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Emergency Department Visits Caused by Adverse Drug Events

Results of a French Survey

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Abstract

Background: Adverse drug events (ADEs) are a substantial cause of hospital admissions. However, little is known about the incidence, preventability and severity of ADEs resulting in emergency department visits. To address this issue, we conducted a prospective survey in emergency departments of French public hospitals.

Methods: This study was performed over two periods of 1 week each, one in June 1999 and one in December 1999, in emergency departments of five university hospitals and five general hospitals throughout France. All patients aged ≥15 years presenting with medical complaints were included in the study. Trauma patients, those with gynaecological conditions and those with alcohol intoxication or intentional drug poisoning were excluded from the study. Each patient was assessed by two local emergency physicians to determine whether the visit was the result of an ADE. All medical records were subsequently validated by an independent group of medical lecturers in iatrogenic disorders.

Results: Out of a total of 1937 patients consulting, 1562 were taking at least one drug during the previous week and were included for analysis; 328 (21%; 95% CI 19, 23) of these patients consulted an emergency physician because of an ADE. Patients with ADEs were older than those without (mean age 63.5 vs 54.8 years; $p < 0.0001$). Furthermore, ADE patients were more likely to have a higher severity presentation than the non-ADE group ($p = 0.019$). The number of drug exposures was significantly higher in patients with an ADE than in those without (mean number of medications 5.17 vs 3.82; $p < 0.0001$). On multivariate analysis, only

age and the number of medications taken were significantly associated with adverse events. In total, 410 drugs were incriminated in the occurrence of 328 ADEs. The most frequently incriminated drug classes were: (i) psychotropic agents (n = 84; 20.5%); (ii) diuretics (n = 48; 11.7%), anticoagulants (n = 38; 9.3%) and other cardiovascular drugs (n = 63; 15.4%); and (iii) analgesics, including NSAIDs (n = 57; 13.9%). Preventability could be assessed in 280 of the 328 cases. In 106 cases (37.9%), the ADE was judged to be preventable.

Conclusion: ADEs leading to emergency department visits are frequent, and many are preventable, confirming that there is a need to develop prevention strategies.

Background

Adverse drug events (ADEs) occur frequently among hospitalised patients. Based on a meta-analysis of prospective studies, Lazarou et al.[1] estimated that >2 million hospital patients experienced a serious adverse drug reaction (ADR) resulting in approximately 100 000 fatalities in the US in 1994. According to a survey conducted under the auspices of French pharmacovigilance centres, ADEs appeared to be responsible for 3.19% (95% CI 2.37, 4.01) of hospitalisations in France.[2] Furthermore, earlier studies emphasised that ADEs could often be prevented if physicians took into account possible risk factors.[3-6] For instance, 51% of ADEs among patients in nursing homes in Massachusetts, US, were judged to be preventable,[3] whereas 27.6% were deemed preventable among older persons in the ambulatory clinical setting according to a US cohort study.[4] Moreover, one-third of ADRs leading to admission to a French emergency department were considered to be preventable.[5]

In 1997, it had been estimated that ADRs leading to hospital admission yielded direct costs of DM1050 million (€525 million) per year in Germany.[7] At that time, published data revealed about 30% of all ADEs to be preventable, suggesting that DM350 million (€175 million) per year could be saved by preventing ADEs in Germany.[7] Bates et al.[8] found that an ADE was associated with $US2595 of additional costs to the hospital in the US in 1997. For preventable ADEs, the figure was almost twice as high, notably because of a longer mean hospital stay, namely 4.6 days for preventable ADEs versus 2.2 days for all other ADE categories.[8]

Risk factors for ADEs include patient characteristics, drug-drug interactions (DDIs), inappropriate number or dose of drugs and poor compliance.[9] A recent study found that ADEs occurred in 25% (95% CI 20, 29) of outpatients in ambulatory care, of which many were preventable (28%) or ameliorable (11%).[10]

It is within this context that the French National Pedagogical Association for Therapy Instruction (APNET) has for several years been working to avert preventable ADEs.[11] The objective of this study was to evaluate the frequency and severity of ADEs for which patients consulted emergency departments and to analyse the patient characteristics, severity of clinical presentation, drug classes implicated and, lastly, the preventability of these ADEs. Thus, this study was about ADEs that occurred in the ambulatory setting and led to hospital visits in emergency departments.

