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Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands

Eline M. Rodenburg,[1,2] Bruno H. Ch. Stricker[1,2,3] & Loes E. Visser[1,4]

[1]Department of Epidemiology, Erasmus Medical Center, Rotterdam, [2]Inspectorate of Health Care, The Hague, [3]Department of Internal Medicine, Erasmus Medical Center, Rotterdam and [4]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands

Correspondence
Bruno H.Ch. Stricker, PhD, Department of Epidemiology, Erasmus Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands.
Tel.: + 31 10 704 3482
Fax: + 31 10 704 4657
E-mail: b.stricker@erasmusmc.nl

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Women are more at risk for developing adverse drug reactions (ADRs) due to differences in pharmacokinetics, pharmacodynamics and drug use. ADRs regularly lead to hospital admissions.

WHAT THIS STUDY ADDS

There are differences between the sexes in hospital admissions attributed to ADRs. The risk of being hospitalized with an ADR varies between the sexes in the type of reaction and the causative drug.

AIM

Adverse drug reactions (ADRs) are a major burden in health care, regularly leading to hospital admission, morbidity or death. Women tend to have a higher risk of adverse drug reactions with a 1.5 to 1.7-fold greater risk than men. Our primary aim was to study differences in ADR-related hospitalizations between the sexes.

METHODS

We conducted a nationwide study of all ADR-related hospitalizations in the period between 2000 and 2005 in the Netherlands, which were selected from all 9 287 162 hospital admissions in this period. ADR–drug group combinations with at least 50 admissions in one of the sexes were selected. Relative risks and confidence intervals were calculated with respect to total admissions and total prescriptions with men as reference.

RESULTS

In total, 0.41% of the 4 236 368 admissions in men (95% CI 0.40, 0.42%) and 0.47% of the 5 050 794 admissions in women (95% CI 0.46, 0.48%) were attributed to an ADR by medical specialists (57% of all ADR-related admissions were in women). Differences between the sexes in risk for ADR-related hospitalization were found for antineoplastic and immunosuppressive drugs, antirheumatics, anticoagulants and salicylates, cardiovascular and neurological drugs, steroids and antibiotics. In certain drug categories, risks for hospitalization changed after taking into account total drug prescriptions.

CONCLUSION

In all different drug classes, significant differences exist between the sexes in ADR-related hospital admissions. Cardiovascular drugs account for the most pronounced differences between men and women. More research is needed to explain the clear sex differences in ADR-related hospital admissions.

Introduction

Drug action and biological reaction is a continuous topic of interest, as pharmacotherapy is the most frequently employed medical intervention, and the continuous development of new drugs and removal of old products from the market are representative of a dynamic discipline. Both beneficial and adverse drug reactions are important considerations for defining optimal treatment strategies. The World Health Organization defined an adverse drug reaction (ADR) as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function' [1].

Sex is an important determinant of drug use and drug response. Women tend to have a higher risk of adverse drug reactions with a 1.5 to 1.7-fold higher risk as compared with men [2–4]. More data on drug response in women are needed. Although the authorities emphasized the importance of including more women in clinical trials as early as 1986, women are still under-represented in clinical research nowadays [5–7]. The policies and guidelines, set up by the National Institute of Health (NIH), Food and Drug Administration (FDA), and the European Medicines Agency (EMA), have unfortunately not resolved this inequality [8–10].

A clear overview of sex differences in pharmacology is complicated by the large variety of drugs, indications for use, and pharmacokinetic and pharmacodynamic differences between the sexes. Pharmacokinetics, pharmacodynamics and the number and amount/dose of drugs used all contribute to the risk for the occurrence of adverse reactions [11–14].

Sex differences in drug use can be explained by differences in incidence of disease (e.g. rheumatoid diseases) or by the drug response itself. The effect of a drug on the body depends on the combination of pharmacokinetic factors. Women have a different volume of distribution and clearance than men, which could result in differences in effective drug concentrations [11–15]. A sex difference in pharmacodynamics, the effect of the body on the drug, is, for example, the occurrence of drug-induced torsade de pointes, which is much more frequent in women [16, 17].

ADRs are a major healthcare issue, regularly leading to hospital admission, morbidity or death [18–23]. In a population-based study in Sweden, fatal ADRs were the seventh cause of death [20]. In hospital patients, ADRs were ranked from the fourth to sixth cause of death [24]. Data on ADRs leading to hospital admissions vary among smaller and larger studies (0.2–41.3%) [23]. Generally, the incidence of hospital admissions caused by ADRs is between 3 and 6% of all hospital admissions [18, 19, 23–25].

