins as type A (part of the drug's pharmacological action, predictable and dose-dependent) or type B (idiosyncratic, usually not dose-dependent and not predictable) reactions.[25]

Intensified Surveillance of ADR

We simultaneously conducted an intensified ADR surveillance over a 2-month period on one of the general neurological wards, the stroke unit and the intensive care unit. ADRs were registered by daily visits, review of patients charts and evaluated by a clinical pharmacologist together with the attending neurologist.

The recording and analysis of patient data, prescription and evaluation of the ADR was performed as described above for the CSS. In addition, length of hospital stay of patients with an ADR was recorded.

Data Analysis

Demographic data, number of drugs administered and duration of hospitalisation are given as mean, median and range. The positive predictive value of LFS was the percentage of LFS that were classified as an ADR. The data obtained from those wards during the time period, where both approaches were conducted simultaneously, allowed for calculation of sensitivity and specificity. The sensitivity of each approach was defined as the percentage of ADRs detected with one method as compared with the total number of ADR found with both methods together. The specificity of the CSS was estimated as the percentage of patients without ADR *and* without LFS out of the total number of patients without ADR.

Results

ADR Detected by Computerised Surveillance of Pathological Laboratory Values

During the 3 month surveillance period, a total of 600 patients with a mean age of 64 years (median 66; range 16 to 93; 52.0% of female gender) were admitted to the department of neurology. The leading diagnoses were ischaemic stroke, intracerebral haemorrhage, convulsive disorders, multiple sclerosis, Parkinson's disease and sleep disorders.

Five hundred and one pathological laboratory values in 231 patients were detected by the computer method, i.e. 38.5% of all 600 patients were evaluated further for a potential ADR because of their pathological laboratory values.

One hundred and twenty-one (24.2%) of these LFS were assumed to be related to an ADR in 111 (newly admitted and already hospitalised) patients with a mean age of 68 years (median 69; range 38 to 81), of whom 56% were of female gender. Patients with pathological laboratory values but without an ADR (n = 156) had a comparable age with 65 years (median 67; range 24 to 85).

Table III shows the pathological laboratory values 'possibly', 'probably' and 'definitely' associated

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Table III. Laboratory filter signals (LFS) detected and positive predictive value: LFS associated 'probably', 'probable' or 'definitely' with an adverse drug reaction (ADR)

LFS Parameter	Detected (n)	Associated with ADR (n)	Positive predictive value (% of LFS)
White blood cell count	2	1	50.0
Platelet count	17	1	5.9
Haemoglobin level	91	11	12.1
Eosinophil count	1	0	0.0
ALT level	40	15	37.5
AST level	49	8	16.3
Alkaline phosphatase level	42	13	31.0
Total bilirubin level	11	1	9.1
Creatinine level	60	11	18.3
Sodium level	25	6	24.0
Potassium level	33	13	33.3
PTT	25	23	92.0
INR	7	7	100.0
Drug concentrations	10	10	100.0

INR = international normalised ratio; **PTT** = partial thromboplastin time.

with an ADR. About half of all ADRs (n = 56; 50.5%) were characterised as being 'possibly' related with drug treatment, whereas 36.1% of ADRs (n = 40) were classified as 'definite'. 89.2% of ADRs were classified as type A reactions and only 4.5% belonged to type B reactions, another 6.3% of ADRs could not be classified.

The majority of the detected ADRs (95; 80.2%) were of minor severity (grade 1 and 2); however, a therapeutic consequence such as reduction of dose or withdrawal of the drug followed in 59%.

The drugs causing most of these less severe ADRs were heparin and phenprocoumon resulting in coagulation parameters exceeding the therapeutic range; however, these occurred without any or with only minor bleeding complications. The most commonly observed alterations in laboratory values and the causative agents are shown in figure 1. It should be noted that carbamazepine was not only suspected to cause liver toxicity but also three cases of otherwise unexplained hyponatraemia. Patients with an ADR of severity grade 1 and 2 were given a mean of 6.0 drugs (median 5.0; range 3 to 9).

