Frequency and cost of serious adverse drug reactions in a department of general medicine

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Aims To assess the frequency and cost of drug reactions causing or prolonging hospitalization.

Methods All patients admitted to an internal medicine ward over 6 months were evaluated to identify serious adverse reactions. The number of drug classes on admission or at the time of the adverse drug reaction (ADR) was counted. Excess ADR-related hospital stay was computed using a) raw excess duration of hospital stay, b) correction of duration of hospital stay by age, sex, and number of drug classes, and c) estimation by investigator of excess hospital stay.

Results Three hundred and twenty-nine patients were evaluated: 212 male, 117 female, mean age 57.2 (males: 52.2, females: 66.2 ($P < 0.05$)), range 17–95 years. They stayed a total of 3720 hospital days (mean stay 11.3 days). 298 had no ADR (mean age 55.8, taking a mean of 2.7 drug classes, 10.7 days hospital stay); 31 had ADRs: in 10, the ADR caused admission in patients with a mean age of 84 ($P < 0.01$ vs the two other groups), taking 6.3 drug classes, who stayed a mean of 15.1 days; 21 occurred in hospital in patients with a mean age of 63.6, taking 4.2 drug classes ($P < 0.01$), who stayed a mean of 19.2 days ($P < 0.01$ vs patients without ADRs). In four the ADR was fatal (13% of ADRs, 40% of deaths). Raw ADR-related excess hospital stay was 318 days (8.6% of all hospital days), after multivariate correction 282 days (7.6% of all hospital days), and with investigator estimation 197 days (5.3% of all hospital days). Point prevalence of ADRs at admission was 3%, incidence rate in hospital was 5.6/1000 patient-days.

Conclusions 3% of the admissions were related to ADRs. In addition, 6.6% of hospitalized patients had significant ADRs. Between 5 and 9% of hospital costs were related to ADRs. In 24 of the 31 patients with ADRs (77%), these were related to the pharmacological properties of the involved drugs, and may possibly have been avoidable.

Keywords: adverse drug reactions

Introduction

Adverse drug reactions (ADRs) represent a sizeable part of overall medical expenses. It has been estimated that 3 to 8% of hospital admissions in Internal Medicine are related to ADRs [1, 2], and these occur in addition in up to 20% of all hospitalized patients [3, 4].

In a previous study [5], we had found that 2.5% of all patients presenting to the emergency unit of a General Hospital did so because of an adverse drug reaction, involuntary overdose, or an underdose.

However, that study was incomplete, in that the diagnosis of drug-related admission was defined at admission, so that patients admitted with a diagnosis whose relationship with a drug was not immediately obvious were not included. Moreover, in addition to being admitted for drug-related diseases, patients may also suffer from adverse drug reactions during their stay in hospital.

We therefore studied prospectively all patients admitted to a department of general medicine of the same general hospital, over a 6-month period. We estimated how many were admitted because of a drug-related diagnosis or suffered from a significant adverse drug reaction in hospital, and have attempted to identify risk factors and compute the number of excess hospital days related to ADRs.

Methods

All patients hospitalized in a 29-bed ward of the department of internal medicine of the general hospital Jacques Monod in Le Havre (France), over a period of 6 months were prospectively evaluated daily for the presence of serious adverse reactions, by the same physician. This hospital also includes departments of most medical specialties, as shown by the patients' admission diagnosis profile (Table 1).

Serious reactions were defined as those causing hospitalization, that were fatal or life-threatening, or that resulted in significant changes in the patient's treatment (presumably thereby prolonging hospitalization). Suicide attempts (volun-

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Table 1 Diagnostic categories at admission in 329 consecutive patients hospitalized over a 6 month period.

Alcohol-related disorders and alcoholism	28.3%
Depression, anxiety, and panic attacks	17.0%
Suicide attempts	14.6%
Social reasons	11.2%
Falls	10.6%
Neurological disorders	5.8%
seizures	2.7%
stroke	3.0%
Rheumatological disorders	5.5%
Bronchopulmonary disorders	4.2%
Cancer	2.7%

tary overdoses) were not included as adverse drug reactions, whereas involuntary over- or under-dosing were.

