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Incidence of fatal adverse drug reactions: a population based study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Although drugs generally are safe and effective therapies for numerous diseases, adverse drug reactions do occur and may even be fatal.
- The incidence of fatal adverse drug reactions in hospitalized patients has been estimated to be approximately 5%.
- In previous studies the incidence of fatal adverse drug reactions in hospitalized patients has been reported, but the incidence of fatal adverse drug reactions in the general population is largely unknown.

WHAT THIS STUDY ADDS

- Fatal adverse drug reactions account for approximately 3% of all deaths in the general population.
- Haemorrhages amount to almost two-thirds of the fatal adverse drug reactions and antithrombotic agents are implicated in more than half of the suspected fatal adverse drug reactions.
- Fatal adverse drug reactions are estimated to be the seventh most common cause of death in Sweden.

AIMS

To determine the incidence of fatal adverse drug reactions (FADRs) in a Swedish population.

METHODS

Every seventh randomly selected deceased in three counties in South-east Sweden during 1 January 2001–31 December 2001 was identified in the Cause of Death Register. Relevant case records (hospitals and/or primary care centres and medicolegal files) were reviewed to identify suspected drug-related fatalities.

RESULTS

Of 1574 deceased study subjects, 49 (3.1%; 95% CI 2.2%, 4.0%) were suspected to have died from FADRs. The most common suspected FADRs were gastrointestinal haemorrhages ($n = 18$; 37%), central nervous system haemorrhages ($n = 14$; 29%), cardiovascular disorders ($n = 5$; 10%), other haemorrhages ($n = 4$; 8%) and renal dysfunction ($n = 3$; 6%). The drugs most commonly implicated in FADRs were antithrombotic drugs ($n = 31$; 63%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) ($n = 9$; 18%), antidepressants ($n = 7$; 14%) and cardiovascular drugs ($n = 4$; 8%). Of all the 639 fatalities in hospital 41 (6.4%; 95% CI 4.5%, 8.3%) were suspected to be due to FADRs.

CONCLUSIONS

The medical burden of FADRs is significant. Haemorrhages were seen in a majority of the FADRs; antithrombotic agents or NSAIDs were implicated in most of these events. These results suggest that preventive measures should be taken to reduce the number of deaths caused by drugs.

Introduction

Adverse drug reactions (ADRs) constitute a major problem for the individual as well as for the community. In previous studies, the prevalence of hospital admissions due to ADRs ranged from 2.4% to 12.0% [1–3]. In contrast, the number of fatal adverse drug reactions (FADRs) is largely unknown. The incidence of FADRs in patients admitted to hospital has been reported ranging from 0.05% to 0.44% [1–9] while the incidence of FADRs in patients experiencing ADRs during hospital stays ranges from 0.05% to 0.19% [4, 7, 8]. In a Finnish, single hospital study, 5.0% of all deaths during 1 year were considered to be drug-related [5]. A large meta-analysis of hospitalized patients in the US estimated that ADRs accounted for 4.6% of all fatalities [4]. To the best of our knowledge, no previous study has investigated the incidence of FADRs using a population based methodology. Therefore, the objective of this study was to determine the incidence of suspected FADRs in a Swedish general population.

Methods

This study was conducted in three counties in South-east Sweden, Östergötland County, Jönköping County and Kalmar County. All 11 015 fatalities in the area during the study period, 1 January 2001–31 December 2001, were identified in the Cause of Death register held by the National Board of Health and Welfare, Sweden. One out of every seven deceased in the population was selected at random. All Swedish residents receive a unique personal identification number making it possible to link different registers, e.g. the Cause of Death Register and case records. Hence, it is possible to examine an individual's contact with the health care system, his or her diseases, and drug prescriptions. Therefore, it was possible to obtain a thorough drug history for each study subject focusing particularly on the 14 days preceding death.

The death certificates, relevant case records (hospitals and/or primary care centres and medicolegal files) and case information from the Swedish Medical Products Agency's national database for spontaneously reported ADRs were scrutinized in a stepwise manner. The first examination was performed by four health care professionals especially trained in ADRs. Their evaluation focused on pharmacological treatment, clinical course of outcome and laboratory and/or autopsy findings. Second, a first assessment as to whether the death was due to an FADR was performed by two pharmacists (KW, AKJ) and one clinical pharmacologist (SH). The possible FADRs identified in the first assessment were re-evaluated by two specialists (OS, clinical pharmacologist and HD, forensic pathologist). In order for an event to be classified as a suspected FADR, consensus had to be reached between all assessors. To validate the methodology used, one out of every 10 fatalities not categorized as a FADR was selected at random and scrutinized again.

