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Adverse Drug Reaction-Related Hospitalisations

A Nationwide Study in The Netherlands

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Abstract

Background: The incidence of adverse drug reaction (ADR)-related hospitalisations has usually been assessed within hospitals. Because of the variability in results and methodology, it is difficult to extrapolate these results to a national level.

Objectives: To evaluate the incidence and characteristics of ADR-related hospitalisations in The Netherlands in 2001.

Methods: We conducted a nationwide study of all hospital admissions in 2001. Data were retrieved from a nationwide computer database for hospital discharge records. All acute, non-planned admissions to all Dutch academic and general hospitals in 2001 were included in the study (n = 668 714). From these admissions we selected all hospitalisations that were coded as drug-related, but intended forms of overdose, errors in administration and therapeutic failures were excluded. Hence, we extracted all ADR-related hospitalisations. We compared age, sex and the risk of a fatal outcome between patients admitted with ADRs and patients admitted for other reasons, as well as the most frequent main diagnoses in ADR-related hospitalisations and which drugs most frequently caused the ADRs. In addition, we evaluated to what extent these ADRs were reported to the Netherlands Pharmacovigilance Centre Lareb for spontaneous ADR reporting.

Results: In 2001, 12 249 hospitalisations were coded as ADR related. This was 1.83% of all acute hospital admissions in The Netherlands (95% CI 1.80, 1.86). The proportion increased with age from 0.8% (95% CI 0.75, 0.85) in the <18 years group to 3.2% in the ≥80 years group (95% CI 3.08, 3.32). The most frequent ADR-related diagnoses of hospitalisations were bleeding (n = 1048), non-specified 'unintended effect of drug' (n = 438), hypoglycaemia (n = 375) and fever (n = 347). The drugs most commonly associated with ADR-related hospitalisations were anticoagulants (n = 2185), cytostatics and immunosuppressives (n = 1809) and diuretics (n = 979). Six percent of the ADR-related hospitalisations had a fatal outcome (n = 734). Older age and female gender were associated with ADR-relat-

ed hospitalisations. Only approximately 1% of the coded ADRs causing hospitalisation were reported to our national centre for spontaneous ADR reporting.
Conclusion: The proportion of ADR-related hospitalisations is substantial, especially considering the fact that not all ADRs may be recognised or mentioned in discharge letters. Under-reporting of ADRs that result in hospital admission to our national centre for spontaneous ADR reporting was considerable.

Background

Studies have estimated a wide variation in the frequency of adverse drug reaction (ADR)-related hospitalisations. Meta-analyses have estimated that hospitalisations attributed to ADRs account for between 2.4% and 6.4% of all hospital admissions in Western countries.[1-5] For the elderly this percentage has been estimated to be between 3.4% and 16.6%.[4,6] Approximately 80% of ADRs causing admission or occurring in hospital are type A (dose-related) reactions, which suggests that they are predictable from the known pharmacology of the drug and, therefore, potentially avoidable.[2,7] Most epidemiological studies evaluating the extent of ADR-related hospitalisations were conducted within (single) units, departments or hospitals, hence different settings and methods were used. Because of the variability of the results and methodology, and a lack of representativeness, it is difficult to confidently extrapolate these results to a national level. In 1998, a national prospective cross-sectional study was performed in France.[8] However, only a nationwide sample of medical wards in public hospitals was taken and studied for 14 days to estimate their national incidence of ADR-related hospitalisations. To estimate our national incidence of ADR-related hospitalisations, we conducted a study of all hospital admissions in The Netherlands in 2001. To our knowledge, this is the first nationwide study performed to evaluate ADR-related hospitalisations.

Methods

Data were retrieved from a nationwide computer database for hospital discharge records. The database contains basic patient characteristics, admission and discharge dates, discharge/main diagnosis (coded), secondary diagnoses (coded), medical specialism (coded) and special codes indicating drug-related hospitalisations (E-codes), based on the International Classification of Diseases (9th Edition)-Clinical Modification (ICD-9-CM) coding system.[9] Characteristics of all hospitalisations are registered by medical doctors on the basis of hospital discharge letters and coded by professional code clerks. For every admission, one discharge/main diagnosis (mandatory) and up to nine secondary diagnoses (optional) are registered. The coding is independent of reimbursement of hospital or specialist. All diagnoses are submitted in the same format and mostly electronically.