All identified cases were reviewed with a specialist in drug-induced diseases. They were classified according to the type of adverse reaction in A (augmented), related to the pharmacological properties of the drugs involved and B (bizarre), unrelated to the pharmacological properties, and presumably allergic (also called idiosyncratic) [6]. Patients were therefore classified into patients without ADR, patients admitted because of an ADR, and patients with a serious ADR while in hospital.

For all patients, age, sex, duration of hospital stay, number and type of drug classes taken (according to the classification of the Vidal drug dictionary [7]), and diagnoses were recorded. In addition, the observer noted for all adverse reactions the number of extra hospital days if any, related to the adverse reaction (medical evaluation), for reactions occurring in hospital.

The number of excess hospital days attributable to the adverse drug reactions was computed according to three different methods:

In all three, the exact number of hospital days for patients admitted because of an ADR was included.

For patients having an ADR in hospital, the calculations included:

(1) The raw number of excess hospital days, i.e. the sum of the differences between raw individual duration of hospital stay of patients having had an ADR in hospital and the mean duration of hospital stay for patients without ADR.

(2) The corrected number of excess hospital days, i.e. the sum of the differences between duration of hospital stay of patients with ADRs in hospital, and the mean duration of hospital stay for patients without ADR, after correction of duration of hospital stay for age, sex and number of drug classes (multivariate regression analysis).

(3) The number of excess days in hospital estimated by the physician in charge of the patient (see above).

The total number of excess days was the sum of the excess days related to ADRs causing admission or occurring in hospital, giving three results according to the computation method used.

Cost of excess hospital days was estimated by multiplying the total number of excess days by the reference daily hospital cost, as given by the hospital administration, i.e. 1923.90 FF (287.15 Euro or £ 240.46) for this medical

department. This value is used by the hospital to charge insurance companies or the health system.

Statistical analyses were done with the Chi square test for qualitative variables, regression analysis and analysis of variance with or without covariates for quantitative variables, as needed. Analyses were done using Systat®. The statistical significance level was set at 0.05.

Results

a) General characteristics of the whole population

Over the 6 months of the study, from May 2 to October 31, 1993, 335 patients were admitted to the ward. 329 (98.2%) were included in the study. The six excluded patients were hospitalized for a single night for an acute non-drug related problem.

The overall population characteristics are given in Table 2.

● There was a significant difference in age, duration of hospital stay and number of drug classes between men and women, the latter being older, staying longer in hospital, and taking drugs from more different classes.

● Duration of hospital stay was correlated with age ($\text{duration} = 0.55 + 0.19 \times \text{age}$, $r = 0.42$, $P < 0.01$) (Figure 1), and with number of drug classes ($\text{duration} = 6.71 + 1.6 \times \text{number of drug classes}$, $r = 0.33$, $P < 0.001$).

● Number of drug classes was also correlated with age ($\text{number of drug classes} = -0.64 + 0.062 \times \text{age}$, $r = 0.66$, $P < 0.001$) (Figure 2). When age was accounted for, the correlation of duration of hospital stay with number of drug classes was no longer significant ($P = 0.16$).

The major determinants of duration of hospital stay in the overall population, regardless of ADR status, were age and gender.

b) Adverse drug reactions

Thirty-one of the 329 patients had significant adverse drug reactions: in 10 the ADR caused admission to the hospital, and in 21 it occurred in hospital. Two hundred and ninety eight patients had no adverse drug reaction. The characteristics of these groups are given in Table 3. None of the patients admitted because of an ADR had another ADR while in hospital.

● Patients admitted for ADRs were older, more often female, and took more drug classes than the other patients.

● Patients who had a significant ADR during their hospital stay were not older, but were more often female, and took more drug classes than patients who did not have ADRs.

● All ADRs in patients admitted for ADRs and 14 out of 21 in those occurring in hospital (66%) were type A reactions, i.e. related to the drugs' pharmacological properties.

The adverse drug reactions involved are given in Table 4.

Because some patients had several reactions simultaneously or successively (e.g., dehydration with hypotension, fall with hip fracture), the total number of reactions is greater than the total number of patients having the reactions.

None of the adverse drug reactions was new, i.e. unlabelled (not in the Summary of Product Characteristics) at the time of the event.

Table 2 Characteristics of the overall study population.

