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Incidence and Costs of Adverse Drug Reactions During Hospitalisation

Computerised Monitoring Versus Stimulated Spontaneous Reporting

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Abstract

Objective: To implement a computer-based adverse drug reaction monitoring system and compare its results with those of stimulated spontaneous reporting, and to assess the excess lengths of stay and costs of patients with verified adverse drug reactions.

Design: A prospective cohort study was used to assess the efficacy of computer-based monitoring, and case-matching was used to assess excess length of stay and costs.

Setting: This was a study of all patients admitted to a medical ward of a university hospital in Germany between June and December 1997.

Patients and participants: 379 patients were included, most of whom had infectious, gastrointestinal or liver diseases, or sleep apnoea syndrome. Patients admitted because of adverse drug reactions were excluded.

Methods: All automatically generated laboratory signals and reports were evaluated by a team consisting of a clinical pharmacologist, a clinician and a pharmacist for their likelihood of being an adverse drug reaction. They were classified by severity and causality. For verified adverse drug reactions, control patients with similar primary diagnosis, age, gender and time of admission but without adverse drug reactions were matched to the cases in order to assess the excess length of hospitalisation caused by an adverse drug reaction.

Results: Adverse drug reactions were detected in 12% of patients by the computer-based monitoring system and stimulated spontaneous reporting together (46 adverse reactions in 45 patients) during 1718 treatment days. Computer-based monitoring identified adverse drug reactions in 34 cases, and stimulated spontaneous reporting in 17 cases. Only 5 adverse drug reactions were detected by both methods. The relative sensitivity of computer-based monitoring was 74% (relative specificity 75%), and that of stimulated spontaneous reporting was 37%

(relative specificity 98%). All 3 serious adverse drug reactions were detected by computer-based monitoring, but only 2 out of the 3 were detected by stimulated spontaneous reporting. The percentage of automatically generated laboratory signals associated with an adverse drug reaction (positive predictive value) was 13%. The mean excess length of stay was 3.5 days per adverse drug reaction. 48% of adverse reactions were predictable and detected solely by computer-based monitoring. Therefore, the potential for savings on this ward from the introduction of computer-based monitoring can be calculated as EUR56 200/year ($US59 600/year) [1999 values].

Conclusion: Computer monitoring is an effective method for improving the detection of adverse drug reactions in inpatients. The excess length of stay and costs caused by adverse drug reactions are substantial and might be considerably reduced by earlier detection.

Adverse drug reactions are common and cost-intensive. The percentage of patients experiencing an adverse drug reaction during hospitalisation has been reported to range from 1.5 to 35%.[1-3] The diversity of results may be explained by the use of different definitions of adverse drug reactions, different adverse drug reaction reporting systems and the rigor with which adverse drug reactions were sought. Comorbidity and the number of medications also may influence the incidence of adverse drug reactions and the frequency with which they are detected.[4-6] Fatal adverse drug reactions are expected in approximately 0.32% of hospitalised patients.[7] Between 1.1 and 8.4% of all hospital admissions are reportedly caused by adverse drug reactions.[8-11] Apart from the medical impact, adverse drug reactions also have an economic impact. It has been suggested that adverse drug reactions prolong hospitalisation and increase healthcare expenditures substantially.[12]

Up to now, spontaneous adverse drug reaction reporting has been the basis of most drug safety evaluation programmes in postmarketing surveillance. However, this method is limited by difficulties in adverse drug reaction recognition, under-reporting, biases, and insufficient report quality.[13,14] Because of the low costs, most hospitals identify adverse drug reactions by spontaneous or stimulated spontaneous reporting.[15]

Chart review identifies considerably more adverse drug reactions than other methods, but its expense makes it impractical for ongoing quality monitoring in hospitals.[16] Computer-based adverse drug reaction monitoring systems are not widely used because of lack of experience with them, uncertainty about their efficiency and the lack of appropriate hospital information systems.[17] Recently it has been shown that computerised monitoring using automatically generated laboratory signals allows an earlier detection and increased recognition of adverse drug reactions in hospitalised patients.[18]

The present study was performed: (i) to evaluate and compare the detection rate of adverse drug reactions using a computer-based monitoring system and stimulated spontaneous reporting; and, (ii) to assess the additional resource utilisation associated with a verified adverse drug reaction, e.g. the excess length of hospital stay and extra costs.