In the Netherlands, three major studies focussed on different aspects of ADR-related hospitalizations in the Dutch population. Van der Hooft *et al*. [26] studied ADR-related hospitalizations in the Netherlands in 2001. The proportion of females with ADR related hospitalizations varied between the different age categories, increasing with increasing age from 50.5% in the age group 65–79 years to 66.6% in the highest age group (80 years and older). The proportion of ADR-related hospitalizations increased with age from 0.8% in patients aged <18 years to 3.2% in patients aged ≥80 years. Another population-based study in the Netherlands showed a prevalence of ADR-related admissions of 5.35% after standardizing to the Dutch population [27]. This study did not focus on sex differences in specific adverse events and drug groups. A third study in 21 Dutch hospitals showed that important patient-related risk factors for admission with an adverse drug event (ADE) due to medication use or medication error, were impaired cognition, presence of 4 or more diseases, dependent living situation, impaired renal function and nonadherence to the medical regimen [25]. Risk factors for ADE-related admissions in this study were impaired cognition, presence of other diseases, living situation, renal function and non-adherence. This study did not focus on sex differences in specific adverse events and drug groups either.

While female sex has been identified as a risk factor for ADRs, sex-related differences in hospital admissions attributed to ADRs have not been studied as a primary outcome in large populations. We have studied the differences between the sexes in hospital admission attributed to ADRs in a nationwide study over a 6 year period, taking into account the different ADRs, drug groups involved and differences in drug use.

Methods

Data sources

Data on hospital admissions and drug use were obtained from separate sources. Data on hospital admissions were obtained from a nationwide registry of hospital discharges. This registry contains patient characteristics, demographics, dates of admission and discharge, main diagnoses at discharge (coded), secondary diagnoses (coded), medical specialisms (coded) and special codes indicating drug-related hospitalizations (E-codes), based on the ICD-9-CM coding system [28]. Characteristics of all hospital admissions 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 hospital or specialist. All diagnoses are submitted in the same format, mostly electronically. All patients with an acute, non-planned admission to a Dutch hospital in the period between 2000 and 2005 were included in the study.

Data on drug use were retrieved from 'Stichting Farmaceutische Kengetallen' (SFK), where information on drug prescriptions is collected from 1805 pharmacies in the

Netherlands (of the 1960 pharmacies in total). Data from this database were selected on ATC-4 level per year within the study period. Per ATC code, the cumulative number of prescriptions was calculated.

Adverse drug reactions

An ADR-related hospitalization was defined as a hospitalization with an E-code as secondary diagnosis, indicating an ADR as the reason for hospitalization (E-code referring to main diagnosis). ADRs occurring during hospital admission were excluded from the analysis. The E-code indicates the drug group involved in the ADR. E-codes referring to intended overdoses, errors in administration and therapeutic failure were not included in the analysis. Unique combinations of main diagnoses and E-codes were selected, resulting in assessment of ADRs per drug group.

Data analysis

We assessed the number of ADR-related hospital admissions and expressed this as the proportion of all acute admissions in the Netherlands between 2000 and 2005. We calculated relative risks (RR) and 95% confidence intervals (95% CIs) for hospitalizations due to an ADR with respect to all acute hospitalizations for women compared with men. We adjusted for the possible confounding effect of age using logistic regression analyses. Given the size of the study population, the odds ratios (OR) are a good proxy for the RR. The analyses were performed for all possible ADR-drug group combinations separately. To make a more valid comparison, we only included the ADR–drug group combinations with at least 50 admissions in the study period in at least one of the sexes. Adverse drug reactions pointing out the same reaction, but described in different terms, were clustered (e.g. congestion and constipation). Furthermore, the ADRs within the drug group annotated with the terms 'other drugs' and 'unspecified drugs' were excluded from further analyses.

Separate calculations were performed for all ADR–drug group combinations to measure the RR for ADR related hospitalizations in relation to the total number of prescriptions per drug group. For every ADR–drug group combination the number of hospitalizations per sex was divided by the total number of prescriptions within the study period for the involved drug group. Prescription data were combined with the data on hospitalisations based on drug(s) covered by the E-code. Codes were combined as specific as possible. Calculations were performed using SPSS software (version 15.0; SPSS Inc., Chicago, Illinois, USA) and Microsoft Office Excel 2003.

