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Adverse drug events caused by medication errors in medical inpatients

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Summary

Principles: In view of growing concern in recent years regarding medication errors as causes of adverse drug events (ADEs), we explore the frequency and characteristics of error-associated ADEs in medical inpatients.

Methods: All patients with ADEs or ADE-related hospital admission in a cohort of medical inpatients identified by "event monitoring" (SAS/CHDM database, Br J Clin Pharmacol 2000:49:158–67) were evaluated independently by two experienced physicians. ADEs were first divided into ADEs occurring during cohort stay (incident ADE) and ADE present prior to/at admission. ADEs were then grouped as error-associated ADEs (eADEs: indication error, missed contraindication, wrong dosage regimen or inadequate surveillance) and adverse drug reactions (ADRs: indication established, no contraindications, appropriate dosage regimen and adequate surveillance).

Results: Among the 6383 patients analysed (100%), 481 (7.5%) experienced at least one incident ADE. Incident ADRs occurred in 457 (7.2%). Incident eADEs were recorded in 28 patients, corresponding to an eADE incidence of 0.4% (95% CI: 0.2, 0.7). Error types were missing/inappropriate indication (4 cases), missed contraindications (9), relative overdoses (8), absolute overdoses (3) and inadequate clinical surveillance (4). The responsible drugs included antithrombotics (6), cardiovascular drugs (5), antibiotics (5), hypnotics (4) and non-steroidal anti-inflammatory drugs (3). ADE-related hospital admissions were observed in 262 patients (4.1%); 183 (2.9%) were classified as ADRs and 79 (1.2%) as eADEs.

Conclusions: Incident eADEs were observed in 1 out of 250 patients and accounted for approximately 6% of ADEs. In contrast, eADEs accounted for 30% of ADE-related hospital admissions. Hence, in medical inpatients, eADEs represented a small fraction of total incident ADEs, whereas they contributed significantly to hospital admissions.

Key words: adverse drug events; preventable adverse drug events; adverse drug reactions; medication error; medical inpatients

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Introduction

Adverse drug events (ADEs), usually defined as harm caused by the (appropriate or inappropriate) use of a drug [1], constitute a major health concern for the individual patient and the community. It has been estimated that ADEs account for approximately 5% of all hospital admissions, occur during 10–20% of hospitalisations [2] and are responsible for 7–9% of hospitalisation days [3, 4]. ADEs can be classified according to their potential preventability. They cannot be prevented if the causative drug is used for an established indication, in the absence of contraindications, at the appropriate dosage and under adequate surveillance. These non-preventable ADEs are classified as adverse drug reactions (ADRs). All other ADEs are potentially preventable. These include ADEs where the causative drug is used without an established indication, despite the presence of contraindications, at an inappropriately high dosage, as an inappropriate formulation, by an incorrect route or under inadequate surveillance. These potentially preventable ADEs can be classified as error-associated adverse drug events (eADEs).

The currently available estimates of the inci-

dence of eADEs in hospitalised patients vary considerably. In 1991, Leape et al. evaluated the incidence of several types of adverse event by reviewing the records of more than 30 000 inpatients [5]. Among 178 ADEs, 17.7%, corresponding to approximately 32 ADEs, were caused by errors, resulting in an eADE incidence of 0.11%. On the basis of a review of 15 000 medical records from Utah and Colorado, the incidence of eADEs was estimated at 0.17% for patients aged between 16 and 64 years and at 0.64% for patients over 64 [6]. A prospective study in 1120 paediatric inpatients resulted in a comparable eADE incidence of 0.45% [7]. In contrast, in three prospective studies Bates et al. estimated considerably higher eADE incidences of 1.3%, 1.8% and 3.6% [8–10]. Furthermore, extrapolations of medication error-associated death rates yielded an eADE-related mortality estimate of up to 98 000 deaths per year for the US [11], though these latter studies were controversial [12–14]. Since detailed knowledge of the incidence and characteristics of eADEs are a prerequisite for appropriate planning of error prevention strategies and for adequate allocation of financial resources, we evaluated the contribution of medication errors to total ADEs recorded prospectively in the pharmaco-epidemiological database SAS/CHDM (Stiftung für Arzneimittelsicherheit/Comprehensive Hospital Drug Monitoring) [4]. We determined the overall eADE incidence and characterised eADEs with respect to types of error, drugs involved and types of event. We further estimated the contribution of eADEs to hospital admissions.