Most of the severe ADRs (grade 3 to 5, n = 16) were decreases in haemoglobin level as a marker for serious bleeding events (n = 9). Two of these nine bleeding events (intracranial and gastrointestinal bleedings) were caused by phenprocoumon (one fatality), four cases by heparin alone and in three cases the antiplatelet drugs were co-administered. Three serious ADRs (one fatality) were caused by unintended drug overdosing of digitoxin, phenytoin and primidone. In total, two ADR-associated deaths were recorded. Other severe ADRs were renal failure following co-treatment with an ACE inhibitor, a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic, as well as two cases of amantadine-induced psychotic disorders. The latter two cases were detected because of abnormal laboratory values, which were not related to the psychosis; however, an alert was generated by the LFS. Patients with more severe ADRs received a mean of 6.6 drugs (median 5.5; range 3 to15).

With regard to polypharmacy, drug interactions were considered to be the cause of 24 of 111 ADRs. Obviously, bleeding episodes were seen more frequently in patients receiving more than one anticoagulant and/or antiplatelet drug. Liver toxicity was observed in seven cases following administration of anticonvulsive combination therapy or coadministration of antibiotics known to cause hepatotoxicity. Increases in serum creatinine levels

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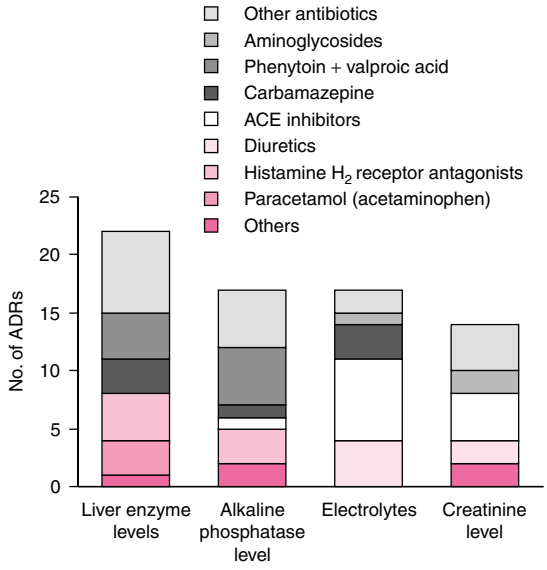

Fig. 1. The most frequently observed alterations in laboratory values associated with adverse drug reactions (ADRs) and the implicated drugs.

were observed in five cases following combination treatment with ACE inhibitors, NSAIDs and/or diuretics.

A total of 55 ADR were considered to be a 'probable' or 'definite' ADR. In relation to the number of patients admitted (n = 600) to the department of neurology, 9.2% of all patients experienced any ADR; 1.7% (n = 10) experienced an ADR severity grade 3 to 5. Only in five cases did the ADR contribute to hospital admission, accounting for 0.8% of all admissions to the department of neurology during the observation period. These were all severe ADR such as amantadine-induced psychotic disorders, phenytoin/primidone overdose with coma or phenprocoumon-associated stem-ganglion bleeding.

ADRs Detected by Intensified Surveillance

During the intensified surveillance period, 332 patients [51.2% females; mean age 63 years (median 66 years, range 16 to 93)] were admitted to the three wards of the department of neurology included in the intensified surveillance programme. Daily control of patient charts and spontaneous reporting by attending neurologists resulted in detection of 82 ADRs (table IV) occurring in 51 patients (19 females) with a mean age of 66 years (median 65, range 41 to 93). By means of intensified monitoring we identified nine patients being admitted due to an ADR (2.7% of 332 patients), of whom five had severe neuropsychiatric symptoms, e.g. hallucinations and antipsychotic-induced Parkinson syndrome (n = 3), 12.6% of all patients admitted to these wards experienced at least one ADR during their hospital stay.

In 56.1% (n = 46) of the ADRs the relationship to drug treatment was characterised as 'possible', in 22 of these cases the classification of the relationship to one drug was hampered due to interactions, e.g. heparin and aspirin (acetylsalicylic acid) both contributing to a bleeding episode. Of the ADRs, 35.4% (n = 29) were considered to be 'probable' and 4.8% (n = 4) cases were considered 'definite'.