Results

In the period between 2000 and 2005, 9 287 162 hospital admissions were registered in the Netherlands; 4 236 368 in men (46%) and 5 050 794 in women (54%). Of these

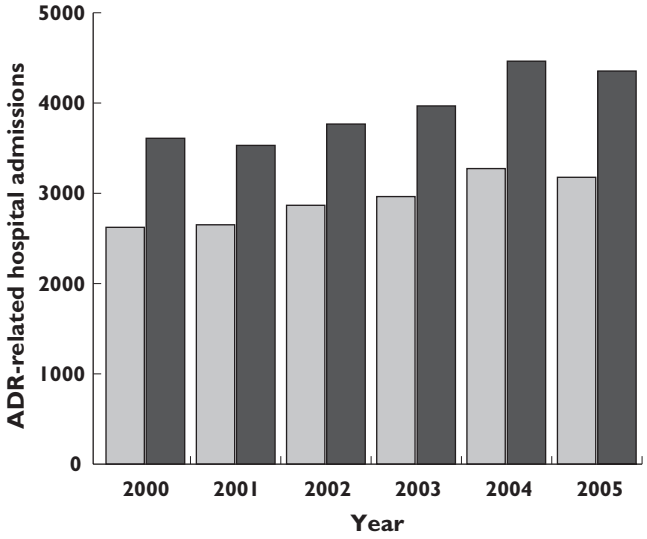

Figure 1

ADR-related hospital admissions in men and women per year. Male (□); Female (■)

hospital admissions, 41 260 admissions had an E-code referring to the main diagnosis, indicating that the admission was attributed to an adverse drug reaction. For men, ADR-related admissions in this period accounted for 17 561 admissions (0.41% of all admissions in men and 43% of all ADR-related admissions); for women 23 699 admissions occurred (0.47% of all admissions in women and 57% of all ADR-related admissions). Figure 1 shows the total number of ADR-related admissions per sex. The total number of prescriptions was nearly two times higher in women than in men with an increasing number over the years in both sexes. In women, more than 455 million prescriptions were recorded in the period of 2000 to 2005 as compared with nearly 286 million prescriptions in men. With these prescriptions, women were prescribed nearly 20 989 million defined daily doses (DDDs) and men were prescribed 13 580 million DDDs (see Table 1 for an overview). Figure 2 shows the difference in hospital admissions between the sexes during the study period, taking into account the total number of prescriptions.

Causes of admission varied widely. In total, 4750 unique combinations of diagnosis and ADR-associated drug groups were identified in the database. Eighty of these combinations led to at least fifty hospital admissions per combination within the study period in either one of the sexes. Eighteen of the selected combinations could be combined with another selected, similar drug-ADR combination. Six combinations were excluded from further analyses because of lack of additional information.

Seven large drug classes could be distinguished as drug groups leading to hospitalization: antineoplastic and immunosuppressive drugs, antirheumatics, anticoagulants and salicylates, drugs acting on the nervous system, drugs

Table 1

ADR-related hospital admissions and prescriptions in men and women between 2000 and 2005

	ADR-related admissions		Total prescriptions		Total Defined Daily Doses (DDD)	
	Men	Women	Men	Women	Men	Women
2000	2 624	3 611	43 348 659	70 877 424	1 940 059 960	3 169 985 513
2001	2 653	3 531	45 283 605	73 431 636	2 075 935 477	3 334 278 357
2002	2 867	3 768	46 687 293	75 185 906	2 167 674 617	3 422 053 655
2003	2 964	3 969	48 717 748	77 967 105	2 333 542 622	3 627 575 647
2004	3 275	4 464	50 004 412	78 045 769	2 459 947 493	3 639 307 300
2005	3 178	4 356	51 813 349	79 949 354	2 603 010 013	3 795 615 958
Total	17 561	23 699	285 855 066	455 457 194	13 580 170 182	20 988 816 430

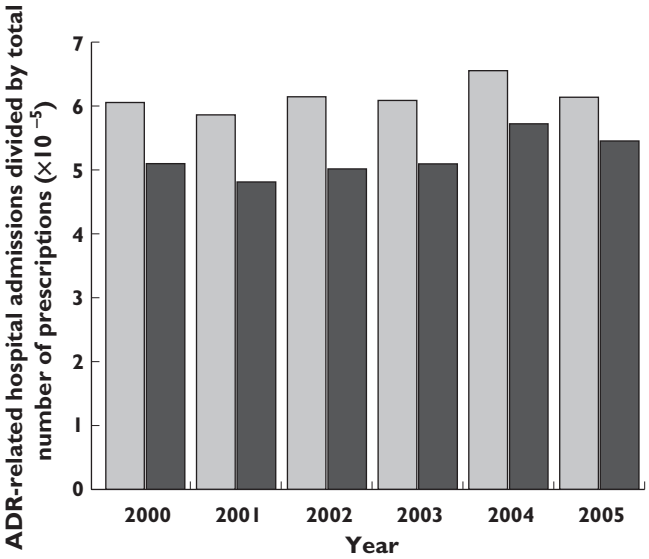

Figure 2

ADR-related hospital admissions divided by total prescriptions in men and women per year. Male (□); Female (■)