The underlying cause of death is defined by the World Health Organization (WHO) as, 'The disease or injury that initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury' [10]. FADRs were classified according to WHO standards [11]. On the basis of the available information, causality between the suspected FADR and the drugs used was assessed as at least *Possible*: (reasonable time sequence to drug exposure, possible lack of dechallenge, other possible explanations may exist) according to the WHO criteria [12]. Furthermore, the FADRs were classified as type A (dose-dependent) or type B (idiosyncratic) reactions according to Rawlins & Thompson's classification [13]. All suspected FADRs were categorized according to the WHO Adverse Reaction Terminology (WHO-ART) [14]. It was allowed that more than one drug was suspected of having contributed to the outcome for each FADR.

Approval of this study was obtained from the National Board of Health and Welfare. The study complies with current Swedish laws.

Statistical analyses were performed using the statistical program package Statistica (version 7; Statsoft, OK, US). The analyses included Chi-square tests for dichotomous variables. P values < 0.05 were considered statistically significant.

Results

The cause of death certificates were retrieved for all subjects and medical case records were available for 1503 subjects (95%). Forensic autopsies were carried out in 83 subjects (5.3%), and medicolegal files were available in all of these subjects. In 1553 subjects (99% of the total study population) information about drug prescriptions during the last year before death could be retrieved. Of 1574 deceased study subjects, FADRs were suspected in 49 subjects (3.1%; 95% CI 2.2%, 4.0%). Twelve initially suspected FADRs were not counted as FADRs since consensus was not reached. The underlying causes of death across all fatalities in Sweden, for the study population and for subjects with FADRs are shown in Table 1. As seen from the table, the distribution of the most common underlying causes of death for the entire study population matched the distribution for the total Swedish population.

The characteristics of the subjects representing the 1574 deaths in the study population are presented in Table 2. The proportion of subjects who died in hospital was significantly higher in the FADR group (84%) than in the remaining subjects (39.2%; $P < 0.001$). Of all hospital fatalities, 6.4% (41/639; 95% CI 4.5%, 8.3%) were suspected

Table 1

Underlying causes of death [10] in the Swedish population in total, in the study population and in subjects with suspected fatal adverse drug reactions (FADRs) in 2001

		Underlying cause of death		
ICD-10 chapter	Title	Swedish population [15] (%) (n = 93 809)	Study population (%) (n = 1574)	Subjects with suspected FADRs (%) (n = 49)
I	Certain infectious and parasitic diseases	1.2	1.2	–
II	Neoplasms	24.0	22.6	12
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0.3	0.3	2
IV	Endocrine, nutritional and metabolic diseases	2.4	2.2	–
V	Mental and behavioural disorders	4.6	4.3	2
VI	Diseases of the nervous system	2.3	1.9	–
VII	Diseases of the eye and adnexa	–	–	–
VIII	Diseases of the ear and mastoid process	0.0	–	–
IX	Diseases of the circulatory system	45.5	48.0	49
X	Diseases of the respiratory system	6.5	6.0	–
XI	Diseases of the digestive system	3.1	3.2	24
XII	Diseases of the skin and subcutaneous tissue	0.2	0.2	2
XIII	Diseases of the musculoskeletal system and connective tissue	0.5	0.6	–
XIV	Diseases of the genitourinary system	1.5	2.4	6
XV	Pregnancy, childbirth and the puerperium	0.0	–	–
XVI	Certain conditions originating in the perinatal period	0.2	0.2	–
XVII	Congenital malformations, deformations and chromosomal abnormalities	0.3	0.4	–
XVIII	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2.6	2.1	–
XIX–XX	Injury, poisoning and certain other consequences of external causes *and* external causes of morbidity and mortality	5.0	4.8	2

ICD-10, International Classification of Diseases version 10; FADRs, fatal adverse drug reactions.