Methods and Materials

Design

This prospective study included all patients admitted to a 9-bed medical ward at a university hospital in Germany between June and December 1997. Most patients in this ward have infectious, gastrointestinal or liver diseases, or sleep apnoea syndrome. Patients admitted to the hospital because of adverse drug reactions were not considered. The study was approved by the institutional Ethics Review Board.

Definitions and Procedures for Identifying Adverse Drug Reactions

We defined adverse drug reactions according to the World Health Organization definition.[19] Two methods were used for identifying adverse drug reactions, as follows.

(i) Nurses and staff physicians were asked thrice weekly by the clinician of the pharmacoepidemiological team to report all observed events (stimulated spontaneous reporting).

(ii) Absolute values of laboratory tests that might indicate potential adverse drug reactions were defined and used as automatic laboratory signals (table I). The computer-based monitoring system generated a daily list of alerts (automatically generated laboratory signals) including the patient's name, medical record number and date of event.[20]

A pharmacoepidemiological team, consisting of a clinical pharmacologist, a clinician, and a pharmacist, reviewed each patient's medical chart to assess whether an alert or report was associated with an adverse drug reaction. Multiple computer-generated alerts could be associated with a single adverse drug reaction.

Classification of Adverse Drug Reactions

For the evaluation of the probability of an event to be an adverse drug reaction, the Naranjo algorithm score with some minor adaptations was used (see Naranjo et al.[21]). Only possible and probable adverse drug reactions were taken into consideration. The severity of verified adverse drug reactions was assessed using a severity algorithm score (table II). Furthermore, we classified adverse drug reactions according to their predictability. Predictable adverse drug reactions are related to the pharmacological characteristics of administered drugs, e.g. toxicity, interactions or secondary effects, and are often avoidable. Unpredictable adverse drug reactions are based on idiosyncratic or allergic re-

Table I. Positive predictive value of automatically generated laboratory signals (ALS) from the computer-based monitoring system

Adverse reaction	ALS with limits	No. of ALS	No. of ALS associated with adverse drug reactions	Positive predictive value (%)
Hepatotoxicity	GGT >45 U/L	128	17	13
	AST >35 U/L	102	11	11
	ALT >30 U/L	97	12	12
	Bilirubin >1.5 mg/dl	85	4	5
	Alkaline phosphatase >330 U/L	NS		
	LDH >450 U/L	18	3	17
Haematological toxicity	Platelets <70 000/μl	16	4	25
	Leucocytes <500/μl	16	3	19
	Haemoglobin <9 g/dl	12	2	17
Renal toxicity	Serum creatinine >1.5 mg/dl	13	1	7
	BUN >60 mg/dl	1	0	0
Electrolytes	Potassium <2.7 mmol/L	1	0	0
	Potassium >6 mmol/L	3	0	0
	Sodium <125 mmol/L	3	1	33
	Sodium >160 mmol/L	NS		
	Calcium <1.7 or >3.2 mmol/L	NS		
Metabolic	Blood glucose <50 mg/dl	1	0	0
Drug concentrations	Digitoxin >20 μg/L	2	2	100
	Digoxin >2 μg/L	NS		
	Theophylline >20 mg/L	3	3	100
Total		**501**	**63**	**13**

GGT = γ-glutamyl transferase; **LDH** = lactate dehydrogenase; **NS** = no signals recorded during the study period.

actions or intolerance and are usually not avoidable.[22]

Matching and Selection of Control Patients

Matched controls were selected from patients without adverse drug reactions admitted to the ward between June and December 1997. The matching criteria included gender, age, time of admission and primary admission diagnosis. At least 1 control was matched to each case patient.