acting on the cardiovascular system, steroids and antibiotics. Tables 2–4 show the number of ADR-related hospitalizations and relative risks in women compared with men due to antineoplastic and immunosuppressive drugs, antirheumatics, and anticoagulants and salicylates, respectively. Tables 5–8 show the number of ADR-related hospitalizations due to drugs acting on the nervous system, drugs acting on the cardiovascular system, steroids and antibiotics. Of these seven drug groups, three drug groups were most prominently associated with ADRs, i.e. antineoplastic and immunosuppressive drugs, anticoagulants and salicylates and drugs acting on the cardiovascular system. Frequently occurring adverse drug reactions in the group with antineoplastic and immunosuppressive drugs included agranulocytosis, fever and nausea/vomiting. In the drug group with anticoagulants and salicylates, frequent reactions included gastro-intestinal bleeding, epistaxis, intracranial bleeding and other haemorrhages. For drugs acting on the cardiovascular system, poisoning by cardiotonic glycosides, collapse due to coronary vasodilators, and hypovolaemia and electrolyte disorders due to diuretics accounted for the majority of adverse reactions.

Sex differences

Antineoplastic and immunosuppressive drugs Per ADR-drug group combination, as shown in Tables 2–8, RRs were calculated for the sexes. The tables show the RRs of the occurrence of the specific ADR in women as compared with men, with and without adjustment for age. ATC codes are given to show the drug groups used to present background drug use. Due to antineoplastic and immunosuppressive drugs, women were more frequently hospitalized with agranulocytosis, fever, and symptoms such as nausea and vomiting (Table 2). Men were more frequently admitted due to pneumonia. Relative to total admissions, hospital admission because of fever attributed to antineoplastic and immunosuppressive drugs was higher in women than in men, but after adjustment for drug prescriptions the results showed the opposite. Only the relative risk for hospitalization due to nausea/vomiting remained significantly higher for women after taking into account total prescriptions.

Antirheumatics Gastro-intestinal bleeding was the major ADR cause of admissions due to antirheumatic drug use. Ulcers were significantly more frequent in men. Regarding all hospital admissions attributed to this drug group, women were more frequently hospitalized with an ADR. However, after taking into account the total number of prescriptions in this drug group, the risk of ADR-related hospitalizations attributed to antirheumatic use was higher in men (Table 3).

Anticoagulants and salicylates The risk of hospitalizations for bleeding in any specific form due to anticoagulant use or use of salicylates was significantly higher in men (except for non specified haemorrhage and, after taking into account total prescriptions, gastro-intestinal bleeding)

Table 2

Antineoplastic and immunosuppressive drugs *(L)*

Adverse reaction	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Agranulocytosis	839	548	**1.28 (1.15, 1.43)**	**1.31 (1.18, 1.46)**	0.95 (0.85, 1.05)
Anaemia	510	419	1.02 (0.90, 1.16)	1.05 (0.92, 1.19)	**0.75 (0.65, 0.86)**
Fever	1182	903	**1.10 (1.01, 1.20)**	**1.13 (1.03, 1.23)**	**0.81 (0.74, 0.88)**
Malaise or fatigue	227	159	1.20 (0.98, 1.47)	**1.24 (1.01, 1.52)**	0.88 (0.72, 1.08)
Nausea/vomiting	542	248	**1.83 (1.57, 2.13)**	**1.87 (1.61, 2.18)**	**1.35 (1.16, 1.57)**
Non-infectious/toxic gastro-enteritis	257	228	0.95 (0.79, 1.13)	0.98 (0.82, 1.17)	**0.69 (0.58, 0.83)**
Unwanted drug effect	377	299	1.06 (0.91, 1.23)	1.09 (0.93, 1.27)	**0.78 (0.67, 0.91)**
Pneumonia	43	67	**0.54 (0.37, 0.79)**	**0.56 (0.38, 0.82)**	**0.40 (0.27, 0.58)**
Poisoning by cytostatics	78	74	0.88 (0.64, 1.21)	0.90 (0.66, 1.24)	**0.65 (0.47, 0.89)**

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

Table 3

Antirheumatics *(M01)*

Adverse reaction	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Anaphylactic shock	136	88	1.30 (0.99, 1.70)	**1.32 (1.01, 1.73)**	0.97 (0.74, 1.27)
Gastro-intestinal bleeding	190	133	1.20 (0.96, 1.50)	1.24 (0.99, 1.55)	0.89 (0.72, 1.12)
Poisoning by antirheumatics	73	47	1.30 (0.90, 1.87)	1.29 (0.90, 1.87)	0.97 (0.67, 1.40)
Unwanted drug effect	117	81	1.21 (0.91, 1.61)	1.22 (0.92, 1.63)	0.90 (0.68, 1.20)
Duodenal/ventricular ulcer	59	69	0.90 (0.76, 1.06)	0.92 (0.78, 1.09)	**0.67 (0.57, 0.79)**