	Total	Men	Women
Number	329	212	117
Mean age (range)	57.2 (16–95)	52.5 (17–95)	66.2* (16–95)
Mean duration of stay in days (range)	11.3 (1–50)	9.7 (1–50)	14.2* (1–49)
Mean number of drug classes (range)	2.9 (0–8)	2.6 (0–8)	3.4* (0–8)

* $P < 0.001$, men *vs* women, ANOVA. **Figure 1** Relationship between duration of hospital stay and age, for patients with no adverse drug reaction (circles). Patients admitted because of an adverse drug reaction (triangles) and patients having an adverse reaction in hospital (squares) are also indicated.

The regression shown between age and duration of hospital stay is for patients without ADR (duration = $-0.10 + 0.19 \times \text{age}$, $r = 0.43$, $P < 0.01$).

Drug use is shown in Table 5, including both those taken by the whole population and those involved in the ADRs, with the percentage and 95% two-sided confidence intervals.

c) Duration of hospital stay (Table 6)

Patients admitted for ADRs did not stay in hospital significantly longer than patients without ADRs, whereas patients with ADRs in hospital did. Since duration of hospital stay was correlated with age, sex and number of drug classes taken, we corrected duration of hospital stay in the different groups by these factors (analysis of covariance). The least squares corrected mean durations of stays for the three groups are given in Table 6.

After correction, patients admitted because of ADRs spent slightly less time in hospital than patients without ADRs (though this was not significant); Patients with an ADR in hospital stayed longer than the other two groups (19 *vs* 10 days).

Figure 2 Relationship between age and number of drug classes for all patients without adverse drug reaction (circles). Patients admitted because of an adverse drug reaction (triangles) and patients having an adverse reaction in hospital (squares) are also indicated.

The regression shown between number of drug classes and age is for patients without ADR (number of drug classes = $-0.53 + 0.058 \times \text{age}$, $r = 0.64$, $P < 0.01$).

d) Excess hospital days due to ADRs

The total number of hospital days for patients admitted because of ADR was 139 days. Total excess hospital days were:

(1) Using the raw figures (Table 6): a mean excess of 8.5 days per patient with in-hospital ADR, for a total excess of 178.5 days, added to the 139 days in patients admitted for ADRs gave a total of 317.5 excess days, out of a total of 3720 hospital days for the whole population (8.5%).

(2) Using the values corrected for age, sex and number of drug classes (Table 6), 142.8 excess days, added to the 139 above for a total of 281.8 days (7.6% of total hospital days).

(3) Using medical estimates of excess duration related to ADRs, as assessed by the physician in charge of the patient, i.e. a total of 58 days, added to the 139 days for a total of 197 days (5.3% of total days).

When these 317.5, 281.8 or 197 excess days are multiplied by the cost of a hospital day in internal medicine, as given by the hospital financial department (1923.90 F/day), total

	No ADR	ADRA	ADRH	All ADR
Number	298	10	21	31
Type A	—	10	14	24
Men/Women	198/100	2/8*	12/9*	14/17*
Mean age	55.8	83.9*†	63.5	70.2*
(range)	(16–95)	(72–93)	(34–95)	(34–95)
Mean number of drug classes (range)	2.7 (0–8)	6.3*†(4–8)	4.2* (2–8)	4.9* (2–8)

* $P < 0.001$ vs No ADR; † $P < 0.05$, ADRA vs ADRH.

Table 4 ADR descriptions.

ADR	Number of cases	Drugs	Comments
Allergy	8	antibiotics (6)	All occurred in hospital
skin reactions (4)		calcium heparinate (1),	
angioedema (1)		fluoxetine (1)	
bronchospasm (1)			
Orthostatic hypotension	6	antihypertensive drugs, neuroleptics	Often with falls, resulting in one
		tricyclic antidepressants	hip fracture, with fatal outcome
			outcome in an elderly patient
Dehydration	5	diuretics for hypertension or heart failure	In elderly patients
Sleepiness and falls	5		Associated with the two previous
			disorders
Hypokalaemia	3	diuretics and digoxin	One case of dysrhythmia with
			favorable outcome
Dysrhythmia	3	digoxin,	
		- with β -adrenoceptor blocker (1)	
		- with diuretic (1)	
Hypoglycaemia	3	insulin (1),	In elderly patients with decreased
		sulphonamides (2)	food intake without dose
			adjustment
Gastro-intestinal disorders	5		
● candidosis	1	antibiotic treatment,	
● epigastric pain	3	NSAIDs	
● duodenal haemorrhage	1	NSAID	Fatal outcome
Neurological:			
● extrapyramidal signs	1	neuroleptics	
● confusion and agitation	1	first dose of viloxazine	
Renal failure	1	gentamycin	Fatal renal failure
Thrombocytopenia with	1	low molecular weight heparin	95 year old woman, fatal outcome
thrombosis			
Urinary retention	1	trihexyphenidyle	Resulted in discovery of prostate
			carcinoma