All patients with an acute, non-planned admission to a Dutch hospital in 2001 were included in the study (n = 668 714). An ADR-related hospitalisation was defined as a hospitalisation with an E-code that indicated an ADR as the reason for hospitalisation (E-code referring to the main diagnosis) or an ADR occurring during a hospitalisation (E-code referring to the secondary diagnosis). The E-code does indicate the drug group involved. Intended forms of overdose, errors in administration and therapeutic failures were not included in our analysis.

We assessed the proportion of ADR-related hospitalisations of all acute admissions in all Dutch academic (n = 8) and general (n = 100) hospitals in a subset of acute admissions to the departments of internal medicine, paediatrics, cardiology, lung diseases, gastroenterology and clinical geriatrics, and in different age groups. We also assessed what were the most frequent main diagnoses in ADR-related hospitalisations and which drugs most frequently caused the ADRs. We compared age, sex, duration of hospital stay and the risk of a fatal outcome between patients with ADR-related hospitalisations and patients with other acute admissions.

Furthermore, in the ADR-related hospitalisations with an E-code directly referring to the *main* diagnosis (n = 6209), we evaluated to what extent these ADRs were reported to the Netherlands Pharmacovigilance Centre Lareb for spontaneous ADR reporting. All Dutch healthcare providers are recommended to report serious ADRs to Lareb, such as ADRs leading to hospitalisation, permanent disability or death.[10] It is known that under-reporting of ADRs exists in any spontaneous reporting system and that signal detection of new and serious ADRs is the main aim of such a system.[11] However, little is known about the extent of under-reporting of serious ADRs in The Netherlands.[12] Therefore, the national hospital discharge records of 2001 were linked by sex and birth date to the Lareb database of spontaneous ADR reports in 2001. If the reported ADR, discharge diagnosis and the corresponding drug matched well and the date of ADR reporting was within 1 month after or 2 weeks before the date of admission, we assumed this to be the same case and classified this ADR-related admission to be reported to Lareb.

Descriptive analyses were conducted using SPSS 11.0. Statistical comparison consisted of standard t-tests (unpaired) and Chi squared-tests. A Mann-Whitney test was used for non-normally distributed data. Ninety-five percent confidence intervals around estimates were calculated based on a binomial distribution.

The ethical review board of the institution that holds the database gave consent for performing this study.

Results

The baseline characteristics of the study population (n = 668 714) are shown in table I. The mean age of patients with acute, non-planned admissions was 48 years and 53.4% of patients were female. The most frequent main diagnoses of acute admissions were 'chest pain' (5.3%), 'abdominal pain' (2.8%) and pneumonia (1.8%). 12 249 hospitalisations were coded as ADR related; of which, 6209 admissions were coded as an ADR-related main diagnosis. Based on this number (12 249), the incidence of ADR-related hospitalisations in The Netherlands was 76.3 per 100 000 inhabitants in 2001. The proportion of ADR-related hospitalisations was 1.83% of all acute, non-planned hospital admissions in The Netherlands (95% CI 1.80, 1.86%). 734 patients (6.0%) died during an ADR-related hospitalisation.

Table I. Baseline characteristics of study population (n = 668 714)

Characteristic	Value
Mean age (y)	48.4
Female sex (%)	53.4
Most frequent main diagnoses (% of hospitalisations)	Chest pain (5.3) Abdominal pain (2.8) Pneumonia (1.8) Atrial fibrillation (1.6) Chronic obstructive lung disease (1.5)
Median duration of admission in days (interquartile range)	5.0 (2.0–11.0)
Died during admission (%)	5.6
ADR-related diagnoses (%)	1.8

ADR = adverse drug reaction.

The proportion of ADR-related hospitalisations was 0.8% (95% CI 0.75, 0.85) in patients aged <18 years, 1.32% (95% CI 1.28, 1.36) in patients aged 18–64 years, 2.81% (95% CI 2.73, 2.89) in patients aged 65–79 years and 3.2% (95% CI 3.08, 3.32) in patients aged ≥80 years (table II).