Methods

The SAS/CHDM (Stiftung für Arzneimittelsicherheit/Comprehensive Hospital Drug Monitoring) project maintains a pharmaco-epidemiological database for study of ADEs in a cohort of medical inpatients [4]. The cohorts are located at the Departments of Medicine of Zürich University Hospital and the Kantonsspital St. Gallen. While the former is mainly a tertiary referral centre and serves only as a primary hospital for some parts of the city, the latter serves as a primary city hospital and as a secondary referral centre for northeast Switzerland. At Zürich University Hospital the monitored units belong to the Department of Internal Medicine, where admissions are based on available beds irrespective of the suspected diagnoses, whereas in the Kantonsspital St. Gallen the monitored units belong to one of three divisions of the Department of Internal Medicine, preferentially focusing on infectious, endocrine and pulmonary diseases. For each patient admitted to one of the monitored units we collect on admission structured data regarding patient characteristics, drug exposure before hospitalisation and the cause(s) of hospital admission. During cohort stay, structured data on "events" (symptoms, laboratory results) and drug exposure are prospectively collected on a daily basis and entered into the database. At discharge, data on diagnoses (ICD10) are added. The monitoring physician also evaluates the cause(s) of hospital admission and all clinical events and pathological laboratory results with respect to drug therapy and the patient's disease(s). All possibly drug-related events resulting in considerable discomfort, drug withdrawal or dose reduction and/or initiation of therapeutic measures are classified and recorded as *adverse drug events (ADEs)*. Intentional (e.g. suicidal) drug overdoses are excluded. Further details of the data recording procedures in the SAS/CHDM project have been reported previously [4].

Among the hospitalisations monitored up to December 2000, we first extracted those who experienced at least one adverse drug event(s) during cohort stay and/or adverse drug events leading to hospital admission. For each ADE extracted we determined whether the ADE was first observed during cohort stay, i.e. represented an *incident ADE* or was already present at hospital admission, i.e. represented an *ADE at admission* (figure 1). The latter were further classified into ADEs leading to hospital admission, i.e. *ADE-related admissions*, and other ADEs already present at but unrelated to hospital admission, i.e. *admissions with ADE*.

Two experienced physicians independently re-evaluated all ADEs on the basis of database entries, physician's discharge letters and medical records, and determined whether the ADE represented an ADR or an eADE (figure 1). ADEs were classified as *adverse drug reaction (ADR)* if the causative drug was administered for an established indication in the absence of contraindications, at the appropriate dosage and under adequate surveillance. Indications were considered appropriate if they were either included in the labelling or had been described elsewhere. In contrast, ADEs were classified as *error-associated (eADE)*, if the causative drug was used inappropriately with respect to selection, dosage or surveillance. *Selection errors* included missing or inappropriate indications (indication errors), missed contraindications and missed drug interactions. *Dosage errors* included a) absolute overdoses, i.e. dosages exceeding the usual therapeutic, prophylactic or diagnostic dosages, b) relative overdoses, i.e. dosages too high for the individual patient, such as e.g. the standard therapeutic digoxin dosage in the case of impaired renal function, and c) administration errors such as inappropriate formulation, wrong route of administration or wrong dosage interval. *Surveillance errors* included eADEs caused by inadequate clinical surveillance or insufficient laboratory checks. For *ADEs at admission*, an additional category called *patient errors* included eADEs caused by the patients themselves. ADE severity was graded into a) *significant*, i.e. ADEs demanding a dosage reduction or therapy cessation, b) *moderate*, i.e. ADEs requiring additional therapeutic measures, c) *serious*, i.e. ADEs prolonging hospitalisation, leading to permanent defects or life-threatening complications, and d) *lethal* i.e. ADEs leading to death.

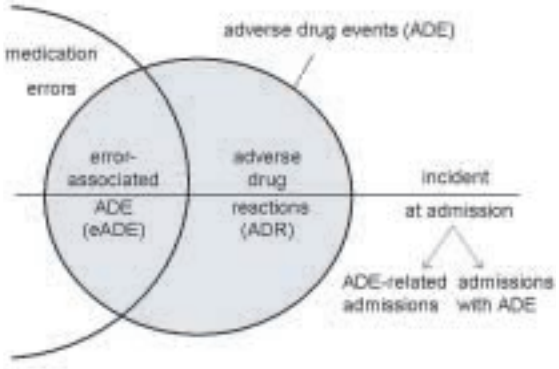

Figure 1

Venn diagram on adverse drug events (ADE) and its subdivision into incident ADE vs. ADE at admission and error-associated ADE (eADE) vs. adverse drug reaction (ADR).