cost over 6 months was 610 838, 542 155, or 379 008 FF, respectively (91 167, 80 919 and 56 568 Euro, or £76 354, £67 769 and £47 376, respectively). Table 7 also indicates yearly costs overall, yearly cost per ward bed and cost per patient with an ADR.

e) Prevalence and incidence of adverse reactions

The point prevalence of adverse drug reactions at admission was 3%: 10 of 329 admissions; the rate of incidence during hospitalisation was 5.6 per 1000 patient-days (21 cases over 3720 patient-days in hospital); the prevalence of reactions during hospitalisation can be computed as number of days with reaction over total hospital days, i.e.: 5.3 to 8.5% according to computation method used, taking into account the duration of adverse reactions.

Table 3 Characteristics of patients admitted for ADR (ADRA), with ADR in hospital (ADRH), and without ADR (No ADR).

Discussion

Drug-induced diseases represent an important proportion of the disease burden in the general population. It can be assessed at various points, e.g., in the general non-hospitalized population or in an out-patient setting, at admission to the hospital, or in hospitalized patients. Some indication of these frequencies can be found in recent literature, summarized below: these studies are somewhat difficult to compare because of different settings, different methods to retrieve reactions, some studies considering only adverse reactions, others adding involuntary over or underdosing, some considering only clinically manifest reactions where others also looked for biological disturbances [8]. However, all in all, these studies give coherent results:

Table 5 Frequency of ADRs for each drug class.

Drug class	Number of users (% use frequency)	Number of ADRs	% ADR in users	95% confidence interval
Antibiotics	122 (37.1)	6	4.9	1.8–10.6
Antidepressants	85 (25.8)	9	10.6	4.9–19.2
Neuroleptics				
Anxiolytics				
Hypnotics	95 (28.8)	2	2.1	0.3–7.4
Antihypertensives	36 (10.9)	4	11.1	3.1–26.6
Diuretics	61 (18.5)	3	4.9	1.0–13.7
Antiarrhythmics	40 (12.2)	0	0	0–8.8
Digitalis	45 (13.7)	3	6.7	1.4–18.3
Anticoagulants				
oral	20 (6.1)	0	0	0–17.0
injectable	11 (3.3)	1	4	0.23–41.0
NSAIDs	38 (5.4)	3	7.9	1.7–21.4
Antiparkinsonian	10 (3.0)	1	10	0.25–44.0
Antidiabetic agents	15 (4.5)	3	20	4.3–48.1
Lipid lowering agents	12 (3.6)	1	8.3	0.2–38.5
Steroids	4 (1.2)	0	0	0–60.2
Hormone	3 (0.9)	1	33.3	0.8–90.6
replacement therapy				
Muscle relaxants	15 (4.6)	0	0	0–21.8
Analgesics	98 (29.8)	0	0	0–3.7

Table 6 Duration of hospital stay in raw figures, and after correction for age, sex, number of drug classes.

	No ADR	ADRA	ADRH
Number of patients	298	10	21
Mean duration of stay in days	10.7	13.9	19.2*
(range)	(1–50)	(5–21)	(3–36)
Corrected duration of stay ($\pm$ s.e. Mean)	10.9 $\pm$ 0.5	8.3 $\pm$ 2.9	17.7 $\pm$ 1.9*†

No ADR: patients without ADR; ADRA: patients admitted because of ADR; ADRH: patients with ADR in hospital.

* $P < 0.05$ vs No ADR, † $P < 0.05$ vs ADRA.