Table 2

Characteristics of the 1574 deaths in the study population

Variable	FADRs (n = 49)	Remaining subjects (n = 1525)
Sex, *n* (%)		
Male	24 (49)	787 (51.6)
Female	25 (51)	738 (48.4)
Age, median (range)		
Male	83 (37–92)	79 (0–101)
Female	81 (41–94)	84 (0–104)
Number of drugs 2 weeks before death, median (range)	7.0 (1–17)*	7.0 (0–28)†
Fatalities in hospital, *n* (%)	41 (84)	598 (39.2)
Clinical autopsy performed, *n* (%)	5 (10)	110 (7.2)
Forensic autopsy performed, *n* (%)	2 (4)	81 (5.3)

*Information available for 48 subjects. †Information available for 1505 subjects. FADRs, fatal adverse drug reactions.

to be due to FADRs. In the review of every 10 of the fatalities not categorized as FADR we did not identify any (95% CI 0.00, 0.02) misclassified subjects.

Among the FADRs, 17 different diagnoses were registered. The characteristics of the FADRs are shown in Table 3. Haemorrhages were the most common FADR; in these cases, antithrombotic agents (31/36; 86%), selective serotonin reuptake inhibitors (SSRIs) (7/36; 19%) and non-steroidal anti-inflammatory drugs (NSAIDs) (6/36; 17%) were the drugs most often implicated. In total, 33 different substances were implicated in the 49 FADRs; in 19 cases (39%) more than one substance was suspected. Drug groups implicated in subjects with FADRs are shown in Table 4. Acetylsalicylic acid was the most common substance (43%), followed by warfarin (16%), dalteparin (14%), citalopram (12%) and dipyridamole (8%). In all subjects where antithrombotic agents were implicated, a haemorrhage was suspected to have contributed to the death. The FADRs were classified as type A reactions in 79% (61/77) and as type B reactions in 21% (16/77).

Table 3

Characteristics of the 49 fatal suspected adverse drug reactions

Adverse drug reaction	Number of deaths (%)	Sex M/F	Median age (years) (range)	Suspected drugs ($n = 33$)*
Blood disorders				
GI haemorrhages	18 (37)	10/8	83 (55–92)	Acetylsalicylic acid (6), dalteparin (2), acetylsalicylic acid + naproxen (1), acetylsalicylic acid + rofecoxib (1), cetylsalicylic acid + dipyridamole + dalteparin (1), citalopram (1), citalopram + celecoxib (1), citalopram + clopidogrel (1), ketoprofen (1), prednisolone (1), warfarin (1), warfarin + sertraline (1)
CNS haemorrhages	14 (29)	7/7	80 (48–91)	Warfarin (4), acetylsalicylic acid (3), acetylsalicylic acid + citalopram (1), acetylsalicylic acid + dipyridamole (1), acetylsalicylic acid + dalteparin + naproxen (1), acetylsalicylic acid + enoxaparin + tenecteplase (1), acetylsalicylic acid + alteplase + dipyridamole + heparin (1), indomethacin (1), warfarin + dalteparin (1)
Other haemorrhages				
Intra-abdominal haemorrhage	2 (4)	0/2	77 (71, 83)	Acetylsalicylic acid + dalteparin + heparin (1), acetylsalicylic acid + citalopram + dalteparin (1)
Intravesical haemorrhage	1 (2)	1/0	85	Warfarin (1)
Respiratory tract haemorrhage	1 (2)	1/0	85	Acetylsalicylic acid + citalopram (1)
Agranulocytosis	1 (2)	0/1	87	Amiloride + hydrochlorothiazide + glibenclamide (1)
Cardiovascular disorders				
Bradycardia	1 (2)	1/0	85	Propranolol (1)
Cardiac failure	1 (2)	0/1	78	Diclofenac (1)
Cardiomyopathy	1 (2)	1/0	37	Clozapine (1)
Pulmonary embolism	1 (2)	0/1	53	Oestrogen + norethisterone (1)
Hypotension	1 (2)	1/0	88	Bupivacaine (1)
Various				
Renal dysfunction	2 (4)	1/1	78 (75, 81)	Diclofenac (1), celecoxib + rofecoxib (1)
Cystitis	1 (2)	0/1	84	Prednisolone (1)
Hyperkalaemia	2 (4)	1/1	74 (63, 86)	Enalapril (1), losartan + potassium chloride + spironolactone (1)
Colitis pseudomembranous	1 (2)	0/1	94	Flucloxacillin (1)
Grand mal convulsions	1 (2)	0/1	41	Clonazepam† + olanzapine (1)

*More than one drug could be suspected to have contributed to one adverse drug reaction. †Suspected withdrawal reaction after stopping clonazepam. CNS, central nervous system; F, females; GI, gastrointestinal; M, males.