Interphysician rating differences were evaluated using Cohen's Kappa together with proportion of observed agreement (p_o) and the observed proportions of positive (p_{pos}) and negative (p_{neg}) agreement, where the p_{pos} and p_{neg} indicate the consistency of the two observers on positive and negative decisions [15, 16].

Incidence and prevalence rates were determined by dividing the number of patients with a corresponding incident event or event at admission by the number of monitored or exposed patients. The reported 95% confidence interval corresponds to the exact 95% confidence interval for proportions calculated by solving equations (777) and (778) given in [17] for pe (the lower limit of the 95% confidence interval) and pr (the upper limit of the 95% confidence interval).The corresponding procedure was programmed in Splus5.1, as the available tables with exact 95% confidence intervals [17] are only applicable to samples with a number of observations not exceeding 100.

Results

Among 6383 patients (100%) monitored between 1996 and 2000, 62% were recorded in Zürich and 38% in St. Gallen. 3710 (58%) were males and 2673 (43%) females. The median (Q_1, Q_3) age was 61 (45, 74) years. In 65%, 30%, 21% and 23% of the hospitalisations at least one diagnosis concerned the cardiovascular system (ICD10 I00-I99), the respiratory system (ICD10 J00-J99), infectious diseases (ICD10 A00-B99) and neoplasms (ICD10 D50-D89) respectively. The median (Q_1, Q_3) number of different drugs per patient and day amounted to 6 (4, 8). The median (Q_1, Q_3) cohort stay was 8 (5, 15) days. 344 patients (5.2%) died during hospital stay.

An *incident ADE* and/or *ADE at admission* were recorded in 715 patients, corresponding to 11.2% of all patients monitored. At least one *incident ADE* was recorded in 481 patients (7.5%) and an *ADE at admission* in 279 (4.4%). Thus, 45 patients who were *admitted with ADEs* also experienced an *incident ADE* during hospitalisation. Database entries, discharge letters and medical records of these 715 patients were evaluated independently by two experienced physicians. Cohen's Kappa and the related parameters for the classification of *ADE*s as *eADE* or *ADR* amounted to 0.5 with $p_o = 0.97$, $p_{pos} = 0.5$, $p_{neg} = 0.99$ for the *incident ADEs* and 0.9 with $p_o = 0.96$, $p_{pos} = 0.93$, $p_{neg} = 0.97$ for *ADEs at admission*.