Table 7 Estimated costs of adverse drug reactions in a 29-bed ward of general medicine in FF, Euro and £.

	Unit	Raw estimate	Corrected estimate	Medical evaluation
Cost over 6 months	FF	610 838	542 155	379 008
	Euro	91 169	80 918	56 568
	£	76 354	67 769	47 376
Yearly cost	FF	1 221 676	1 084 310	758 016
	Euro	182 339	161 837	113 136
	£	152 709	135 538	94 752
Yearly cost per hospital bed	FF	42 126	37 390	26 138
	Euro	6287	5580	3901
	£	5265	4673	3267
Cost per ADR patient	FF	19 704	17 488	12 226
	Euro	2940	2610	1824
	£	2463	2186	2528

a) in the outpatient population, Chrishilles *et al.* [9] found 10% adverse reactions in 3170 patients above 65 years of age, of whom 10% (0.7% of total) were sent to hospital because of this reaction. Prince *et al.* [10] found 293 adverse reaction in 10184 patients (2.8%) of whom 71 (0.7%) were hospitalized, and Schneider *et al.* [11] in 463

elderly outpatients found 97 adverse reactions (21%) of whom 12 were admitted to hospital (2.6% of total). Of these 13 817 patients, overall 707 (5.1%) had ADR, and 105 (0.8%) were admitted because of these ADRs.

These studies of general population can be compared with three studies in digitalis-treated patients reporting 0.7, 0.8, and 0.8% of hospital admissions because of digitalis adverse reactions and overdosing [12–14].

Overall about 5–10% of all patients have adverse drug reactions, and slightly under 1% of all patients are sent to hospital because of these.

b) At hospital admission: ADRs causing hospital admission occur before admission, and represent the more serious of these reactions, these approximately 10% of outpatients reactions that are sent to hospital, concerning slightly under 1% of the general population, as described above. There are a greater number of these cross-sectional studies, in different settings with different patient populations, captured in general emergency or admission departments, or at admission in different speciality wards. In addition, variations occur in the definitions of the captured events (ADRs only, over and underdoses, including only clinical events, or also non-symptomatic biological abnormalities).

Table 8 summarizes results from various recent papers [15–26], where the proportion of patients admitted for drug-related reactions varies from 3% to 20%, the smaller figures occurring in the very specialized departments such as cardiology, the larger numbers in elderly patients or in internal medicine. Overall, these 13 publications studying 9420 patients found 520 drug-related admissions, i.e. 5.5%, not counting underdoses. This figure is comparable with that found by Einarson [1] who compiled 36 studies published between 1966 and 1989, with overall 5% of the patients admitted for ADRs.

The very close similarity between the figures found in the outpatient and admissions studies is striking.

c) In hospital, fewer studies have been done: instead of the simpler cross-sectional studies at admission, these require the follow-up of all hospitalized patients for the duration of the hospital stay. In addition, patients may be under greater scrutiny in hospital. Differences in the intensity of scrutiny may explain variations found in the literature: six studies were found between 1990 and 1995 [27–29], whose results are shown in Table 9. The numbers of patients involved vary from 64 to 36000, for an overall mean of 3%, ranging from 1.5% to over 20% (in HIV-positive patients). This result is overshadowed by one very large study. The others together show a total of 875 ADRs for 13872 patients, i.e. 6.3%.

Despite large variations between the studies, related to the patient population studied, and the way in which the reactions were looked for and ascertained, the figures are quite consistent overall. The data suggest that drug-related diseases occur in 5–7% of the general treated population,

with approximately 10% resulting in hospitalization (0.7% of the total population). This represents about 5% of all hospital admissions; reactions occur in approximately 5% of all patients hospitalized in medical wards.

How does our study compare with these figures? We found that 3% of the admission were related to drug reactions, a figure that is rather low. Our setting is a community hospital including various specialty departments, and the department is one of general medicine, therefore receiving patients not admitted to the specialty wards, including large numbers of patients with alcohol-related problems (28% of the admitted patients), or drug suicide attempts (14.6%). If these are excluded, adverse drug reactions represent about 5.5% of admissions. These were all type A reactions, in elderly patients taking many drug classes, of whom 90% had associated heart failure, and 60% renal failure.

