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Contribution of adverse drug reactions to hospital admission of older patients

CYNDIE K. MANNESSE, FRANS H. M. DERKX[1], MARIA A. J. DE RIDDER[2], ARIE J. MAN IN 'T VELD[1], TISCHA J. M. VAN DER CAMMEN

Department of Geriatric Medicine, University Hospital Rotterdam Dijkzigt and Harbour Hospital, Rotterdam, The Netherlands
[1]Department of Internal Medicine I, University Hospital Rotterdam Dijkzigt, Rotterdam, The Netherlands
[2]Institute for Epidemiology and Biostatistics, Erasmus University Rotterdam, Rotterdam, The Netherlands

Address correspondence to: C. K. Mannesse, Department of Geriatric Medicine, Albert Schweitzer Hospital, PO 306, 3300 AH, Dordrecht, The Netherlands. Fax (+31) 78 6523569. Email c.mannesse@worldonline.nl

Abstract

Objective: to describe the severity of adverse drug reactions as a factor in hospital admission of older patients, and to identify risk indicators for severe adverse drug reactions in these patients.
Design: observational cross-sectional study.
Setting: Five wards in a university hospital in the Netherlands.
Subjects: patients aged 70 and over admitted to general medical wards.
Methods: use of statistical comparison and Kramer's algorithm.
Results: a severe adverse drug reaction was present in 25 (24%) of 106 patients. Thirteen patients (12%; 95% confidence interval 6.1–18.6%) were admitted probably because of an adverse drug reaction. Risk indicators for a severe adverse drug reaction were a fall before admission (odds ratio 51.3, $P = 0.006$), gastrointestinal bleeding or haematuria (odds ratio 19.8, $P < 0.001$) and the use of three or more drugs (odds ratio 9.8, $P = 0.04$).
Conclusion: adverse drug reactions are an important cause of hospital admissions in older people. A fall before admission may indicate a severe adverse drug reaction.

Keywords: *adverse drug reactions, falls, hospital admission, Kramer's algorithm, old age, risk indicators*

Introduction

Clear definitions of adverse drug reactions (ADRs) [1] and of the causal relationship between the clinical manifestation and the drug are given in few reports of drug-related hospital admissions [2–11]. Many studies have found an increase of ADRs in later life [2, 3, 5, 8, 10–16], although this age effect disappears [17, 18] when there is correction for the number of drugs taken or for the number of co-existing diseases [5, 14, 15].

We have determined the proportion of admissions most probably caused by ADRs and further analysed which subjects had severe ADRs.

Methods

Patients

We performed the study on the five general medical wards (158 beds) of the University Hospital, Rotterdam. Using the computerized hospital administration system we identified all admissions of patients aged 70 and over between 1 February and 1 May 1994. We excluded patients transferred from other hospital wards, as well as readmissions within a month. We used the same patient population for another study in which we examined whether older patients recognize ADRs [19].

Data collection

We collected data on medication (including non-prescription drugs) during the interview of patient and caregiver, and examined all packages and pills.

We analysed patients for the presence and severity of ADRs using data from medical history, physical examination and laboratory tests, including plasma concentrations of drugs when available.

For identification of risk indicators for severe ADRs, we collected the following characteristics: age, gender, number of drugs, social setting, marital state,

whether the patient was a car driver, use of cigarettes and alcohol, acuteness of admission, assistance with medication, mobility score [20], activities of daily living index [20], number of diagnoses, falls before hospital admission, presence of bleeding (gastrointestinal, haematuria) and category of diagnoses. The mobility score ranged from 0 (no mobility problem) to 16 points (complete immobility) and the activities of daily living index from 0 (independent) to 20 points (completely dependent).

Definition of an ADR

An ADR was defined as an undesirable clinical manifestation consequent to and caused by the administration of a particular drug [21] or interacting drugs, excluding intentional overdose, substance abuse and therapeutic failure [1, 5, 15]. The clinical manifestation may be an abnormal sign, symptom or laboratory test, or a cluster of abnormal signs, symptoms and tests, but (except in a case of asymptomatic high drug concentrations in the blood) never a laboratory test alone [7].

An ADR was defined as severe [9, 12, 13, 22] when it was potentially life-threatening or led directly to hospital admission.

Causality of ADRs

Suspected ADRs were those mentioned as such in the *British National Formulary* [23].

To determine whether the clinical manifestation was an ADR, the investigator (C.K.M.) evaluated each suspected ADR using the validated Kramer's algorithm [21] with Hutchinson's questionnaire [24]. The diagnostic criteria in Kramer's algorithm are divided into six axes, with a scoring system incorporated into each axis. The cumulative score corresponds with the probability that the clinical manifestation represents an ADR (Table 1).