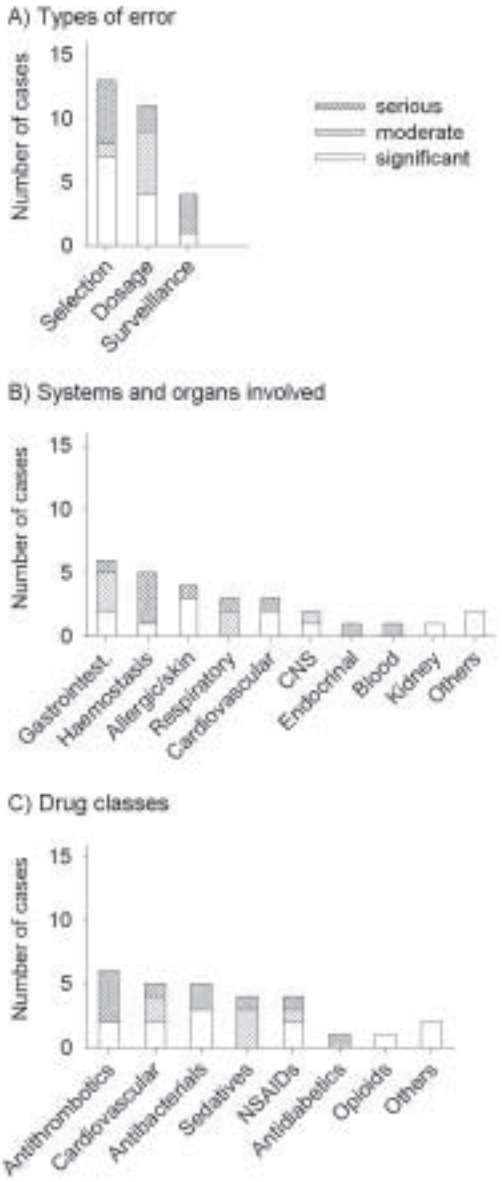

Figure 2

Incident error-associated adverse drug events (eADE) in medical inpatients according to type of error (A), systems or organs (B) and drug class (C). *Significant*: ADEs demanding a dosage reduction or therapy cessation, *moderate:* ADEs requiring additional therapeutic measures and *serious:* ADEs prolonging hospitalisation or leading to a permanent defect or life-threatening complication. Types of error include *selection errors* i.e. indication errors, missed contraindications and missed drug interactions, *dosage errors* i.e. absolute overdoses, relative overdoses, dosing frequency and route errors and *surveillance errors* i.e. inadequate clinical surveillance or neglected laboratory determinations. The drug classes are *antithrombotics* (ATC: B01), *cardiovascular* drugs (C), *antibacterials* for systemic use (J01), *sedatives* (N05B and N05C), *NSAIDs* i.e. non-steroidal anti-inflammatory drugs (M01A), *antidiabetics* (A10) and *opioids* (N02A).

Incident ADE

Among the 481 patients with at least one *incident ADE*, 457 experienced ADRs, resulting in an ADR incidence of 7.2% (table 1). Overall, 28 incident eADEs were identified, corresponding to an eADE incidence of 0.4%. Thus, 6% of all *incident ADEs* or about 1 in 17 *incident ADEs* were due to error. Four of the patients with incident eADEs also experienced an incident ADR. In 12 (0.19%) of the eADE cases, the eADE was classified as *significant*, in 6 (0.09%) as *moderate* and in 10 (0.16%) as *serious* (table 1). None of the incident eADE was *lethal*. The causes of incident eADEs were *selection errors* in 13 patients (0.20%), *dosage errors* in 11 (0.17%) and *surveillance errors* in 4 (0.06%) (figure

Table 1

Incidence of adverse drug reactions (ADRs) and error-associated adverse drug events (eADEs) in medical inpatients.

	patients		
	No.	**%**	**(95% CI)**
Total number of patients	6383	100	
Patients with at least 1 *incident ADE*	481	7.5	(6.8, 8.2)
Patients with ADR *	457	7.2	(6.5, 7.8)
Patients with eADE *	28	0.4	(0.2, 0.7)
significant	12	0.19	(0.08, 0.30)
moderate	6	0.09	(0.01, 0.17)
serious	10	0.16	(0.03, 0.26)
lethal	0	0	(0, 0.05)

* In 4 patients, an ADR as well as an eADE was observed.

2A). The systems and organs most frequently affected by eADEs were the gastrointestinal tract, the haemostasis system, the skin and the respiratory and cardiovascular systems (figure 2B). The drug classes most frequently causing eADEs were antithrombotics (ATC B01), cardiovascular drugs (C*), antibacterials (J01), sedatives (N05B/C) and non-steroidal anti-inflammatory drugs (NSAIDs, M01A) (figure 2C). If we compare the number of eADEs with the number of patients exposed to the corresponding drug classes, eADE incidences were 0.42% for NSAIDs, 0.20% for antibacterials, 0.15% for antithrombotics, 0.12% for cardiovascular drugs and 0.11% for sedatives. Thus, eADEs were observed with an overall incidence of 0.4%, related chiefly to *selection* and *dosage errors* and involving several organ systems and drug classes.

Table 2 reports additional details on the eADEs in the 28 incident cases. Among the *selection error*s, 4 cases represented indication errors and 9 missed contraindications. In 2 of the 4 cases with indication errors, the patients had no clear indication for anticoagulation but experienced bleeding complications. Among the cases caused by missed contraindications, 4 patients experienced allergic skin reactions against antibacterials despite known allergy against the same drugs. Three further patients suffered from bleeding complications in the presence of known contraindications against NSAIDs and/or anticoagulants. Among the *dosage errors*, the causes were mainly overdoses of benzodiazepines (4 cases) and digoxin (4 cases). The 3 absolute overdose cases included 2 cases of benzodiazepine overdose occurring during intravenous sedation with midazolam for a medical intervention and after repeated generous lorazepam administrations in an opioid-addicted patient. The third patient with an absolute overdose developed somnolence while receiving high doses of combined clozapine and morphine. Two further patients exhibiting benzodiazepine oversedation suffered from polymorbidity with

Table 2

Medical inpatients with an eADE.