Seventy-eight ADRs were classified as type A and only four as type B reactions. Patients with an ADR received a mean of 5.3 drugs (median 5.5; range 1 to 10). One half of patients with an ADR received at least one cardiovascular drug, since cardiovascular diseases were the most frequently observed concomitant diagnoses.

Thirty-nine (47.6%) of these adverse events in 30 patients were categorised as ADR of minor severity (grade 1 and 2, table IV). Seven ADRs consisted of specific neuropsychiatric adverse effects of neurotropic drugs such as extrapyramidal disorders or increased sedation. Cardiovascular events such as a decrease in blood pressure following treatment with fentanyl and clomethiazole and bradycardia induced by verapamil, diltiazem, sotalol and clonidine, mainly occurred in patients on the intensive care or stroke unit. Further ADRs and suspected drugs are shown in table IV.

Twenty-one patients developed 43 ADRs of severity grade 3 to 5 (table IV). Comparable with the ADRs of minor severity, the predominant disorders were neuropsychiatric in nature, e.g. increased

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Table IV. Adverse drug reactions (ADRs) detected by intensified collection classified according to severity and the most frequent symptoms/disorders

Body system/symptom	Type of ADR (no. of cases)	Suspected drugs
Grade 1 and 2 severity		
CNS	Increased sedation (2), dyskinesia (4)	Benzodiazepine, levodopa + carbidopa, phenytoin, promethazine
Gastrointestinal system	Diarrhoea (4), meteorism (1), nausea (1), constipation (1)	Antibiotics, theophylline, acarbose, bisacodyl
Cardiovascular system	Bradycardia (8), hypotension (2)	Fentanyl + clomethiazole, calcium channel blockers, sotalol, clonidine, promethazine
Haematological system	Haematoma (3)	Heparin
Endocrine-metabolic system	Hyperglycaemia (1), Cushing's syndrome (1), hyperprolactinaemia (1), hypoglycaemia (1)	Corticosteroids, levomepromazine, glibenclamide (glyburide)
Immune system	Oral candidiasis (1), conjunctivitis (1)	Corticosteroids
Changes in laboratory values without symptoms	Increase in serum creatinine (2), increase in digitoxin level (1), alkaline phosphatase (1)	Gentamicin, aciclovir, digitoxin, phenytoin
Others	Skin reaction (1), headache (2)	Interferon-1β, carbamazepine, phenytoin
Grade 3 to 5 severity		
CNS	Increased sedation (13), dyskinesia (2), psychosis (1), delirium (1), antipyschotic-induced parkinsonism (2), psychomotor restlessness (2), confusion (2)	Benzodiazepines, clomethiazole, propofol, haloperidol, levodopa + carbidopa, phenytoin, promethazine, digitoxin
Gastrointestinal system	Gastroparesis (1), nausea (2)	Fentanyl, clomethiazole
Cardiovascular system	Hypotension (3)	Urapidil, midazolam, clonidine
Haematological system	Intracerebral bleeding (3), haematemesis (1), bleeding at injection site (2)	Heparin, tirofiban, aspirin (acetylsalicylic acid) + clopidogrel + nadroparin, phenprocoumon
Respiratory system	Respiratory depression requiring intubation (3) or drug withdrawal (2)	Midazolam, clomethiazole, fentanyl
Immune system	Opportunistic infections (2): herpes virus encephalitis, pneumonia	Corticosteroids
Others	Angioedema (1)	ACE inhibitor

sedation (mainly after benzodiazepines), psychomotor restlessness following treatment with haloperidol, cerebellar syndrome and nystagmus, both induced by phenytoin. Anticoagulant therapy caused inguinal and cerebral bleeding as well as haematemesis. Midazolam was found to be the most frequent agent provoking severe ADRs: three serious cases of pulmonary depression occurred and one significant fall in blood pressure.

Again, a high number of all ADRs detected by intensified surveillance were caused by drug interactions. Two severe bleeding events, including one fatality, were observed after the combination of three anticoagulative drugs: tirofiban with aspirin and heparin (following cardiological intervention); nadroparin with clopidogrel and aspirin (fatal outcome).