Data Analysis

The adverse drug reactions detected by each method (automatically generated laboratory signals *vs* stimulated spontaneous reporting) were compared for rate, severity and medication classes involved, and the degree of overlap between both detection methods was assessed. Patients with adverse drug reactions on admission were not included. The relative sensitivity of the respective methods (automatically generated laboratory signals *vs* stimulated spontaneous reporting) was defined as the percentage of positive adverse drug reactions detected with one method as compared with the total number of detected adverse drug reactions using both methods together. The relative specificity was defined as the percentage of negative adverse drug reactions without automatically generated laboratory signals or spontaneous reports out of the total number of negative adverse drug reactions. Since the real total number of adverse drug reactions is not known, the absolute sensitivity of the detection systems could not be evaluated. For each automatically generated laboratory signal, the positive predictive value was calculated as the number of automatically generated laboratory signals associated with an adverse drug reaction divided by the total number of automatically generated laboratory signals.

The influence of the variables gender, age and incidence of an adverse drug reaction on the length of hospital stay was estimated by multiple linear regression analysis. The α-level was set to 0.05. Information on length of stay and total charges was obtained from billing data. The costs were estimated by multiplying the excess days of hospitalisation by the hospital-specific daily costs, which are currently EUR370/day (US$395/day) [1999 values].

Results

During the study period of 6 months, 1718 treatment days in 379 patients (246 male, 133 female; mean age 50.8 years, age range 17 to 88 years) were monitored. Overall, 46 adverse drug reactions were detected in 45 patients (30 male, 15 female) by computer-based monitoring and stimulated spontaneous reporting together. 21 adverse drug reactions

Table II. Adverse drug reaction severity score. The severity of the adverse drug reaction is classified according to the total score. A score of 1 to 4 indicates a mild, a score of 5 to 8 a moderate, and a score of >8 a severe adverse drug reaction

Criterion	Yes	No	Unknown
Did the adverse drug reaction impair the patient's quality of life?	+1	–1	0
Was the (immediate) discontinuance of the drug necessary or recommended?	+1	0	0
Was the use of a different drug or other therapy necessary or recommended?	+1	0	0
Did the adverse drug reaction prolong or lead to hospitalisation?	+1	0	0
Did the adverse drug reaction cause temporary malfunctioning of an organ (system)?	+1	0	0
Did the adverse drug reaction cause permanent malfunctioning of an organ (system)?	+2	0	0
Did the adverse drug reaction cause temporary inability to work?	+1	0	0
Did the adverse drug reaction lead to permanent inability to work?	+2	0	0
Was the adverse drug reaction			
potentially dangerous? (treated in ward)	+1	0	0
(potentially) life threatening? (treated in critical care unit)	+2	0	0
fatal?	+3	0	0

Table III. Classification of the adverse drug reactions (ADRs) observed in this study

Characteristic of ADR	Number of ADRs				
	total	detected by CMS	detected by CMS and predictable	detected by SSR	detected by CMS and SSR
Severity[a]					
Mild	22	18	12	7	3
Moderate	21	13	11	8	0
Severe	3	3	3	2	2
Probability[b]					
Doubtful[c]	6				
Possible	21				
Probable	25				
Total	**46**	**34**	**26**	**17**	**5**

a See table II.

b See Naranjo et al.[21]

c Not taken into consideration.

CMS = computer-based monitoring system; **SSR** = stimulated spontaneous reporting.

that were regarded as possible and 25 regarded as probable were taken into consideration.

Three patients experienced a serious adverse drug reaction, representing 6% of all reactions. The serious adverse drug reactions were: (i) pancytopenia and neurotoxic reactions caused by fluorouracil in a patient with dihydropyrimidine dehydrogenase deficiency; (ii) fulminant cholestatic hepatitis after administration of a phenothiazine and valproic acid (sodium valproate); and (iii) leucopenia, thrombocytopenia and hepatic injury induced by antiretroviral therapy. All serious adverse drug reactions were predictable. In one patient the adverse drug reaction was fatal. Moderately serious adverse drug reactions were identified in 21 patients (46%) and mild adverse drug reactions in 22 patients (48%). The majority of adverse drug reactions (74%) were considered to be predictable (table III).