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

Table 4

Anticoagulants and salicylates *(B01A)*

Adverse reaction	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Anaemia	222	138	**1.35 (1.09, 1.67)**	**1.29 (1.04, 1.59)**	**1.75 (1.42, 2.17)**
Gastro-intestinal bleeding	1067	1064	**0.84 (0.77, 0.92)**	**0.82 (0.75, 0.89)**	**1.09 (1.00, 1.19)**
Epistaxis	285	337	**0.70 (0.60, 0.83)**	**0.71 (0.60, 0.83)**	0.92 (0.79, 1.08)
Haemoptysis	59	115	**0.43 (031, 0.59)**	**0.44 (0.32, 0.60)**	**0.56 (0.41, 0.76)**
Haematuria	74	223	**0.28 (0.22, 0.36)**	**0.28 (0.21, 0.36)**	**0.36 (0.28, 0.47)**
Intracranial bleeding	370	598	**0.52 (0.46, 0.59)**	**0.51 (0.45, 0.58)**	**0.67 (0.59, 0.77)**
Haemorrhage non-specified	930	692	**1.13 (1.02, 1.25)**	**1.13 (1.02, 1.24)**	**1.46 (1.33, 1.61)**
Duodenal/ventricular ulcer	351	479	**0.61 (0.54, 0.71)**	**0.61 (0.53, 0.70)**	**0.80 (0.70, 0.92)**

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

(Table 4). Hospitalizations for haematuria and haemoptysis were much more frequent in men than in women with a RR of 0.28 (95% CI 0.22, 0.36) and 0.43 (95% CI 0.31, 0.59), respectively. These differences remained after adjusting for age and taking into account total prescriptions [RR 0.36 (95% CI 0.28, 0.47) and RR 0.56 (95% CI 0.41, 0.76), respectively].

Drugs acting on the nervous system Considering all hospitalizations related to use of drugs acting on the nervous system, admissions due to ADRs were in general higher in women (Table 5). Poisoning and constipation were the most frequent ADRs related to use of drugs acting on the nervous system. Relatively more women were hospitalized due to poisoning than men, but after taking into account the difference in drug prescriptions, the RR for admission disappeared. Risk to be hospitalized for constipation was highest in men (RR 0.59; 95% CI 0.48, 0.71). Nausea and vomiting causing hospital admission due to (other) opiates and related narcotics was more profound in women both

Table 5

Drugs acting on the nervous system

Adverse reaction per drug type	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Antidepressants *(N06A)*					
Poisoning (unintended)	60	22	**2.29 (1.41, 3.73)**	**2.27 (1.39, 3.69)**	**1.29 (0.79, 2.11)**
Aromatic analgesics *(N02B)*					
Poisoning (unintended)	72	32	**1.89 (1.25, 2.86)**	**1.87 (1.24, 2.84)**	**1.05 (0.69, 1.59)**
Opiates and related narcotics *(N02A)*					
Constipation	208	200	0.87 (0.72, 1.06)	0.90 (0.74, 1.10)	**0.59 (0.48, 0.71)**
Nausea/vomiting	57	17	**2.81 (1.64, 4.83)**	**2.91 (1.69, 5.00)**	**1.90 (1.10, 3.26)**
Poisoning (unintended)	89	42	**1.78 (1.23, 2.57)**	**1.84 (1.28, 2.66)**	**1.20 (0.83, 1.73)**
Anticonvulsants *(N03A)*					
Poisoning (unintended)	69	67	0.86 (0.61, 1.20)	0.87 (0.63, 1.22)	0.88 (0.63, 1.23)
Benzodiazepine-based tranquillizers *(N05B)*					
Poisoning (unintended)	163	91	**1.50 (1.16, 1.94)**	**1.51 (1.17, 1.95)**	**0.89 (0.69, 1.16)**
Psychotropics *(N06B)*					
Poisoning (unintended)	186	89	**1.75 (1.36, 2.25)**	**1.82 (1.41, 2.34)**	**6.38 (4.96, 8.22)**
Unwanted drug effect	58	19	**2.56 (1.53, 4.29)**	**2.66 (1.58, 4.46)**	**9.32 (5.55, 15.65)**