Patient	drug	events, contraindications and risk factors	severity
Selection errors:	Indication errors		
F 89	phenprocoumon	skin and muscle haematomas	moderate
M 72	phenprocoumon	muscle haematoma	significant
F 60	iloprost	hypotension, abdominal cramping	significant
F 70	nasal decongestant	rhinitis medicamentosa	significant
Indication errors:	Missed contraindications		
M 68	amoxicillin, clavulanic acid	rash and skin oedema, known amoxicillin allergy	serious
M 46	amoxicillin, clavulanic acid	rash, known amoxicillin allergy	significant
M 62	amoxicillin, clavulanic acid	rash, known amoxicillin allergy	significant
M 58	co-trimoxazole	rash, known co-trimoxazole allergy	significant
M 40	diclofenac, acetylsalicylic acid	GI bleeding, history of peptic ulcer disease	moderate
F 80	acetylsalicylic acid	GI bleeding, history of peptic ulcer disease	serious
M 75	phenprocoumon	subdural haematoma, multiple risk factors for falls	serious
F 63	ceftriaxone	thrombopenia, previous ceftriaxone-associated thrombopenia	serious
M 69	flurbiprofen	aggravation of known renal insufficiency	significant
Dosage errors:	Absolute overdoses		
M 36	midazolam	respiratory insufficiency	serious
M 19	lorazepam	somnolence	moderate
M 93	morphine, clozapine	somnolence	significant
	Relative overdoses		
F 78	digoxin	nausea and vomiting, renal insufficiency	moderate
F 96	digoxin	vomiting, renal insufficiency	moderate
M 79	digoxin	nausea, renal insufficiency	significant
F 84	digoxin	blurred vision, renal insufficiency	significant
M 43	midazolam	respiratory insufficiency, hepatic insufficiency	moderate
M 69	lorazepam	nocturnal apnea episodes , multimorbidity	moderate
F 75	metoprolol	bradycardia and hypotension, rapid dose escalation	serious
M 92	paracetamol	toxic liver injury, old age and poor nutrition	significant
Surveillance errors			
F 45	phenprocoumon, heparin	large psoas haematoma leading to N. femoralis impairment	serious
M 60	heparin	haematoma requiring surgical treatment and transfusions	serious
F 84	intravenous insulin	hypoglycaemia, inadequate control of blood glucose levels	serious
M 77	iron	phlebitis after paravenous infusion	significant

For each of the 28 incident cases, patient data (sex, age), the causative drug(s), the eADE predisposing risk factors (for relative overdosages) and the severity are included. The cases are classified according to the types of error.

impaired renal function and hepatic insufficiency respectively, and were therefore classified as relative overdoses. All four patients with digoxin toxicity exhibited impaired renal function and thus also represented relative overdose cases. Since, overall, 594 patients were treated with digoxin, the eADE incidence for digoxin was 0.64%. Among ADEs caused by *surveillance errors*, two further patients exhibited bleeding complications. On the basis of the 4 phenprocoumon-associated eADEs and the 946 phenprocoumon-treated patients, the eADE incidence for phenprocoumon was 0.42%. In summary, the eADEs consisted mainly of allergic reactions to antibacterials in patients with known allergy, bleeding complications associated with inappropriate indications, missed contraindications and/or inadequate surveillance and overdoses of benzodiazepines and digoxin.