Based on information from the death certificates, the incidence of FADRs in the study population was 8 (0.5%). The drugs stated as the underlying causes in the FADR cases were clonazepam, clozapine, flucoxacillin, prednisolone, warfarin and a combination of acetylsalicylic acid, alteplase, dipyridamole and heparin. Among all suspected FADRs found in the present study, only 8 (16%) were noted on the death certificates. Only one of the suspected FADRs identified in the present study (2%) had been reported to the Swedish Medical Products Agency as an ADR. This report concerned a subject who developed cardiomyopathy during treatment with clozapine.

Discussion

In the present study, which included subjects who died in hospitals as well as outside hospitals, 3.1% of the deaths were suspected to be caused by FADRs. Assuming the same incidence of FADRs for Sweden as a whole would rank FADRs as being the seventh most common cause of death [15]. This comparison seems reasonable since the general cause of death patterns in the study population were similar to that in the total Swedish population.

The results of this study can be compared with two previous studies from the US and Canada where FADRs in hospitalized patients were shown to be the 4th and 19th most common causes of deaths, respectively [4, 9]. The incidence of fatalities in hospital caused by ADRs (6.4%) in our study is of the same order of magnitude as in a US meta-analysis (4.6%) [4]. However, in the Canadian study a substantially lower figure (0.05%) was reported [9]. In other studies, the incidence of FADRs in patients admitted to hospital ranges from 0.05% to 0.44% [1–9] while the incidence of FADRs in patients experiencing ADRs during hospital stays ranges from 0.05% to 0.19% [4, 7, 8]. The reasons why the incidence of FADRs has varied between studies might easily be explained by differences in study design and the populations studied. Moreover, most studies have investigated hospitalized patients [1–9]. Furthermore, it is likely that studies investigating death certificates only [16] or registering spontaneously reported cases only [16–18] substantially underestimate the number of FADRs.

All FADRs found in this study were labelled in the Swedish Physicians' Desk Reference 2006 (Pharmaceutical Specialities in Sweden, FASS) [19]. This is expected since the study was not designed to identify new FADRs, but rather to establish the incidence of FADRs. The most common FADRs were haemorrhages, specifically gastrointestinal (GI) haemorrhages, which supports findings in previous studies of hospitalized patients [1, 5, 8]. This observation is in agreement with a previous UK study [2] in which more

Table 4

Drugs and fatal adverse drug reactions in the 49 subjects

Drug group (ATC code)	Number of deaths (%) $n = 49$*	Proportion of drug group users experiencing FADRs (%) $n = 1553$	Suspected drugs ($n = 33$)	ADRs ($n = 17$)
Antithrombotic agents (B01)†	16 (33)	9 (16/174)	Warfarin (8), dalteparin (7), heparin (2), alteplase (1), enoxaparin (1), tenecteplase (1)	GI haemorrhages (5), CNS haemorrhages (8), intra-abdominal haemorrhages (2), intravesical haemorrhage (1)
Platelet aggregation inhibitors excluding heparin (B01AC)	21 (43)	5 (21/463)	Acetylsalicylic acid (20), dipyridamole (3), acetylsalicylic acid + dipyridamole (1), clopidogrel (1)	GI haemorrhages (10), CNS haemorrhages (8), intra-abdominal haemorrhages (2), respiratory tract haemorrhage (1)
Non-steroidal anti- inflammatory drugs, NSAIDs (M01A)	9 (18)	8 (9/111)	Celecoxib (2), diclofenac (2), naproxen (2), rofecoxib (2), indomethacin (1), ketoprofen (1)	GI haemorrhages (4), renal dysfunction (2), CNS haemorrhages (2), cardiac failure (1)
Antidepressants (N06A)	7 (14)	2 (7/317)	Citalopram (6), sertraline (1)	GI haemorrhages (4), CNS haemorrhages (1), intra-abdominal haemorrhage (1), respiratory tract haemorrhage (1)
Cardiovascular system (C)	4 (8)	0.4 (4/1006)	Amiloride + hydrochlorothiazide (1), enalapril (1), losartan (1), propranolol (1), spironolactone (1)	Hyperkalaemia (2), agranulocytosis (1), bradycardia (1)
Antipsychotic agents (N05)	2 (4)	0.3 (2/740)	Clozapine (1), olanzapine (1)	Cardiomyopathy (1), grand mal convulsions (1)
Corticoids for systemic use (H02)	2 (4)	0.8 (2/257)	Prednisolone (2)	Cystitis (1), GI haemorrhage (1)
Anti-epileptics (N03)	1 (2)	1.4 (1/69)	Clonazepam (1)	Grand mal convulsions (1)
Drugs used in diabetes (A10)	1 (2)	0.4 (1/227)	Glibenclamide (1)	Agranulocytosis (1)
Mineral supplements (A12)	1 (2)	0.5 (1/198)	Potassium chloride (1)	Hyperkalaemia (1)
Sex hormones (G03)	1 (2)	1 (1/94)	Oestrogen + norethisterone (1)	Pulmonary embolism (1)
Antibacterials for systemic use (J01)	1 (2)	0.5 (1/214)	Flucloxacillin (1)	Colitis pseudomembranous (1)
Anaesthetics (N01)	1 (2)	9 (1/11)	Bupivacaine (1)	Hypotension (1)