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

Table 6

Drugs acting on the cardiovascular system

Adverse reaction per drug type	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Cardiac rhythm regulator *(C01B)*					
Heart dysrhythmia	49	52	0.79 (0.54, 1.17)	0.76 (0.52, 1.13)	1.10 (0.74, 1.62)
Cardiotonic glycosides *(C01A)*					
Unwanted drug effect	190	77	**2.07 (1.59, 2.70)**	**1.94 (1.49, 2.53)**	**1.66 (1.27, 2.16)**
Poisoning	291	101	**2.42 (1.93, 3.03)**	**2.30 (1.84, 2.89)**	**1.93 (1.54, 2.43)**
Coronary vasodilators *(C01D)*					
Syncope/collapse	128	170	**0.63 (0.50, 0.79)**	**0.62 (0.50, 0.79)**	**0.68 (0.54, 0.86)**
Saluretics and diuretics *(C03A + C)*					
Disorder kidney/ureter	57	48	1.00 (0.68, 1.47)	0.95 (0.64, 1.39)	**0.62 (0.42, 0.91)**
Hypo-osmolarity/hyponatraemia	642	101	**5.33 (4.32, 6.58)**	**5.02 (4.06, 6.19)**	**3.33 (2.70, 4.10)**
Hypokalaemia	163	40	**3.42 (2.41, 4.83)**	**3.53 (2.50, 4.99)**	**2.13 (1.51, 3.01)**
Hypovolaemia	348	231	**1.26 (1.07, 1.49)**	1.15 (0.97, 1.36)	**0.79 (0.67, 0.93)**
Renal failure	57	34	1.41 (0.92, 2.15)	1.38 (0.90, 2.11)	0.88 (0.57, 1.34)
Sympatholytics *(C04A)*					
Heart dysrhythmia	118	82	1.21 (0.91, 1.61)	1.20 (0.90, 1.59)	1.04 (0.79, 1.38)
Other antihypertensive agents *(C02A + C)*					
Angioneurotic oedema	83	66	1.05 (0.76, 1.45)	1.09 (0.79, 1.51)	0.89 (0.64, 1.23)

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

with respect to admissions (RR 2.81; 95% CI 1.64, 4.83) and with respect to prescriptions (RR 1.90; 95% CI 1.10, 3.26).

Drugs acting on the cardiovascular system Drugs acting on the cardiovascular system cover several different drugs related to various ADRs (Table 6). Within this category, the risks for ADR-related admissions were most pronounced, as compared with other drug classes. Diuretics and saluretics appeared to be the main drugs causing hospital admissions. Differences between the sexes were remarkable. Women had a RR of 5.33 (95% CI 4.32, 6.58) for hospitalization due to hypo-osmolarity or hyponatraemia and a RR risk of 3.42 (95% CI 2.41, 4.83) for hospitalization due to hypokalaemia as compared with men. These higher risks for women remained after adjustment for the total number of prescriptions of these drugs (RR 3.33; 95% CI 2.70, 4.10 and RR 2.13; 95% CI 1.51, 3.01, respectively). Cardiotonic glycosides were also a frequent cause for hospital admissions in women, with a RR of 2.07 (95% CI 1.59, 2.70) for unwanted drug effect and 2.42 (95% CI 1.93, 3.03) for poisoning. Syncope or collapse due to coronary vasodilators and hypovolaemia due to saluretics occurred more frequently in men (RR 0.68; 95% CI 0.54, 0.86 and RR 0.79;

Table 7

Steroids

Adverse reaction per drug type	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Adrenal cortical steroids *(H02A)*					
Diabetes mellitus	143	136	0.88 (0.70, 1.12)	0.91 (0.72, 1.15)	**0.78 (0.62, 0.99)**
Osteoporosis	165	49	**2.82 (2.05, 3.88)**	**2.93 (2.13, 4.03)**	**2.50 (1.82, 3.43)**
Anterior pituitary hormones *(H01A-B)*					
Ovarian hyperfunction	216	0	Na	Na	Na
Ovarian disorder (non-inflammatory)	64	0	Na	Na	Na
Unwanted drug effect	66	0	Na	Na	Na
Insulin and antidiabetic agents *(A10)*					
Hypoglycaemia	1126	946	1.00 (0.92, 1.09)	1.04 (0.95, 1.13)	1.00 (0.92, 1.09)
Hypoglycaemic coma	108	120	**0.75 (0.58, 0.97)**	0.78 (0.60, 1.02)	**0.76 (0.59, 0.98)**
Ovarian hormones *[G03 (exG03B)]*					
Pulmonary embolism or lung infarction	63	1	**52.84 (7.33, 380.95)**	52.30 (7.25, 377.10)	0.30 (0.04, 2.16)

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

Table 8

Antibiotics

Adverse reaction per drug type	Women (*n*)*	Men (*n*)*	RR (95% CI)†	RR (95% CI)‡	RR (95% CI)§
Penicillins *(J01C)*					
Dermatitis	68	43	1.33 (0.91, 1.95)	1.33 (0.91, 1.95)	1.35 (0.92, 1.97)
Anaphylactic shock	59	56	0.88 (0.61, 1.27)	0.89 (0.62, 1.29)	0.90 (0.62, 1.29)
Unwanted drug effect	129	78	**1.39 (1.05, 1.84)**	**1.40 (1.06, 1.85)**	**1.41 (1.06, 1.86)**
Other specified antibiotics *(J01G-M-R-X)*					
Non-infectious gastro-enteritis or colitis	66	39	1.42 (0.96, 2.11)	1.46 (0.99, 2.18)	**0.53 (0.36, 0.79)**
Unwanted drug effect	59	58	0.85 (0.59, 1.22)	0.87 (0.60, 1.25)	**0.32 (0.22, 0.46)**
Sulfonamides *(J01E)*					
Unwanted drug effect	65	40	1.36 (0.92, 2.02)	1.38 (0.93, 2.05)	**0.54 (0.36, 0.80)**