ADE at admission

Overall, 279 (4.4%) patients presented with an *ADE at admission* (table 3). 194 (3.0%) of these exhibited ADRs and 85 (1.3%) eADEs. Among the 194 patients with ADR at admission, 183 (2.9%) were admitted for the ADR and therefore classified as ADR-related admissions. The remaining 11 (0.2%) presented with an ADR at admission but were admitted for other conditions and thus represent admissions with ADR. In 79 (1.2%) of the 85 patients with eADE at admission, the eADE was the cause of the admission and these cases therefore represent eADE-related admissions. In 6 patients (0.1%) the eADE was detected at admission but the patients were admitted for other conditions, i.e. they represented admissions with eADE. Errors were thus causative in about 1 in 3 cases for both subgroups of *ADE at admission*, i.e. for *ADE-related admissions* and *admissions with ADE*. The causes of eADEs at admission were *selection errors* in 36 cases (0.56%), *dosage errors* in 10 (0.16%) and *surveillance errors* in 15 (0.23%) (figure 3A). Among the *selection errors*, 14 were indication errors, 9 missed contraindications and 13 missed drug interactions. The *dosage errors* occurred due to relative overdoses in 4 cases and to absolute overdoses in 3. In the remaining 3 cases, the errors concerned the route of administration and the dosage interval. Interestingly, in 24 (0.4%) of the 85 cases with eADE at admission the error was induced by the patient and not by a health professional, and these cases thus represent *patient errors*. The eADEs at admission most frequently concerned the gastrointestinal tract, the kidney and the cardiovascular or central nervous systems (figure 3B), and were commonly caused by NSAIDs, cardiovascular drugs and antithrombotics (figure 3C). Frequently observed eADEs at admission were NSAID-associated gastrointestinal complications (25 cases): of these, 8 cases took the NSAID without contacting a health professional (*patient errors*), 5 were caused by a combination of NSAIDs with anticoagulants (missed drug interactions), 2 received an NSAID despite a known history of peptic ulcer (missed contraindications) and 2 were treated with a combination of two or more NSAIDs (indication errors). Five patients were admitted for NSAID-associated renal insufficiency (2 *patient errors*, 2 indication errors and 1 missed contraindication). 13 patients were admitted for cardiovascular agent-induced hypotension or bradycardia (3 missed drug interactions, 6 *surveillance errors*, 2 *patient errors*, 1 indication error and 1 relative overdose). The severity of the e*ADEs at admission* was *signifi-*

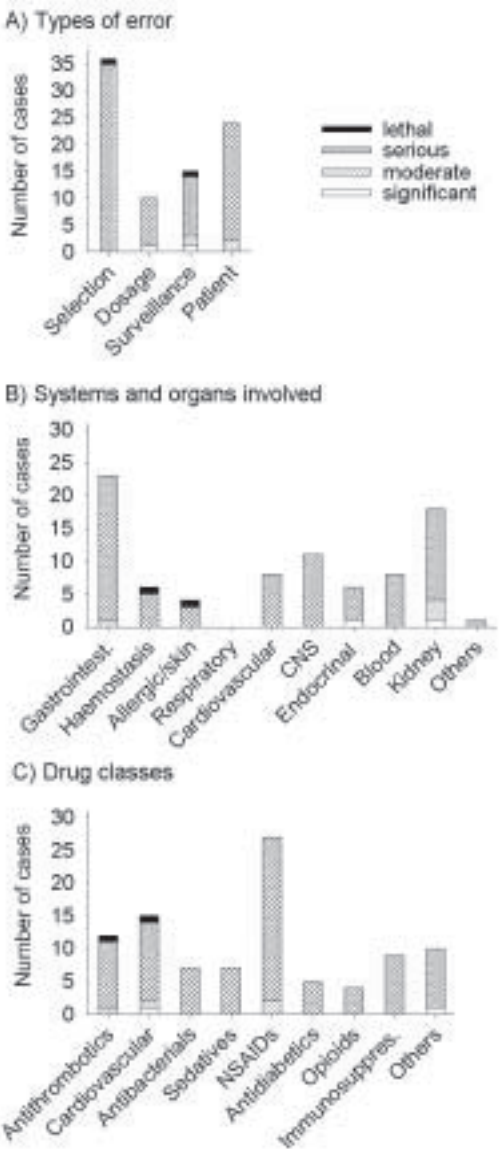

Figure 3

Error-associated drug events (eADE) at admission according to type of error (A), systems or organs (B) and drug class (C). *Significant*: ADE demanding a dosage reduction or therapy cessation, *moderate:* ADEs requiring additional therapeutic measures, *serious:* ADEs prolonging hospitalisation or leading to a permanent defect or life-threatening complication and *lethal*: ADEs leading to the patient's death. Types of error include selection *errors* i.e. indication errors, missed contraindications and missed drug interactions, *dosage errors* i.e. absolute overdoses, relative overdoses, dosing frequency and route errors, *surveillance errors* i.e. inadequate clinical surveillance or neglected laboratory determinations and *patient errors*. The drug classes are *antithrombotics* (ATC: B01), *cardiovascular* drugs (C), *antibacterials* for systemic use (J01), *sedatives* (N05B and N05C), *NSAIDs* i.e. non-steroidal anti-inflammatory drugs (M01A), *antidiabetics* (A10), *opioids* (N02A) and *immunosuppressive agents* (L04).