In a subselection of all acute admissions to departments of internal medicine, paediatrics, cardiology, lung diseases, gastroenterology and clinical geriatrics (n = 353 688), the proportion was 2.84% (95% CI 2.79, 2.89) of all acute admissions. In patients aged ≥65 years it increased to 3.75% (95% CI 3.66, 3.84) and it was 4.29% (95% CI 4.12, 4.46) in patients aged ≥80 (table II). We assessed the proportion in this subselection because most patients with ADR-related diagnoses are admitted to these departments and many other studies in this field were performed within one or more of these departments.

The proportion of ADR-related hospitalisations was 1.2% in academic hospitals versus 1.9% in general hospitals. The difference increased with advancing age: 1.9% versus 3.3% in people aged ≥80 years (for these comparisons, $p < 0.001$).

Table II. Percentage of adverse drug reaction (ADR)-related hospitalisations in 2001 in different age groups

Age (years)	Total no. of patients	No. of patients with ADR-related hospitalisation	Percentage (95% CI)
ADR-related hospitalisations (all)			
<18	109 047	871	0.80 (0.75, 0.85)
18–64	314 208	4145	1.32 (1.28, 1.36)
65–79	159 117	4467	2.81 (2.73, 2.89)
≥80	86 342	2766	3.20 (3.08, 3.32)
Total	**668 714**	**12 249**	**1.83 (1.80, 1.86)**
ADR-related hospitalisations[a]			
<18	74 824	838	1.12 (1.04, 1.20)
18–64	120 885	3276	2.71 (2.62, 2.80)
65–79	105 163	3660	3.48 (3.37, 3.59)
≥80	52 816	2266	4.29 (4.12, 4.46)
Total	**353 688**	**10 040**	**2.84 (2.79, 2.89)**

a Departments of internal medicine, paediatrics, cardiology, lung diseases, gastroenterology and clinical geriatrics.

The most frequent main diagnoses of ADR-related hospitalisations are shown in table III: bleeding diagnoses (gastrointestinal bleeding, n = 436; non-specified bleeding, n = 264; intracerebral bleeding, n = 178; chronic ulcus ventriculi with bleeding, n = 170), non-specified 'unintended effect of drug' (n = 438), hypoglycaemia (n = 375), fever (n = 347), agranulocytosis (n = 271) and dehydration (n = 255). The drugs most commonly associated with ADR-related hospitalisations were anticoagulants (n = 2185), cytostatics and immunosuppressants (n = 1809), diuretics (n = 979), insulin and other antidiabetic agents (n = 541), salicylates (n = 509) and antirheumatics (n = 496).

The mean age of patients with ADR-related hospitalisations was 62 years versus 48 years in other admissions, 55.2% were female versus 53.4% in other admissions ($p < 0.001$) and 6.0% died during hospitalisation versus 5.6% during non-ADR-related hospitalisations ($p < 0.05$) [table IV]. This sex-associated risk increased with increasing age, but the fatality rate diminished. In the 65–79 years age group, 50.5% of the patients with ADR-related hospitalisations were female versus 46.1% in other admissions. Futhermore, 7.9% died during ADR-related hospitalisations versus 9.8% during other acute admissions. In the highest age group (≥80 years), 66.6% were female versus 62.9% in other admissions and 9.7% died during hospitalisation versus 16.5% during acute hospitalisations for other reasons (for these comparisons, $p < 0.001$).

The mean duration of ADR-related hospitalisations was 12.5 days compared with 10 days in other acute admissions ($p < 0.001$). However, in the age group ≥65 years, no significant difference was found in the mean duration of hospital stay (data not shown).

Only 59 of the 6209 admissions with a coded ADR-related main diagnosis in 2001 were reported to the Netherlands Pharmacovigilance Centre Lareb for spontaneous ADR reporting. This is approximately 1% (95% CI 0.71, 1.19) of all hospitalisations that were caused by an ADR (59/6209). The most reported ADRs were angio-oedema (7/59), anaphylaxis (5/59) and hepatitis (5/59). The drug most often reported to cause an ADR was nitrofurantoin (5/59).

Discussion

In this nationwide study, we found that 12 249 hospital admissions were ADR-related (almost 2% of all acute admissions in 2001). As suggested in other studies, this could mean that approximately 80% or even more of the ADRs that caused or complicated these 12 249 hospitalisations were potentially avoidable because they were type A (dose-related) reactions, and thus predictable from the known pharmacology of the drug.[2,7] Although the suggested preventability is disputable, this study can help us to identify the most frequent ADRs related to hospitalisations, study their nature and target these ADRs to take preventive actions.