In hospitalized patients, significant adverse drug reactions occurred in 6.3% of patients. Two-thirds were type A reactions which may have been expected and perhaps prevented (17 out of 25 reactions in hospital occurring in 14 out of 21 patients).

Patients with adverse reactions were older and took more drugs than the patients without ADRs. The duration of hospital stay was longer in older patients, and they also took more drugs. In addition, women were older, took more drugs, stayed longer in hospital, and had more ADRs. It is therefore important for the computation of excess hospital days related to ADRs to correct duration of hospital stay by age, sex and number of drugs classes taken.

Table 8 Summary of published work on drug related hospital admissions.

Source (reference)	Study population	Total number of patients in study	Number admitted for ADR	%
Chan <i>et al.</i> [15]		1701	34	2
Col <i>et al.</i> [16]	Elderly patients	315	53	17
Garijo <i>et al.</i> [17]		1847	72	3.9
Hallas <i>et al.</i> [18]	Pneumology	313	11	3.5
Hallas <i>et al.</i> [19]	Cardiology	366	15	4
Hallas <i>et al.</i> [8]	Internal Medicine	333	27	8.1
Hallas <i>et al.</i> [20]	Internal Medicine and Geriatrics	607	85	14
Hallas <i>et al.</i> [21]	Gastro-entriology	328	32	9.8
Hallas <i>et al.</i> [22]	Geriatrics	294	33	11.2
Lin & Lin [23]		2695	109	4
Lindley <i>et al.</i> [24]	Elderly patients	416	26	6.3
Smucker <i>et al.</i> [25]	Elderly patients	100	9	9
Van Kraaij <i>et al.</i> [26]	Elderly patients	105	14	13.3

Table 9 Adverse drug reactions in hospitalized patients.

Source	Study population	Total number of patients in study	Number with ADR	%
Carbonin <i>et al.</i> [27]		9148	532	5.8
Classen <i>et al.</i> [3]		36 653	648	1.8
Foreman <i>et al.</i> [28]	Elderly	64	1	1.6
Harb <i>et al.</i> [4]	HIV +	390	79	20.3
Lindley <i>et al.</i> [24]	Elderly patients;	416	77	18.5
O'Neil <i>et al.</i> [29]	Test of methods	3146	133	4.2

It is interesting to note that, when corrected for age and therapy (maybe an indication of the number of underlying disease and their severity), patients with drug-related admissions had a shorter hospital stay than patients with non-drug related diseases. The shorter stay could be related to a shorter diagnostic time for these diseases, ie less time was spent looking for the cause of the disease, and that treatment was usually simple (e.g., stopping or adjusting drug dosage).

Overall, excess drug-related hospital days represent, according to the way they are computed, 5.3 to 8.5% of all hospital days. Age, sex and treatment corrected durations may be the best estimate, giving overall 7.6% of all hospital days.

This represents a considerable cost, around 37 400 FF (5580 Euro or £4700) per hospital bed per year. This costing could be further refined by including the cost of individual procedures and laboratory tests in the computation. It is interesting to note that in recent studies, excess hospital costs of ADRs in the USA were estimated at 2000 to 3000 dollars per patient [30, 31], which is somewhat lower than in our study (Table 7).

Could these drug-related events have been prevented? Probably not for the type B reactions which, unless there is known allergy, are unpredictable. For the type A reactions, a quick evaluation shows that many of them, including the fatal ones, could perhaps have been avoided, resulting in considerable health resource savings, not to mention less patient suffering. Another study has estimated that up to 65% of adverse drug reactions may be avoidable [32], compared with the 70% in our study. Any intervention program that could prove its efficacy would easily become cost effective. Preventing half of the avoidable serious adverse reactions (35% of all reactions) would result in a yearly saving of over £50 000 in this single 29-bed ward. These savings, both in terms of finances and in hospital bed availability could be made available for other patients. Even if all the saved money were reinvested in the prevention program, there would still be a net gain in bed availability and obviously in patient suffering, and therefore in improved hospital or healthcare system efficacy and productivity. This would be an intervention that both improves health care and decreases costs.

This work was done when NM was Associate Professor of Clinical Pharmacology at the University of Rouen Medical School.

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