Table 3

Frequency of adverse drug reactions (ADRs) and error-associated adverse drug events (eADEs) at hospital admission.

	patients		
	No.	**%**	**(95% CI)**
Total number of patients	6383	100	
ADE at admission	279	4.4	(3.8, 4.9)
ADR at admission	194	3.0	(2.6, 3.5)
ADR-related admission	183	2.9	(2.4, 3.3)
Admission with ADR	11	0.2	(0.07, 0.3)
eADE at admission	85	1.3	(1.0, 1.7)
eADE-related admission	79	1.2	(0.9, 1.5)
Admission with eADE	6	0.1	(0.01, 0.2)

cant in 2 cases (0.03%), *moderate* in 4 (0.06%), *serious* in 77 (1.2%) and *lethal* in 2 (0.03%) (figure 3). Bleeding complications from oral anticoagulation without comprehensible indication caused one of the 2 eADE-related fatalities. The other fatality concerned a patient who had consulted at least two physicians for angiooedema and finally died of hypoxic brain damage due to enalapril-induced angiooedema. In summary, 1.2% of all admissions were caused by eADEs, with two-thirds caused by health professionals and one-third by the patients themselves.

Discussion

In this study we determined the incidence of eADE in a cohort of 6383 medical inpatients hospitalised in two Swiss teaching hospitals as 0.4%. Six per cent of all *incident ADE*, or about 1 in 17 *incident ADE*, were caused by error (table 1). The most frequently observed types of error in patients with incident eADE were missed contraindications and relative dosage errors (figure 2, Table 2). Further, eADEs at admission were observed in 1.3% of all patients and contributed about 1 in 3 of *ADEs at admission* (table 3). In the majority of patients with eADEs at admission, the eADE was the cause of hospital admission (table 3). eADEs at admission were eventually lethal in 0.03% of patients. Among the eADEs at admission, the most frequent error types were missed drug interactions, *surveillance* and *patient errors* (figure 3).

The eADE incidence rate of 0.4% obtained in the present study agrees well with the values obtained in several other studies [5–7, 18]. Furthermore, the overall *incident ADE* rate of 7.5% in this study is close to the value of 6.5% reported by Bates et al. [9, 19, 20], although Bates et al. reported considerably higher eADE rates of 1.3%–3.6% [8–10, 19, 20]. Differences between centres are a well-known phenomenon in epidemiological studies and may be due to local differences in drug utilisation, patient populations and/or methodological differences [21]. In our study, for example, the incident eADE list is headed by digoxin, NSAIDs, antithrombotics, cardiovasculars, antibacterials and sedatives, whereas Bates's list is headed by analgesics, antibacterials, sedatives and antipsychotics [9]. This suggests that analgesics and antipsychotics may have been administered less frequently in our patient cohort, resulting in lower eADE rates for these drugs and thus lower overall eADE rates. Another possible cause of eADE incidence differences are differences in patient collectives; our study cohort was limited to general medical care units and did not include intensive care units, which show an approx. twofold higher eADE rate [9]. eADE incidence differences may also have resulted from methodological differences in ADE screening. ADEs in our study were recorded prospectively; the study physicians visited the monitored units daily on workdays, a procedure which has so far resulted in rather high eADE incidence rates [9, 19, 20]. Further, individual differences in the perception of preventability, as discussed recently for error-associated deaths [22], may influence eADE incidence estimates. The internal validity of our results is supported by Cohen's Kappa statistics with moderate to excellent agreement between the two experienced physician evaluators for the classification of *ADE*s as *eADE* or *ADR*. 11 of the 28 incident eADE cases were identified independently by both evaluators and 8 and 9 incident eADE cases were identified by one of them, suggesting that a maximum of 7 incident eADE cases may have been missed by both reviewers. The reported interstudy incidence differences show how important it is to clearly define eADEs, to validate local methodology, to have all ADE cases assessed by independent reviewers, to know the local eADE incidence rates and to evaluate directly changes in local eADE incidence rates in future error intervention studies.