Methods

Setting

We studied the emergency departments of ten hospitals: five university hospitals and five general hospitals. Participating institutions were selected on the basis of their potential information-gathering abilities from 19 facilities that had taken part in an earlier feasibility study. Since one department was understaffed, nine centres (five university and four

general hospitals) effectively participated in the study.

Patients

After first giving their written consent, all patients who visited the emergency departments of selected centres between 8:00am and 10:00pm for the selected weeks were consecutively included in the survey, whether or not they had taken one drug or several drugs. Exclusion criteria included individuals <15 years of age, trauma patients and gynaecological patients. Also excluded were persons who were seen for alcohol intoxication, intentional drug overdose or a social reason.

Design

This study was conducted prospectively over two 1-week periods, the first in June 1999, the second in December 1999. All patients were interviewed and examined by two emergency physicians who determined whether or not the consultation was related to an ADE. In this respect, they took into consideration the following factors: the temporal relationship, the role of concurrent diseases, the known drug actions and interactions as described in drug monographs and/or literature using the MEDLINE database, and the effect of de-challenge. Of note, drug re-challenge was never done. Demographic characteristics were recorded for every patient, as was a medical and drug history. Patient outcome (recovery, convalescence at home, hospitalisation in intensive care or other department, death) was also recorded.

Each file was then reviewed anonymously and validated by two members of an independent expert committee comprising clinical pharmacologists and epidemiologists, and eight hospital practitioners specialised in the diagnosis of iatrogenic disorders. The French causality assessment method was used for determining the degree of imputability of each ADE.[12] Lastly, the expert committee assessed the potential preventability of each ADE by means of a 4-item preventability score described in section 2.4.

Definitions

Classification of ADEs included the WHO's definition of ADRs (i.e. a noxious and unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function), and adverse events related to inappropriate medicine use (i.e. not or not fully in accordance with the approved instructions for use), including therapeutic failures resulting from poor compliance and abrupt discontinuation of medications.[13]

On the whole, patients who had taken at least one drug during the week prior to their hospital visit could be divided into three categories: (i) no iatrogenicity (no ADE); (ii) possible iatrogenicity, but doubtful, corresponding to grade I1 on the French scoring system; (iii) plausible, likely or very likely iatrogenicity, corresponding to scores of I2, I3 and I4, respectively, on the French scoring system.[12]

The nature of the clinical symptoms and their severity upon arrival at the hospital were coded according to the method adopted by emergency care units in France for patient classification.[14] The system entails five stages of increasing severity: S0: no immediate severity; S1: spontaneous regression; S2: regression after symptomatic treatment; S3: hospitalisation for >24 hours with no life-threatening risk; S4: life-threatening risk or death.

Moreover, the preventability of adverse drug effects was evaluated according to a 4-item score: A0: unpreventable – compliance with 'good drug utilisation' practices (compliance with product information for the product implicated); A1: possibly preventable – carelessness (usage precautions not followed); A2: likely preventable – 'improper use of the drug' by the doctor and/or patient (off-label use or contraindication not heeded, inappropriate duration of treatment and/or dosage, disregarded drug-drug interaction, poor assessment of risk/benefit ratio); A3: almost certainly preventable ('misuse of the drug' by the doctor and/or patient, patient error/inappropriate discontinuation of treatment or flagrant poor therapeutic compliance and/or dangerous self-medication). Drug classification was performed

Table I. Characteristics of adverse drug events (ADEs)

Variable	ADEs [n (%)]
Total ADEs	328 (100)
Severity	
S4: life-threatening risk or death	5 (1.5)
S3: hospitalisation > 24 hours	44 (13.4)
S2: regression after symptomatic treatment	92 (28.0)
S1: spontaneous regression	167 (50.9)
S0: no immediate severity	20 (6.1)
Imputability	
I3 and I4: likely and very likely	114 (34.7)
I2: plausible	62 (18.9)
I1: doubtful	152 (46.3)

according the Anatomical Therapeutic Chemical (ATC) classification in 5 levels.

Differences between the two expert's judgments about classification of events as drug related and about the severity of such events were resolved by discussion.

Ethical Committee

Our study was approved by the Commission Nationale de l'informatique et des Libertés, or CNIL, the data protection authority in France. Written consent was obtained for all patients. Under French law, ethics committee approval was not required for this survey as it did not alter patient care.