*Number of admissions in the period 2000–2005; †Relative risk of ADR hospitalizations with respect to total hospital admissions, crude; ‡Relative risk of ADR hospitalizations with respect to total hospital admissions, age adjusted; §Relative risk of ADR hospitalizations with respect to total prescriptions. The bold text refers to significant sex differences.

95% CI 0.67, 0.93, respectively, after adjustment for number of prescriptions).

Steroids Sex differences in ADR-related hospital admissions due to steroids were as expected (Table 7). A few causal ADRs were not assessable, because use of these hormones is sex dependent and therefore none or few hospital admissions occurred in men (anterior pituitary hormones, ovarian hormones). Adrenal cortical steroids and insulins and antidiabetic agents were equally frequently associated with ADRs in both sexes. Admission for osteoporosis due to adrenal cortical steroids was more frequent in women (RR 2.50; 95% CI 1.82, 3.43 after adjustment for total number of drug prescriptions), whereas diabetes due to adrenal cortical steroids and hypoglycaemic coma due to insulin and antidiabetic agents were more frequent in men (RR 0.78; 95% CI 0.62, 0.99 and RR 0.76; 95% CI 0.59, 0.98, respectively, after adjustment).

Antibiotics and other drugs Overall, the risk for ADR-related admissions due to antibiotics seemed to vary per type of ADR between the sexes as a part of total admissions. However, if drug prescriptions were taken into account, men were more frequently hospitalized for ADRs following antibiotic use (Table 8).

Discussion

The primary aim of our study was to give an overview of the differences in ADR-related hospitalizations of the most frequent adverse reactions between men and women. Both drug group and type of ADR were of interest in our study. Because the incidence of ADR-related hospitalizations is related to drug use, drug use of the total population within the study period was taken into account in the analysis. However, we should be careful when interpreting the results, since no individual data were used in this ecological design.

Overall, the risk for ADR related hospital admissions was higher in women than in men, with respect to the total number of hospital admissions. This is in accordance with

other studies focusing on ADR-related hospital admissions [2–4, 18, 19, 22]. However, the cumulative incidences of ADR-related admissions (0.41% in men and 0.47% of total admissions in women) from this study were lower than the incidences reported in the literature. This might be due to under-recognition and to the coding system in which notification of causes is done on a voluntary basis.

Drug use within the study period was higher among women and after adjustment for this use, ADR risk clearly changed in all the different drug groups. For various drug-related admissions, risks for the sexes went in the opposite direction. This was surprising, since female sex is usually indicated as a major risk factor in developing an ADR.

As far as we are aware, this is the first study in which ADRs were combined with prescription data on a national basis. Previous studies have taken into account drug prescriptions, but these studies focused more on drug use per patient when admitted to the hospital, instead of taking into account background use [2, 4, 19, 21, 22]. Martin *et al*. [3] studied the incidence of ADRs in the sexes per drug exposure time. However, this concerned prescriptions for a variety of drugs, not specified per drug group.

According to earlier studies, the risk of ADRs due to antineoplastic agents was highest [2, 19]. In our study, risk for hospitalization due to an ADR following use of antineoplastic and immunosuppressive drugs was higher in men in the majority of the most frequent reactions. This drug group is a good example of personalized drug dosing. Men receive much higher doses of drugs due to the adjustment for body surface or body weight for the majority of these drugs. A possible explanation for this sex difference is the difference in activity of the various drug metabolizing agents involved. Among others, this accounts for cytochrome P450 (CYP) 2B6 and CYP3A4 [11, 12]. Differences between the sexes in metabolizing capacity of these cytochrome enzymes, or involved transporters, could result in prolonged drug exposure.

Three major drug classes that are a burden in drug-related hospitalizations, as described in the literature, are NSAIDs, anticoagulants and cardiovascular drugs [18, 19, 21]. We found higher risks for ADR-related hospitalization due to antirheumatics in men as compared with women after adjustment for total number of prescriptions. Especially, hospitalization for gastrointestinal ulcers differed significantly. A possible explanation for this higher risk in men is that men are more exposed to other risk factors for gastrointestinal ulcers, such as alcohol use, coffee, smoking, *H. pylori* infection or other drugs (e.g. aspirin) [29, 30]. Another theory could be that non-selective COX inhibitors are used more frequently by men.