The errors leading to incident eADEs chiefly involved missed contraindications and relative overdose errors. This is in line with another study on medication errors in inpatients, which also showed a predominance of incorrect drug choices and drug dosage errors [19]. If we extrapolate from the values of 1 in 100 errors leading to an eADE [1, 8], errors should have occurred in about 4% of all patients included in the database. In view of the high error rates reported, electronic prescribing may be a promising way of reducing error rates in the future. For eADE reduction, sophisticated software solutions will be required to ensure that dosages are adjusted according to the individual patient's needs. For example, dosage adjustment for digoxin in renal insufficiency can only be tackled by cross-linking with the patient's age, the patients' plasma creatinine laboratory data and the nurse's recordings on the patients' body weight [23]. Relative overdoses of psychotropics and missed contraindications will be even more difficult to prevent, since this requires cross-linking with structured patients' history and diagnostic data. However, prospective eADE prevention remains the only approach in proving that ADEs classified retrospectively as error-associated are indeed preventable.

Considering the low overall incident eADE rate, it was surprising that 1.2% of all patients were admitted because of eADEs (table 3). Since we lack exposure data, we cannot quantify the associated risk. However, if we consider that annually about 10% of the Swiss population are admitted to hospital, a rough estimate would be that each year up to 0.1% of the population are hospitalised because of eADEs. For eADEs at admission, electronic

prescription and the overview of all medications by a primary care physician or pharmacist would be sufficient to detect and possibly prevent missed drug interactions. However, tackling *patients' errors* and *surveillance errors* will be considerably more difficult.

In this analysis two eADEs with lethal outcome were detected. In addition, we observed five deaths due to incident ADRs and three deaths due to ADRs at admission [4] (data not shown). Thus, ten ADE-related deaths were observed overall, corresponding to 3% of all deaths and 0.16% of all patients. The former number is close to the value of 5% ADE-related deaths in a recent study evaluating 1511 in-hospital deaths [24] and somewhat lower than the 9% directly drug-related deaths in another study also evaluating 732 in-hospital deaths [25]. Most of ADR-related deaths (6 of 8 deaths) were cancer chemotherapy-related [4]. It is reassuring that overall we observed only two eADE-related deaths, both of which occurred in patients admitted for the corresponding eADEs, resulting in an overall rate of eADE-related deaths of 0.03%. Again, the number of 0.03% seems more worrisome, if we consider that 0.03% of the 10% of the population admitted to hospital per year could die of eADEs, corresponding to some 3 eADE-related deaths per 100 000 population per year. Such extrapolations to the entire country must of course remain speculative, since there may be considerable local differences in drug utilisation, prescription and surveillance. However, the patient who died because of enalapril-associated angiooedema despite multiple physician contacts for this complaint demonstrates the importance of adequate therapy surveillance and prompt recognition of possible ADEs.

In conclusion, we determined an overall eADE incidence of 0.4% in a cohort of 6383 medical inpatients and identified missed contraindications and relative dosage errors as the main causes of eADEs in inpatients. eADEs were associated with a variety of drugs and symptoms. Furthermore, with an incidence of 1.2% eADE contribute considerably to hospital admissions. In contrast to in-hospital eADEs, eADEs at admission were chiefly caused by patients' errors, missed drug interactions and surveillance errors. Further investigation will be needed to determine whether sophisticated electronic prescribing and elaborate decision support systems will substantially reduce eADE rates.

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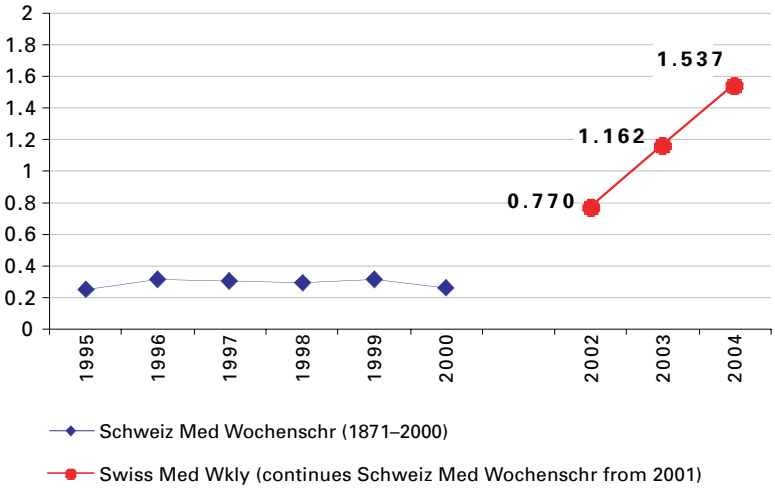

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