We compared the score obtained for a suspected ADR caused by a drug interaction with the scores obtained for the clinical manifestation caused by the separate drugs. When a candidate single drug had a higher score, that drug rather than the interaction was held responsible for the ADR [21, 25].

When a patient had multiple ADRs, we used the ADR with the highest total score in the algorithm in further analysis.

In patients with an ADR leading to hospital admission, the relationship between the clinical manifestation and the use of a specific drug or interacting drugs was deemed significant when statistical comparison showed a correlation between them.

Table 1. The six axes and total score in Kramer's algorithm for adverse drug reactions (amended from [14])

		Scoring of evidence for reaction		
Axis		Favours	Uncertain	Against
I	Previous experience	+1	0	−1
II	No alternative illnesses[a]	+2	0	−1
III	Timing of events	+1	0	−2
IV	Drug levels	+1	0	−1
V	Dechallenge	+1	0	−1
VI	Rechallenge[b]	+1	0	−1
Total score[c]		+7	0	−7

[a]No other illnesses explaining the presence of the clinical manifestation in the patient.
[b]Not done in any of the patients in this observational study.
[c]<0, adverse drug reaction unlikely; 0–3, possible; 4 and 5, probable; 6 and 7, definite.

Number of drugs

The number of drugs per patient per day was determined by counting the different drugs which the patient claimed to have used during the 2 weeks before admission. For the combined preparations, the different pharmacologically active ingredients were counted separately, based on the assumption that the different substances could be candidates for causing different ADRs.

Diagnoses

For each patient we counted the number of diagnoses requiring medication and the number of new diagnoses on admission. The diagnoses relating to ADRs were not included in the total number of diagnoses.

The diagnoses were then categorized into:

- Chronic obstructive pulmonary disease—with or without an exacerbation of symptoms.
- Cardiovascular—any cardiac disease, hypertension, peripheral vascular disease and stroke.
- Diabetes mellitus—non-insulin- and insulin-dependent diabetes mellitus.
- Terminal renal insufficiency—subjects on peritoneal or haemodialysis, or after renal transplantation.

Statistical analysis

We used the χ^2 (if suitable) or Fisher's exact test for dichotomous variables, and the *t*-test or Mann–Whitney test for continuous variables. Only variables with a significant influence univariately ($P \leq 0.05$) were used in backward selection (using $P < 0.05$ as criterion) to build a multiple logistic regression model.

The results of all tests are expressed as a two-tailed *P*-value. A test result is judged to be statistically significant when $P < 0.05$. We performed statistical analyses with the package of SPSS/PC+, version 5.0.1.

Results

During the study period, 128 patients aged 70 or above

Table 2. Age, gender and number of drugs in 106 older medical inpatients

	All ($n = 106$)	Women ($n = 60$)	Men ($n = 46$)
Age (years)			
Mean	78.0	78.4	77.5
Range	70.0–91.1	70.3–91.1	70.0–88.9
25–75 percentiles	73.7–81.5	74.1–83.0	73.3–80.5
No. of drugs			
Total	622	375	247
Mean	5.9	6.3	5.4
Range	0–16	1–16	0–13
25–75 percentiles	3.0–8.0	4.0–8.8	2.0–8.0

were admitted to the general medical wards (24% of all admissions). This percentage is lower than the average in the Netherlands (in general hospitals 45% of the inpatients are aged 65+) as our hospital is a tertiary centre for a wide region, resulting in a relatively young hospital population. At the time of the study we had no dedicated elderly care ward. The patient characteristics indicate that the study population was typical of elderly medical admissions.

We excluded 22 patients (17%): 15 according to protocol design (nine transfers, six readmissions), one who refused, three who died before inclusion and three who were missed for other reasons.

Of the 106 patients included, four used no medication. Age, gender and number of drugs are shown in Table 2. We found no difference in age or number of drugs between men and women.

Twelve subjects lived in residential homes and four in nursing homes. Of the 622 drugs counted, the most frequent types were cardiovascular (used by 67% of the patients), central nervous system (used by 44%) and gastrointestinal (used by 43%).

At the end of study, 15 patients (14%) had died. None of the deaths was directly ADR-related.

Patients with ADRs

According to the definition of ADR used and Kramer's causality algorithm, 44 of the patients (42%) had one or more ADR. Twenty-five (24%) had a severe ADR.

An ADR, with a cumulative score in the algorithm of at least 'possible', led to hospital admission in 22 patients (21%). The admission was most probably caused by an ADR in 13 patients: eight with a 'definitive' or 'probable' ADR according to the algorithm and five in whom statistical comparison gives a significant correlation between bleeding and the use of an oral anticoagulant. These five anticoagulant users were in a group of 12 patients admitted with bleeding, whereas anticoagulants were used by only nine of 94 patients without this ADR ($P = 0.009$). In the algorithm, the total score of bleeding and the use of an oral anticoagulant was 2, indicating a 'possible' ADR, because (i) it was theoretically possible that an alternative illness had resulted in the bleeding, giving a score of 0 on axis II, (ii) the drug was used for a longer period before the occurrence of the bleeding, resulting in a score of 0 on axis III or (iii) an appropriate International Normalized Ratio of prothrombin time according to the *British National Formulary* [23] resulted in a score of 0 on axis IV.