Regarding the use of anticoagulants and salicylates, risk for ADR-related hospitalization varied per type of reaction. Where men seemed to have a higher risk of being hospitalized with specific haemorrhages (haematuria, haemoptysis and cerebral bleeding), women seemed more prone to be hospitalized with anaemia. However, non-specified haemorrhages and gastrointestinal bleeding, which comprised the largest number of hospitalisations, resulted significantly more often in hospital admissions in women than in men. Cytochrome P450 (CYP) 2C9 plays an important role in the metabolism of anticoagulants and salicylates, as well as of certain antirheumatics. The genetic influence of the CYP2C9 enzyme on bleeding risk has been shown, but so far, no clear difference in amount or activity of this enzyme has been determined between the sexes [11, 12, 14, 15, 31, 32]. A possible role for drug transporters must be considered.

Drugs acting on the cardiovascular system include a range of drugs with different sites of action. Men seemed to experience more hypovolaemic symptoms, regarding coronary vasodilators and diuretics. Women were more at risk to be hospitalized due to adverse effects of cardiotonic glycosides and electrolyte disorders following use of diuretics. Adverse effects due to cardiotonic glycosides are well known. Because of slower renal clearance of these drugs in women, drug effects may be greater if doses have not been adjusted. The remarkable difference in risk for electrolyte disorders between the sexes has been noticed earlier [33] and could be explained by higher exposure levels due to lower clearance in women. Genetic variation in drug transporters (e.g. OATP1B1, OAT1, OAT4) might be considered [33, 34] but so far no major sex differences have been found [11, 14]. Adverse reactions due to cardiovascular drugs are of major clinical relevance because of the high impact of potential consequences. Although these ADRs concern known reactions, the sex differences as shown by this study emphasise the importance of sex-based dosing or prescribing.

Antidepressants and other neurological drugs are often thought to cause more ADRs in women [32, 35]. Despite the fact that this can partly be explained by pharmacodynamics, pharmacokinetics and drug use [32, 36], a recent review showed that current evidence has been derived from small studies [35]. In our study, interpretation of the results was impeded by the coding of the events. Poisoning was the most frequent drug reaction to neurologic drugs, but intended overdose could not be ruled out due to contradiction of the E-code and main code. In these cases, the E-code referred to drugs causing adverse effects in therapeutic use while the main code referred to poisoning by drugs, excluding adverse effects. Further studies are needed to assess sex differences within these drug groups.

One of the strengths of our study was the availability of nationwide data on discharge diagnoses of all hospitalizations and data on drug use over a 6 year period. Data on drug use were also available for the same 6 year period, which made it possible to illustrate the use of the various drugs as a background of ADR occurrence. Because of the ecological design of the study, it was not possible to match the data on drug use (which were not discernable on an individual basis) with the ADR-related hospitalizations. Therefore, interaction between the various drugs could not

be studied. Although adjustment for age was done in the first analysis, unfortunately this was not possible in the analysis with total drug prescriptions.

Another limitation was that the data within the drug categories did not match in an exact manner. This was due to the different coding systems used by the two databases in our study. Hospitalizations were only taken into account if the secondary diagnosis of the admission was coded as being due to an ADR. Because of the passive coding of ADRs related to the admission diagnosis at discharge, the cumulative incidence of ADR-related admissions was probably substantially underestimated. However, this underestimation was probably the same for men and women and would not influence the RRs.

Female sex is considered as a risk factor for the development of ADRs to a variety of drug groups. When prescribing drugs to women, one should be aware of the differences in pharmacokinetics and pharmacodynamics compared with men. Although the overall number of ADR-related hospital admissions in our study confirmed the higher risk of women to be hospitalized due to an ADR, our study also suggested that differences in drug use play a role in this gender difference. However, men were also at risk for ADRs, but to other drug groups, and the risk in men should not be overlooked.

It should be realized that the above mentioned factors are not the only ones accounting for the sex differences in drug metabolism. For instance, steroid hormones are likely to contribute to drug response to a great extent. First of all, steroid hormones have been shown to influence target tissues, such as cardiac channel density and thiazide receptor density in the kidneys [37, 38]. Second, besides direct effects on drug metabolizing enzyme (DME) activity and drug transporters, steroid hormones also modulate gene expression [39–41]. Sex differences in patterns of growth hormone (GH) secretion by the hypothalamus result in different expression patterns [42, 43].

To obtain more insight into the difference in risk between men and women more research is needed to study the underlying mechanisms. Additional clinical trials and biomedical research are necessary to determine further the role of steroid hormones and their effects on drug response.

Competing Interests

There are no competing interests to declare.

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