The computer-based monitoring system generated 501 automatically generated laboratory signals, of which 63 were associated with 34 adverse drug reactions. The overall positive predictive value of the automatically generated laboratory signals was 13%. Automatically generated laboratory signals indicating haematological pathology or drug concentrations (positive predictive value 17 to 25%) were more frequently associated with an adverse drug reaction than other automatically generated laboratory signals (table I).

Out of the total of 46 adverse drug reactions, computer-based monitoring detected 34 and stimulated spontaneous reporting detected 17 (out of 23 reports), and 5 adverse drug reactions were detected by both methods. All 3 serious adverse reactions were identified by computer-based monitoring, but only 2 by stimulated spontaneous reporting. Among 21 moderate adverse drug reactions, 13 were identified by computer-based monitoring and 8 by stimulated spontaneous reporting, but none was detected by both methods. Of 22 mild adverse drug reactions, 18 were identified by computer-based monitoring, 7 by stimulated spontaneous reporting and 3 by both methods. The relative sensitivity of the computer-based monitoring system for all adverse drug reactions was 74% (relative specificity 75%), and that of stimulated spontaneous reporting was 37% (relative specificity 98%). The relative sensitivity (relative specificity) for moderate and serious adverse drug reactions was 67% (72%) and 42% (96%) for computer-based monitoring and stimulated spontaneous re-

porting, respectively. For serious adverse drug reactions the relative sensitivity (relative specificity) was 100% (70%) and 67% (94%), respectively. The absolute total number of adverse drug reactions could not be determined, because there was no chart review or check of all hospitalised patients during the study period.

The types of adverse drug reactions detected by computer-based monitoring or stimulated spontaneous reporting varied substantially. Stimulated spontaneous reporting was most effective in detecting symptoms such as allergic reactions or gastrointestinal effects. Computer-based monitoring more reliably identified adverse drug reactions associated with changes in laboratory signals, such as nephrotoxicity and hepatotoxicity.

Antibacterials (13 reactions) were the leading drug class associated with adverse drug reactions. Other drug classes that caused adverse reactions were cardiovascular agents (5 reactions), antiretrovirals (5), antipsychotics (4) and antineoplastics (4). High drug concentrations were associated with 5 adverse drug reactions.

The additional resource utilisation associated with an adverse drug reaction was assessed. The mean length of hospital stay differed significantly between patients with adverse drug reactions and control patients without adverse drug reactions (mean 7.5 *vs* 4.0 days, $p < 0.001$). The extra length of hospital stay that was attributable to an adverse drug reaction was 3.5 days. The mean excess cost of hospitalisation for an adverse drug reaction was EUR1300 ($US1400) [1999 values].

Discussion

Adverse drug reactions are an important source of morbidity and mortality among hospitalised patients, with incidence rates varying from 1.5 to 35%.[1-3] Despite the magnitude of the problem, only limited data are available about the situation in medical departments of European hospitals. A recently published study in Germany focused on an organised stimulated reporting system and detected adverse drug reactions in 7.8% of all patients admitted to the medical department, including the intensive care unit.[15]

In the present analysis, adverse drug reactions were detected in 12% of patients admitted to a medical ward. Computer-based monitoring detected adverse drug reactions in 9%, whereas stimulated spontaneous reporting identified adverse drug reactions in only 4.5% of patients. Five adverse drug reactions were detected by both methods. In a previous retrospective study of the same medical ward with a different patient population, we detected adverse drug reactions in 17% of patients by chart review.[23] Thus, chart review appears to be somewhat more effective in detecting adverse drug reactions, but it is a time-consuming and therefore expensive method for detection of adverse drug reactions. Additionally, chart review is a retrospective method and does not enable the physician to intervene. Early interventions that may result in reduced morbidity and cost savings are therefore not possible. In contrast, computer-based monitoring is a prospective method by which laboratory data are screened online. Therefore, it allows early detection and intervention in drug therapy, requires substantially less staff time than chart review, and apparently detects more adverse drug reactions than stimulated spontaneous reporting. However, as the positive predictive value of the computer-based monitoring system was only 13%, it will be necessary to refine the automatically generated laboratory signals and possibly include other coded medical information to further improve the efficiency and sensitivity of the system.