Six percent of the ADR-related hospitalisations had a fatal outcome (n = 734), although it is unknown what the definite cause of death was. We found that the proportion of ADR-related hospitalisations increased with age from 0.8% in patients aged <18 years to 3.2% in patients aged ≥80 years, which confirms that older people have more ADR-related problems. In the subselection of all acute admissions to departments of internal medicine, paediatrics, cardiology, lung diseases, gastroenterol-

ogy and clinical geriatrics, the proportion increased from 1.1% in the youngest age group to 4.3% in the eldest age group.

The strength of the database that we used is that it includes all admissions in all Dutch general and university hospitals, and that the admission codes are independent of reimbursement. The latter may be a problem in similar databases in some countries (e.g. the US) where some diagnoses pay better than others. Our estimates are in general lower than in previous studies. Some (smaller) studies have produced higher estimations, but most of these studies investigated admissions in specific departments (such as internal medicine or cardiology) and assessed all admissions with the prior hypothesis that drugs may have played a role.[13-16] Such studies might tend to overestimate the proportion of ADR-related hospitalisations. Indeed, it was found that smaller studies show higher proportions of ADR-related hospitalisations, while larger studies display lower proportions.[4]

As in other studies, we found that older age and female sex are associated with more ADR-related hospitalisations. This does not necessarily indicate that increasing age *per se* is a risk factor for the occurrence of ADRs. Several studies have clearly shown that the risk of ADRs (including interactions) is related to the number of drugs taken[17-19] and that the elderly receive more drugs, sometimes inappropriately.[20,21]

In the total group, it seemed that slightly more people died during an ADR-related hospitalisation than during non-ADR-related hospitalisations (6.0% versus 5.6%, $p < 0.05$). However, we found that in the elderly (aged ≥65 years) fewer people died during an ADR-related hospitalisation than during other acute hospitalisations (8.6% vs 12.2%, $p < 0.001$), which indicates that the other hospitalisations were probably for more serious conditions and/or ADRs were easier to treat. It seems that ADR-related hospitalisations in the elderly are in general less life threatening than other disease-related acute admissions in the elderly.

The mean duration of hospital stay in patients with ADR-related admissions was longer than in other acute admissions in the total group (12.5 days vs 9.9 days, $p < 0.001$). This difference disappeared in patients aged ≥65 years (data not shown). The

Table III. Most frequent main diagnoses and drug groups most commonly associated with the adverse drug reaction (ADR) in ADR-related hospitalisations (n = 12 249)

Characteristic	ICD-9-CM code	Frequency	Percentage
Main diagnosis			
Bleeding – all types	–	1048	8.6
gastrointestinal bleeding	578	436	3.6
non-specified bleeding	459.0	264	12.2
intracerebral bleeding	431	178	1.4
chronic ulcus ventriculi with bleeding	531.4	170	1.4
Unintended effect of drug	995.2	438	3.6
Hypoglycaemia	251.2	375	3.1
Fever	780.6	347	2.8
Agranulocytosis	288.0	271	2.2
Dehydration	276.5	255	2.1
Drug group			
Anticoagulants	E934.2	2185	17.8
Cytostatics and immunosuppressants	E933.1	1809	14.8
Diuretics	E944.4	979	8.0
Insulin and antidiabetics	E932.3	541	4.4
Salicylates	E935.3	509	4.2
Antirheumatics	E935.6	496	4.1

ICD-9-CM = International Classification of Diseases (9th Edition)-Clinical Modification.

Table IV. Adverse drug reaction (ADR)-related hospitalisations compared with other acute admissions in different age groups