Statistical Analysis

We used Student's t-test to compare continuous data; the results are presented as means ± SD. The Chi-square (χ^2) test was used to compare categorical data; the results are presented as counts, with percentages. All reported p-values are based on two-tailed tests of significance. The association between the characteristics of the patients and the number of ADEs was determined with a Poisson regression model. A Kappa test was performed to determine inter-rater agreement in expert groups for the classification of events as drug related and their severity. All analysis were conducted with SAS software (SAS Institute, Cary, NC, USA) and Microsoft Excel. A p-value < 0.05 was considered significant.

Results

Inter-Rater Agreement of Experts

Inter-rater agreement, determined before oral consensus was reached, was acceptable for the classification of events as drug related (kappa 0.76; 95% CI 0.62, 0.90) and their severity (kappa 0.78; 95% CI 0.60, 0.96).

Characteristics of Adverse Drug Events (ADEs)

Of the 1937 patients who visited the emergency departments during the 2-week study period, 1562 who had taken at least one drug in the previous week (including early treatment withdrawal cases) were included in the analysis. Of these, 328 (21%; 95% CI 19%, 23%) consulted an emergency physician subsequently determined to be due to a possible ADE (i.e. classified from I1 to I4). Imputability was classified as doubtful (I1) in 152 cases (46.3%), plausible (I2) in 62 cases (18.9%) and likely (I3 and I4) in 114 cases (34.7%) [table I]. Forty-nine (14.9%) of the events were classified as serious (S3 to S4). All results regarding imputability and severity of ADEs are shown in table I. Preventability could be assessed in 280 of the 328 cases. In 106 cases (37.9%), preventability was considered 'probable' (A2) or 'almost certain' (A3). In the A2 to A3 group, inadequate patient practices were observed in 54 cases (50.9%), including poor compliance (24 cases), inappropriate, sudden recent discontinuation of therapy (22 cases) and inappropriate self-medication (eight cases) involving the use of NSAIDs (n = 5), whereas improper prescribing practices were found in the remaining 52 cases. Finally, 18 ADEs were considered as serious (S3 to S4) and preventable (A2 to A3).

The ADE-related symptoms most frequently seen upon arrival in the emergency departments were gastrointestinal (n = 53; 16.2%), neurological (n = 52; 15.9%), cardiovascular (n = 49; 14.9%) and malaise and/or dizziness, with or without associated falls (n = 49; 14.9%).

Table II. Comparison between adverse drug event (ADE) and non-ADE populations

Characteristics	Non-ADE group	ADE group	p-Value
Age (years, mean ± SD)	54.8 ± 22.7	63.5 ± 21.2	<0.0001
Sex ratio (male/female)[a]	621/611	167/161	0.83
No. of medications (mean ± SD)	3.82 ± 2.87	5.17 ± 3.21	<0.0001
Severity of patient presentation: no. of S3 to S4 (%)	125 (10.1)	49 (17.4)	<0.01
Outcomes (n [%])[b]			
Recovery	848 (68.7)	204 (62.2)	
Convalescence at home	53 (4.3)	33 (10.1)	
Hospitalisation	78 (6.3)	32 (9.8)	
Death	37 (3.0)	13 (4.0)	
Unknown	218 (17.7)	46 (14.0)	

a Sex unspecified in two patients.

b Overall outcomes were significantly worse in the ADE group compared with the non ADE group ($p < 0.0001$).

S3 = hospitalisation >24 hours; **S4** = life-threatening risk or death.

In all, 410 drugs were implicated in the occurrence of the 328 observed events. The most frequently implicated drug classes were the psychotropic drugs, including tranquillisers and/or hypnotics, antidepressants and antipsychotics (n = 84; 20.5%); diuretics (n = 48; 11.7%), anticoagulants (n = 38; 9.3%) and other cardiovascular agents (n = 63; 15.4%) and analgesics, including NSAIDs (n = 57; 13.9%).