*More than one drug could be suspected to have contributed to one adverse drug reaction. †Excluding platelet aggregation inhibitors (B01AC). ADRs, adverse drug reactions; ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; FADRs, fatal adverse drug reactions; GI, gastrointestinal.

than half of the fatalities were due to GI haemorrhages. FADRs due to cardiovascular disorders have also been reported to be common in hospitalized patients [1, 8].

In the present study, antithrombotic agents and NSAIDs were the most common drug groups implicated in the FADRs, a finding supported by two previous studies of FADRs in hospital settings [5, 7] and a German study of spontaneously reported ADRs [18]. In the FADR cases where SSRIs were implicated, interactions with antithrombotic agents or NSAIDs were suspected most often. Low-dose acetylsalicylic acid was implicated, alone or in combination with other drugs, in more than one-third of all FADRs. In a recent study on patients admitted to hospital, acetylsalicylic acid was implicated in two-thirds of the FADRs [2]. However, when discussing ADRs it is important to take the benefits of the substances into consideration. For example, acetylsalicylic acid and warfarin prevent cardiovascular events when used appropriately [20, 21]. In this study, no FADRs related to cancer treatment were found. Nevertheless, some delayed deaths due to chemotherapy might have occurred although we found no evidence to support this in the case records.

FADRs registered on the death certificates in the present study were found to be of the same order of magnitude as in a previous Finnish study in which the incidence was 0.5% [5]. Only one of the suspected FADRs in the present study had been reported to the Medical Products Agency. This finding confirms that under-reporting in spontaneous ADR reporting systems is substantial, as also indicated in previous studies [22, 23].

One limitation of this study is its retrospective design. Despite scrutinizing each subject in different registers it is impossible to obtain all relevant information in each case. Moreover, case record forms vary with respect to the quality of information; hence the number of FADRs might have been underestimated. Moreover, most study subjects experiencing FADRs were old and had several diseases and had therefore a limited lifetime expectancy. Thus, the outcome of the ADRs might have been different in younger and healthier patients. Furthermore, information on use of over the counter (OTC) drugs and herbal remedies is usually not documented in the case records. It is hence possible that cases could have been missed. According to wholesale data from the National Corporation of Pharmacies (Apoteket AB) concerning the Swedish population, a high proportion of NSAIDs was prescribed (78%) during 2001. Therefore, the use of NSAIDs registered in the medical case records seems to reflect the actual use.

Another issue is the unique problems related to the assessment of FADRs since dechallenge and rechallenge are not applicable in fatal cases. On the other hand, this study has several strengths compared with previous studies. The population based approach includes a random selection of all deceased subjects (hospitalized patients as well as individuals who died outside hospital) in the study area. In 99% of these, it was possible to follow the general health and drug histories for a relevant period of time prior to death by consulting various sources. Thus, it was possible to perform a thorough evaluation of whether the fatalities could be associated with ADRs. Furthermore, by applying a multidisciplinary approach during evaluation of the suspected FADRs the risk of misclassification clearly decreased. Cases where a more reasonable explanation for the fatality was found, where the assessors did not reach agreement or where there were uncertainties or inconsistencies related to the information found were excluded as suspected FADRs. Using this conservative approach, consensus was reached for all suspected FADR cases included.

In conclusion, our findings suggest that FADRs contribute to a substantial number of deaths resulting in a significant health burden. Haemorrhages were seen in a majority of the FADRs and antithrombotic agents or NSAIDs were implicated in most of these events. These results suggest that preventive measures should be taken to reduce the number of deaths caused by drugs.

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