Table 3. Diagnostic characteristics of 106 patients with and without severe adverse drug reactions which showed significant influence univariately

	Severe adverse reactions		
	Present ($n = 25$)	Absent ($n = 81$)	P-value
Percentage of patients			
With ≥5 diagnoses	64	33	0.006
With fall[a]	20	1	0.003
With bleeding[b]	40	5	0.00006
Using ≥3 drugs	96	77	0.04
Percentage of patients by diagnosis category			
COPD	36	15	0.04
Cardiovascular	88	67	0.04

[a]The cause of the hospital admission in all five patients.
[b]Gastrointestinal bleeding or haematuria was the cause of the hospital admission in 12 of the 14 patients.
COPD, chronic obstructive pulmonary disease.

Risk indicators for severe ADRs

The result of comparison of characteristics between patients with and without severe ADRs is presented in Table 3. In multivariate analysis, a fall before hospital admission (odds ratio 51.3, $P = 0.006$), the presence of gastrointestinal bleeding or haematuria (odds ratio 19.8, $P < 0.001$) and the use of three or more drugs (odds ratio 9.8, $P = 0.04$) were significant factors in identifying patients with severe ADRs.

Discussion

By using Kramer's algorithm [21, 24] and statistical comparisons we found that 12% of patients aged 70 and over were admitted because of an ADR. This proportion is comparable to the results of an earlier Dutch study of hospital patients aged 65 and over, which also used an algorithm [9].

In earlier studies the proportion of hospital admissions due to an ADR varied from 1.4% [10] to 35% [26] in patients of all ages and from 3.5% [6] to 24.8% [27] in older patients. These differences probably reflect a lack of standardization in defining ADRs, especially in the description of the causal relationship between the reaction and the prescription of the drug [1]. In the present study we used the results of statistical

comparison between the presence or absence of a particular reaction in users of a specific drug as a way to describe this relationship. This method has not been used before, probably because of the low frequency of identical ADRs found in earlier studies.

Most previous studies have used definitions to describe the causality of the ADR. In these studies, the percentages of patients admitted because of an ADR were 2.7 [2] and 5.3 [28] in the UK, 4.2 [4] and 9.4 [5] in the USA, 4.0 in Taiwan [11], 4.1 in Israel [3], 5.7 in Germany [3] and 8.1 in Denmark [7]. An algorithm [9, 14] to describe the causal relationship in ADRs has seldom been used. Such an algorithm can improve inter-observer agreement. The percentage of agreement ranges from 40 to 60% [23, 25, 29] without the use of an algorithm and improves to 71% [30], 80% [23, 31] and 85% [25] with it. We used the validated Kramer's algorithm [21, 23] because it provides more detailed operational criteria for the diagnostic decisions in the causality of the ADRs than other algorithms.

We have confirmed that the use of more drugs [3, 5–8, 10, 15] rather than the presence of more diagnoses [4, 5, 15] is related to ADRs. In earlier studies, a contradictory relationship has been found between the presence of ADRs and factors such as gender [3, 5, 7–9], social situation and assistance with medication [6], the acuteness of admission [7, 8], smoking habit [14, 15] and the use of alcohol [14, 15]. We found no relationship between any of these characteristics and the presence or absence of severe ADRs. Significant factors in identifying subjects with severe ADRs were a fall before admission and the presence of gastrointestinal bleeding or haematuria. Earlier studies [6, 15] found that a fall was not a predictor for the presence of an ADR. One explanation for this is that, according to the definition of ADRs, a fall is not a drug reaction as it is not listed as a drug side effect in the *British National Formulary* [23].

The admission of older patients because of ADRs is an important medical problem, responsible for one in six hospital admissions in our study. Risk indicators for this iatrogenic problem are a fall before admission, the presence of gastrointestinal bleeding or haematuria and the use of three or more drugs. A fall before admission may be the presentation of a severe ADR in the older patient.

Key points

- Hospital admission of older patients due to adverse drug reactions is an important medical problem.
- The number of drugs—rather than the number of diagnoses—is an important factor in identifying patients with severe adverse drug reactions.
- Gastrointestinal bleeding or haematuria as a cause for hospital admission may indicate the presence of a severe adverse drug reaction in older patients.
- A fall before admission can be a presentation of a severe adverse drug reaction in the older patient.

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