Comparison between ADE-Related Patients (ADE Group) and Non-ADE Group

The sex ratio was similar in both groups, with or without ADEs (1.04 vs 1.02; $p = 0.83$). Overall, patients with ADEs were significantly older than those without (mean age 63.5 ± 21.2 vs 54.8 ± 22.7 years; $p < 0.0001$). The proportion of patients receiving ≥2 drugs was significantly higher in the ADE patients group than the non-ADE group (91% vs 75%; $p < 0.0001$). Likewise, the mean number of drugs used was significantly higher in the ADE group, namely 5.17 ± 3.21 vs 3.82 ± 2.87 for the non-ADE group ($p < 0.0001$). These data are presented in table II. The frequency of ADEs among patients with an ADE clearly rises as a function of the number of drugs taken: 9.5% with only one drug; 19.4% with 2 to 4 drugs; 28.6% with 5 to 9 drugs; and 35.6% with ≥10 drugs. Moreover, there is a strong correlation between frequency of ADEs among the 1562 patients who visited emergency departments and the number of medications taken (figure 1). Patients with ADEs had a higher severity score than patients without ADEs ($p < 0.01$). The outcomes were significantly worse in patients with ADEs (table II). Multivariate analysis found that age (odds ratio [OR] per period of 10 years 1.10; 95% CI 1.03, 1.17) and the number of medications that a patient took (OR 1.11; 95% CI 1.06, 1.16) were related to the risk of an ADE.

Discussion

In this study, we found that 21% of 1562 outpatients had ADEs leading to their emergency department visits. Of these events, 17% were serious and approximately one-third were likely preventable. The two main independent factors associated with the occurrence of ADEs were age and the number of medications taken, keeping in mind that they were likely confoundings that were not adjusted for.

Our study has some limitations, such as involving only a limited number of emergency departments and being conducted over two periods of 1 week. Thus, its results may not be generalisable. Moreo-

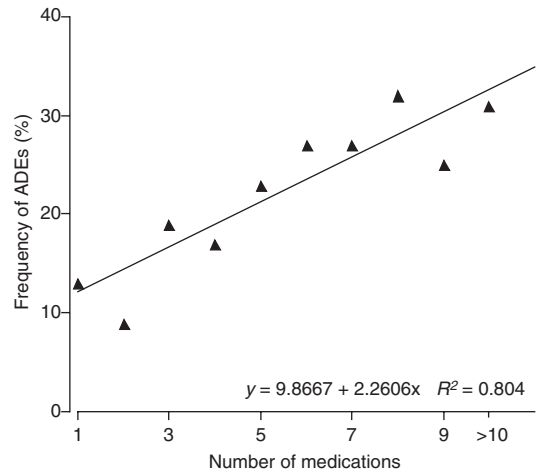

Fig. 1. Correlation between frequency of adverse drugs events (ADEs) and number of medications taken. R^2 = coefficient of determination; y = response variable of linear regression.

ver, there is no gold standard for evaluating the preventability of ADEs, and in some cases, we could not be certain that prescribing patterns were actually inappropriate because of the absence of data on the reasons why certain prescription choices were made. However, our data are consistent with those of earlier reports.

The frequency of ADEs varies by study, notably in terms of the sector under observation (i.e. ambulatory versus hospitalised patients in different departments) and methods of detection, ADE definition and imputability criteria used. Overall, ADEs appear to be responsible for 2–10% of hospital admissions and are seen in 3–15% of hospitalised patients.[15-17] The mortality rate from ADEs is also difficult to ascertain and varies from 0.7–7% depending on the study.[4] The main feature of our study is that it focused on patients who presented to emergency departments, with only the most seriously ill being admitted to hospital. By contrast, most earlier studies evaluated the incidence of ADEs among already hospitalised patients or those admitted to hospital, such as one recent study that recorded an incidence of 6.1 ADRs per 100 admissions (95% CI 4.4, 8.3) at the emergency department of Toulouse, France.[5] In a retrospective chart review, Hafner et al.[15] found an incidence of 1.7% ADE-related emergency department visits. Our survey found that 21% of patients undergoing drug therapy and referred to an emergency department for a medical reason consulted for a possible ADE, the imputability of which appeared to be 'plausible', 'likely' or 'very likely' in 11.3% of cases. This result is in agreement with those found by Gandhi et al.[10] who reported an incidence of 27% among patients in ambulatory care who received at least one prescription and had ADEs during a 3-month observation period.