Two cases of symptomatic intoxication with digitalis glycosides were probably triggered by concomitant administration of calcium channel blockers. Three drug combinations consisting of antipsychotic drugs with zopiclone and clonazepam/clomethiazole led to serious sedation. Cardiovascular adverse effects such as bradycardia were induced by concomitant administration of clonidine and verapamil or diltiazem, whereas clonidine was involved in serious decreases in blood pressure when given concomitantly with midazolam and urapidil or with midazolam and fentanyl. In addition, a case of incipient renal failure followed combined treatment with gentamicin, cefuroxime and furosemide (frusemide) and a case of hypoglycaemia followed therapy with glibenclamide (glyburide), atenolol and the ACE inhibitor enalapril,

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the latter being a not very frequently observed adverse effect of enalapril.[26]

Patients developing an ADR of grade 3 to 5 severity had a mean duration of hospitalisation of 27 days (median 27.5; range 7 to 152); patients experiencing a less severe ADR (grade 1 to 2) had a slightly shorter mean stay of 25 days (median 20; range 2 to 63). In contrast, the average duration of stay of all 332 patients on these three wards during the observation period came to 10.1 days (median 7; range 1 to 152). Since we were not able to correct the duration for all concomitant diagnoses and complications, no statistical comparison was carried out.

Comparison of ADR Detected by Computerised Surveillance of Signals and Intensified Surveillance

Analysis of data received by computer-assisted surveillance restricted to that period of time that the three wards were under intensified surveillance (with n = 332 patients) resulted in 117 filtered laboratory signals for 87 patients with 34 ADRs in 32 patients (table V). Combining both methods a total of 71 patients (21.4%) with 116 ADRs were detected, of which nine patients (2.7%) were admitted because of the ADR and the remaining 62 patients (18.7%) experienced their ADRs during hospitalisation. Only five patients (with 12 ADRs) were detected by both systems with the identical ADR; however, another seven patients (with 21 ADR) were detected with both methods but with different ADRs. Thirty-nine patients with 57 ADRs were found by intensified surveillance only, whereas 20 patients with 20 ADRs were noted only by LFS. The sensitivity of intensified collection came to 71.8%; only some less severe ADR regarding asymptomatic abnormal laboratory values were not observed or were detected earlier by the LFS. In contrast, the sensitivity of the computerised approach came to 45.1% with a specificity of 78.9%. It should be noted, that by means of LFS less than 40% of all patients were documented.

As table V shows, the ADRs identified by the pathological laboratory values were usually of minor severity. The more severe ADRs found by intensified surveillance could be identified either as admission diagnoses, at the routine neurological investigation or during intensive monitoring at the intensive care or stroke unit.

Discussion

ADRs contribute significantly to patients morbidity and mortality as well as to the cost of healthcare worldwide. Therefore, implementation of systems to detect ADRs has been suggested as a means of quality control.[16,17] Moreover, such methods may also be used to identify new ADRs caused by novel drugs[15] or may even be used to estimate incidences of ADRs.[27] Since intensified collection of ADRs is time consuming, we attempted to establish a computer-assisted method.

During the intensified surveillance period, only 2.7% of hospital admissions in the department of neurology were caused by an ADR; however, about 18.7% of all patients experienced an ADR

Table V. Comparison between adverse drug reactions (ADRs) identified by laboratory filter signals (LFS) and intensified collection of ADRs

	Intensified surveillance [n (%)]	LFS [n (%)]
Patients on the observed wards	332	332
Patients recorded (total)		117 LFS/87 patients
Patients with ADR	51	32
No. of ADR	82	34
ADR 'probable' and 'definite'	33 (40.2)	21 (61.8)
ADR 'possible'	49 (59.8)	13 (38.2)
ADR grade 1 and 2	39 (47.6)	30 (88.2)
ADR grade 3 to 5	43 (52.4)	4 (11.8)
No. of patients with ADR missed, but detected with the other method	20	39
No. of ADRs missed, but detected with the other method	20	57