Characteristic	ADR-related hospitalisations	Other admissions	p-Value[a]
<18y (n = 109 047)			
Mean age (y)	4.5	3.8	<0.001
Female sex (%)	46.4	44.2	NS
Mean duration of hospital stay (d)	3.6	5.8	<0.001
Died during hospitalisation (%)	0.4	0.5	NS
18–64y (n = 314 208)			
Mean age (y)	47.5	41.7	<0.001
Female sex (%)	54.5	57.6	<0.001
Mean duration of hospital stay (d)	9.7	7.6	<0.001
Died during hospitalisation (%)	2.7	2.3	NS
65–79y (n = 159 117)			
Mean age (y)	72.8	72.4	<0.001
Female sex (%)	50.5	46.1	<0.001
Mean duration of hospital stay (d)	14.3	13.5	<0.01
Died during hospitalisation (%)	7.9	9.8	<0.001
≥80 (n = 86 342)			
Mean age (y)	84.7	84.9	<0.05
Female sex (%)	66.6	62.9	<0.001
Mean duration of hospital stay (d)	16.5	16.7	NS
Died during hospitalisation (%)	9.7	16.5	<0.001
Total (n = 668 714)			
Mean age (y)	62.1	48.2	<0.001
Female sex (%)	55.2	53.4	<0.001
Mean duration of hospital stay (d)	12.5	9.9	<0.001
Died during hospitalisation (%)	6.0	5.6	<0.05

a Cut-off p-value: 0.05.

NS = not significant.

difference is mainly due to the ADR-related hospitalisations in younger patients (aged 18–64 years) who probably need a relatively longer hospital stay in these than in other hospitalisations, which are usually short and non-complex in this age group (e.g. appendix surgery).

Only 1% of all ADR-related hospitalisations (with an ADR as the main diagnosis) were reported to our National Pharmacovigilance Centre. All Dutch healthcare providers are recommended to report serious ADRs, such as ADRs leading to hospitalisation, permanent disability or death.[10] However, according to our data there is a substantial under-reporting of ADRs leading to hospitalisation, even though the Dutch National Pharmacovigilance Centre is actively encouraging clinicians to reports these serious ADRs. On the other hand, the aim of a spontaneous reporting system is mainly to detect new signals (mostly type B reactions) and not to be overwhelmed by already well known serious type A reactions regularly causing hospitalisations (i.e. gastrointestinal bleeding while using anticoagulants). Hence, we should place this under-reporting into perspective.

Study Limitations

A limitation of this study is that the proportion of ADR-related hospitalisations we found is probably an underestimation of the real situation. There is the potential for misclassification because not all ADRs will be recognised or mentioned in discharge letters and coded accordingly.[22] However, by using the ICD-9-CM coding system, the assessment of ADR-related hospitalisations is unbiased because the code

clerks were not coding as part of a study (with a predefined hypothesis). As mentioned previously, most other studies might come to higher estimations because they assess all admissions with the hypothesis that drugs may have played a role. This method is very sensitive to bias towards overestimation of ADR-related hospitalisations.

Another limitation of this study may be that the ADR-related hospitalisations also include admissions in which the ADR has occurred *during* the admission. Hence, cases are included in which the ADR has not been the reason for admission, but a complication during an admission. This makes a comparison with some other studies more difficult because several investigators define ADR-related hospitalisations only as admissions due to an ADR.[3,4,6,8,13] However, in a meta-analysis Lazarou et al.[2] also combined admissions caused by an ADR and admissions during which an ADR occurred in order to calculate ADR-related hospitalisations.[2] As they suggest, we believe that admissions complicated by an ADR should be included as ADR related, because an ADR may worsen or prolong a hospitalisation or even result in death.

Furthermore, a limitation in our study is that hospitalisations coded with an E-code referring to a secondary diagnosis (n = 6040) may have been admissions *during* which the ADR occurred or admissions *caused* by the ADR. We did not review all main diagnoses of these admissions, but in a sample review the main diagnosis was regularly similar to the secondary diagnosis that was coded with the E-code (i.e. the E-code indirectly referring to the main diagnosis), so in these cases we assumed that the ADR had been the reason for admission. Hence, we do not exactly know which hospitalisations in this 'secondary diagnosis group' had been caused, and which had been complicated, by an ADR. We assumed that hospitalisations coded with an E-code referring to the *main diagnosis* (n = 6209), were hospitalisations *caused* by the ADR.

Conclusion

In conclusion, as far as we know this is the first nationwide study of ADR-related hospitalisations occurring during 1 year in all hospitals in one country. Although our finding that 12 249 hospitalisations (1.83%) were ADR related is considerable, these figures are lower than similar studies using chart review. Furthermore, we found that the underreporting of serious ADRs leading to hospitalisation to our national Pharmacovigilance Centre is substantial.

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