In our study, patients with ADEs were significantly older than those without, and this could either be because older patients tended to take more drugs or because of narrower safety margins observed in seniors because of limited physiologic reserve.[18] However, whether age is an independent risk factor for ADEs is much debated. Some earlier studies found that increased age posed increased risk for ADEs.[2,15,17] Conversely, Gandhi et al.[10] did not find any association between the occurrence of ADEs and any patient characteristics, including age in ambulatory care patients. According to the study by Carbonin et al.,[19] age was not an independent risk factor of ADRs in hospitalised medical patients. Finally, age *per se* did not appear to be an important risk factor for ADE in studies confined to patients in the geriatric age group.[18,20] Also, as observed in our study, ADEs appeared to be more severe in elderly patients. This finding is corroborated by a 1985 US FDA report on 37 000 ADRs according to which patients aged >60 years, who represented 17% of the population in the US, accounted for 37% of ADEs necessitating hospitalisation and 49% of fatal ADEs; in those aged >80 years, 20–25% of hospitalisations appeared to be related to an ADR.[21]

In our study, the sex ratio was the same in both groups, i.e. those with or without ADEs. Furthermore, we found no significant difference in the rate of ADEs among males and females. Though being in line with other reports,[10,19] this result conflicts with the conclusions of most studies which found a significant association between female sex and frequency of ADEs.[2,15,17,22] It is unclear whether this sex-related increase in the incidence of ADEs in females is because of an increased vulnerability to drug toxicity or other causes, such as greater drug consumption, higher consulting rates, differences in dosage regimens and/or severity of underlying disease.[22]

The number of drugs that patients take is a major factor, explained in part by drug interactions, with a very significant increase in ADEs when the number of drugs increases, as our study substantiates (figure 1). We found a good correlation between number of drugs taken and rate of ADEs ($R^2 = 0.80$, figure 1). This link has been previously observed in number of studies.[10,15,19,20,23] For instance, taking >4 drugs was found to be positively correlated with the occurrence of ADRs (OR 2.94; 95% CI 2.38, 3.62) in hospitalised medical patients.[19] Elderly patients admitted to medical wards because of ADEs were taking significantly more drugs (OR 6.7; 95% CI

5.9, 7.5) than those admitted for another reason (OR 5.4; 95% CI 5.0, 5.8).[20] Gandhi et al.[10] found, in a multivariate analysis, that only the number of medications taken was significantly associated with the risk of an ADE; the mean number of ADEs per patient increased by 10% (95% CI 6, 15) for each additional medication.

One of the major findings of our study is the high number of seemingly preventable ADEs (37.9%). Similar conclusions have already been drawn from previous studies conducted in the ambulatory setting as well as in various healthcare facilities.[3-10,17,18,20,24] Half of the preventable ADEs observed in the present survey were ascribable to prescribing errors, such as disregarded contraindications and DDIs as well as inappropriate dosage regimen or monitoring. Therefore, besides educational efforts to improve prescribing patterns, computerised prescribing has been advocated as a drug treatment quality assurance tool, aimed at reminding physicians of potential important drug-drug and drug-disease interactions.[23,25,26] Moreover, the presence of a pharmacist on medical rounds as a full member of the patient care team in a medical intensive care unit was shown to result in a substantially lower rate of ADEs caused by prescribing errors.[20] Like others, we found that a significant proportion of preventable ADEs was related to problems with patient adherence[4,20] and inappropriate self-medication,[5] suggesting that patient education too may be an essential component of efforts to avert ADEs.[4] It has also be emphasised that strategies to improve patient-doctor communication and outpatients' access to pharmacists (to discuss medications and adverse effects) are essential in this area.[10] Finally, since medication errors may occur at different levels, including prescribing, transcription, dispensing, administration and treatment monitoring, prevention strategies should target all stages from drug prescription to utilisation.[3,4,24-29] Hence, the preventive measures leading to optimisation of drug handling should involve not only doctors and pharmacists, but also other caregivers (i.e. midwives, nurses) and patients. The merits of such an approach have already been acknowledged by the French National Academy of Medicine.[29]

Conclusion

Our survey suggests that ADEs leading to emergency department visits are common among outpatients and that more than one-third of such events are preventable. In this respect, our data are in agreement with those of previous studies, highlighting the need to develop prevention strategies, which should include educational interventions, computer-assisted prescribing, pharmacy-based interventions and introduction of safe medication practices.

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