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during their hospitalisation. The rate of ADR-induced hospital admissions of 2.7% is lower than most of the figures reported for departments of internal medicine and geriatrics which range between 2 and 17%.[1-6] During their hospital stay at the department of neurology 18.7% of patients developed an ADR, which is in accordance with findings on intensive care units, in general hospitals, departments of psychiatry and other specialities.[1,7-13]

A number of factors determining the incidence of ADRs have been identified, including age, female gender and number of drugs administered. Classen et al.[20] observed a pronounced increase in the incidence of ADRs above the age of 60 years. Similarly, Moore et al.[10] reported a high incidence of ADRs in older patients receiving a higher number of drugs. We observed only slight differences in the age of patients with and without ADRs; however, the mean age of patients admitted during the whole study was approximately 65 years, and patients with an ADR were only marginally older, 66 years for the intensified surveillance and 68 years for the computerised approach. In most studies, polypharmacotherapy associated with older age represented a major risk factor for an ADR.[3,7,10,20] The mean number of drugs given concurrently in our survey was between five and six drugs, this is about the average number of drugs taken in other studies by those patients developing an ADR. Unfortunately, we were not able to compare this number with the number of drug prescriptions in patients without an ADR. Not surprisingly, our analysis revealed that 21.6% of ADRs (as generated by LFS) were caused by either pharmacokinetic or pharmacodynamic interactions. Examples are the observed pharmacokinetic interactions between calcium channel blockers and digitalis glycosides resulting in digitalis intoxication and the pharmacodynamic interaction between heparin and clopidogrel resulting in severe bleeding.

Female gender has been quoted as a risk factor for ADRs by several authors.[7,10,20] In our study, slightly more ADRs (as indicated by LFS) occurred in women (56%) than in men, although the percentage of females admitted was comparable to the percentage of male patients admitted. In contrast, from a total of 51 patients with an ADR detected by means of intensified surveillance only 19 patients were of female gender. These discrepancies may be due to chance and our relatively small database.

When looking at the type of ADR, in agreement with previous studies, type A reactions were observed in roughly 70 to 80% of patients.[1,8,10,20] Taking into account, that the majority of ADRs were type A reactions, which are usually dose-related, the negligence of age- and gender-related differences in pharmacokinetics and pharmacodynamics may contribute to the somewhat higher incidence of ADR in the elderly and the women.[28,29]

Not only the number, but also the type of drugs used predominantly should have an influence on occurrence of ADRs. In departments of internal medicine cardiovascular drugs, antibiotics, antidepressants and antidiabetic drugs as well as NSAIDs, anticoagulants and antiplatelet drugs are the leading cause of ADRs.[3,10,30] In addition, analgesics and sedatives are responsible for a high number of ADRs, when intensive care units are included in the surveillance.[20,21,30,31] Combining both ADR detection methods applied, we found that the leading drugs causing an ADR on neurological wards were neurotropics and antidepressants, followed by anticoagulants and antiplatelet drugs as well as antiepileptic and cardiovascular drugs. The predominant use of neuropsychiatric drugs as well as their specific adverse effect profiles are responsible for the differences observed in the type and nature of ADRs. Not surprisingly, our intensified surveillance of ADR revealed most frequently neuropsychiatric symptoms such as increased sedation, dyskinesia, neuropsychiatric syndromes, followed by bleeding episodes, bradycardia, respiratory depression and decrease in blood pressure. This ADR profile resembles more closely that described by Gohmann et al.[32] in psychiatric hospitals rather than the ADR profiles described in internal medicine. The ADRs discovered by the

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pathological laboratory values were completely different in nature, such as hepatotoxicity, disturbance of renal function, and decrease in haemoglobin levels, resembling more closely problems occurring on medical wards. On the whole, the adverse effect profile in the department of neurology represented a combination of characteristic adverse effects of neurotropic drugs complemented by a relatively high number of ADRs typical for internal medicine or geriatric wards.