Surprisingly, there was only a small overlap between events found by computer-based monitoring and stimulated spontaneous reporting. Computer-based monitoring was superior to stimulated spontaneous reporting in identifying events associated with quantitative laboratory changes, such as haematological values or hepatic enzymes, whereas stimulated spontaneous reporting was superior in identifying events associated with clinical symptoms. Computer-based monitoring not only identified serious adverse drug reactions but also favoured an early detection of mild and moderate

events, thus allowing the physician to react. Adverse drug reactions detected by stimulated spontaneous reporting tended to be more serious. Because of the small overlap of the adverse drug reactions detected, combination of both systems is likely to be the most efficient approach to reduce the number and severity of adverse drug reactions.

The finding that 29 out of 46 adverse drug reactions (63%), including 1 serious reaction, were not recognised as such by the attending physician is disappointing but not unexpected. Similar findings have led to the requirement by the Joint Commission on Accreditation of Healthcare Organisations for US hospitals to develop written procedures for recording and reporting adverse drug reactions with the aim of reducing their incidence, especially of predictable and preventable events.[24] As the term implies, predictable adverse drug reactions are untoward but often expected consequences of drug therapy through knowledge of the pharmacology of the drug in question. This fact suggests that adverse drug reactions may often be avoided if they are part of the considerations involved in planning and monitoring drug therapy. But, although 74% of adverse drug reactions were classified as predictable in this study, not all of these reactions could have been avoided under clinical conditions. In previously published studies, the incidence of predictable adverse drug reactions varied considerably and ranged up to 80%.[25]

The exact costs attributable to adverse drug reactions are not well known. It has been suggested, however, that adverse drug reactions can prolong hospital stays and add to healthcare expenditure.[12,26,27] Our results have shown that adverse drug reactions significantly prolonged hospitalisation. The attributable mean excess length of stay was 3.5 days. In the literature, the excess length of stay due to an adverse drug reaction varies substantially, ranging from 0.72 to 5.5 days,[2,17,25] and the excess costs associated with adverse drug reactions in those studies ranged from $US677 to $US4685 (1999 values).[12,26,28] Based on the hospital-specific day rate [EUR370/day ($US390/day)] (1999 values) and the incidence of adverse drug reactions, we estimated that the annual cost of adverse drug reactions on the ward studied would be EUR120 000 ($US127 200) [1999 values]. 48% of the adverse drug reactions were both predictable and detected solely by the computer-based monitoring system. Thus, the potential for savings from the introduction of a computer-based monitoring system on this 9-bed ward may be extrapolated to EUR57 600 ($US61 600) [1999 values] annually.

Some limitations of our study should be noted. Patients admitted to the hospital because of an adverse drug reaction were not evaluated, and the real number of adverse drug reactions which occurred in our patient population is unknown because some adverse drug reactions may have been overlooked by both methods. The mean length of stay of our patients was very short. Since patients with longer stays may be more ill and receive more medications, they may have a greater risk of developing adverse drug reactions. On the other hand, patients at a university hospital tend to receive more intensive therapies than patients of other hospitals and may be at a greater risk of experiencing an adverse drug reaction. Therefore, it is unclear whether extrapolation of the frequency of adverse drug reactions in our patients will under- or overestimate the risk of adverse drug reactions in other patient populations. Furthermore, the actual number of adverse drug reactions in our patients might be higher than the number of adverse drug reactions detected during hospitalisation because of the relative short length of hospital stay. Some adverse drug reactions triggered off by the medical treatment during hospitalisation may have occurred in the outpatient setting.

The length of stay was the only factor used to assess the costs of adverse drug reactions in our patients; this provides only a gross estimate and does not account for additional expenses of drug treatment, diagnostic tests and other measures to confirm or treat the adverse drug reaction.

Conclusion

The use of a computer-based monitoring system will probably help healthcare providers to be more

aware of adverse drug reactions. Computer-based monitoring is an important complement to stimulated spontaneous reporting, and may help to avoid or decrease the severity of a large percentage of predictable adverse drug reactions. In turn, this will reduce patient morbidity and healthcare expenditures.

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