Signal generation for ADRs by means of LFS has only been validated for general hospitals as a whole or for departments of internal medicine and intensive care units. Interestingly, the positive predictive value of certain laboratory values, e. g. AST, ALT and alkaline phosphatase with 16.3, 37.5 and 31.0% is higher than predictive values reported for liver function parameters in departments of internal medicine with positive predictive value of about 10 to 13%.[8,11] Even the predictive value of electrolyte disturbances (sodium and potassium) and serum creatinine with 24.0, 33.3 and 18.3%, respectively, is higher in the department of neurology than that reported for these parameters in departments of internal medicine.[8,11] This is most likely due to the fact, that more patients with underlying liver or renal disease are admitted to departments of internal medicine. Moreover, neurotropic drugs and particularly antiepileptics have a relatively high risk of hepatotoxicity. By means of LFS we detected many clinically irrelevant ADRs that were without therapeutic consequences, probably because or signals were close to the upper or lower normal values and did not give rise to concern for the clinician. The positive predictive value of LFS could be increased by modifying the threshold of the LFS, furthermore, the percentage of moderate to severe ADRs detected by LFS would be increased. For example, for liver enzymes we chose a signal generating threshold of two times the upper limit of normal, which is in accordance with internationally accepted criteria.[33] However, there is not much experience with this method and we did not want to miss ADRs.

When comparing ADRs detected by intensified surveillance and LFS there is an astonishing low rate of overlap. However, Dormann et al.[8] reported on a medical ward, that only 11% of ADR were detected by both methods, namely by abnormal laboratory values and stimulated (rather that intensified) reporting of ADR. In their study 74% of all ADR were detected by laboratory values alone, whereas the minor share of ADR were reported by 'stimulated' spontaneous reporting. By means of intensified collection almost 80% of all ADRs were detected in our study, in contrast even stimulated spontaneous reporting by doctors and nurses is characterised by 'underreporting'.[18,34] In comparison to a retrospective chart review (retrospective, but comparable with intensified surveillance) Azaz-Livshits and coworkers[11] reported for LFS a sensitivity of about 65% on a medical ward, which is higher than the 45.1% observed in our study. Only one system[7,19,20] applied at the LDS Hospital in Salt Lake City, Utah, USA, allows for complete computerised ADR surveillance, where pathological laboratory values, the prescription of antidotes and certain diagnostic tests are used for signal generation. Unfortunately, only a very few hospitals provide for fully computerised medical record and the facilities to link patients records with pharmacy and laboratory data as described in the HELP system.[19]

Although the majority of ADR detected by the LFS were of grade 1 to 2 severity, 59% were followed by therapeutic consequences with regard to drug therapy. As described by previous studies,[8,11] most of the computer-generated signals pointed to less severe ADRs; however, this early warning enabled physicians to react before deterioration of organ function develops. For many clinical specialities, and particularly neurology, LFS can not be used to detect all ADRs. But they can and should be used as adjunctive measures to improve quality of medical care.[15-17,20]

As shown for the wards of neurology under intensified surveillance, ADR are responsible for a remarkable prolongation of hospital stay of more than 10 days. This figure is far higher than the ex-

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cess length of hospital stay due to ADRs of 2.2 to 7 days as reported by others.[9,10] However, a pharmacoeconomic evaluation was beyond the scope of our pilot study.

Some shortcomings of our project deserve further comments. Due to personal constraints, we were not able to compare intensified surveillance with laboratory filter signals over a longer period. Seasonal variations or marked changes over time have not yet been reported for ADR occurrence.

Since we did not document drug prescriptions in all patients, we cannot state whether patients with ADRs received more or different drugs than patients without ADRs. This would be useful and feasible with a computerised prescription database to analyse and compare the risk profiles of drugs within the same or from different pharmacological classes. Our method of data collection did also not allow for further demographic and disease-specific comparisons between patients with and without ADR.

Conclusion

The data obtained in this pilot project firstly demonstrate the feasibility and the clinical relevance of ADR detection in the speciality of neurology and secondly, the shortcomings and usefulness of the computer-assisted approach described. According to our finding, 18.7% of patients in a neurological department will experience an ADR, a rate which is comparable with departments of internal medicine and/or geriatrics.

Acknowledgements

We are indebted to all physicians and nurses in the department of neurology during our data collection period and especially Professor Joerg, MD for his continuous advice. We also thank S. Pasche for his technical assistance and Dr C. Zwernemann for his support in data collection.

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the contents of this manuscript.

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