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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Women encounter ADRs more often than do men

Y. Zopf · C. Rabe · A. Neubert · K. G. Gaßmann · W. Rascher · E. G. Hahn · K. Brune · H. Dormann

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Abstract
Background Several publications indicate that the female gender experiences a higher incidence of adverse drug reactions (ADRs) than does the male gender. The reasons, however, remain unclear. Gender-specific differences in the pharmacokinetic and pharmacodynamic behaviour of drugs could not be identified as an explanation. The aim of this study was to analyse ADR risk with respect to gender, age and number of prescribed drugs.
Methods A prospective multicenter study based on intensive pharmacovigilance was conducted. Information on patient characteristics and evaluated ADRs was stored in a pharmacovigilance database—KLASSE.
Results In 2,371 patients (1,012 female subjects), 25,532 drugs were prescribed. In 782 patients, at least one ADR was found. A multivariate regression analysis adjusting for age, body mass index (BMI) and number of prescribed drugs showed a significant influence of female gender on the risk of encountering ADRs [odds ratio (OR) 1.596, confidence interval (CI) 1.31–1.94; $p<0.0001$). Dose-related ADRs (51.8%) were the dominant type in female subjects. Comparing system organ classes of the World Health Organisation (SOC-WHO), cardiovascular (CV) ADRs were particularly frequent in female subjects (OR 1.92, CI 1.15–3.19; $p=0.012$).
Conclusion Our data confirm the higher risk of ADRs among female subjects compared with a male cohort. Several explanations were investigated. No single risk factor could be identified.

Keywords Gender · Risk factors · Adverse drug reaction · Pharmacokinetics

Y. Zopf (✉) · E. G. Hahn · H. Dormann
Department of Medicine 1,
Friedrich-Alexander-University Erlangen-Nuremberg,
Ulmenweg 18,
91054 Erlangen, Germany
e-mail: yurdaguel.zopf@uk-erlangen.de

C. Rabe
Department of Medical Informatics, Biometry and Epidemiology,
Friedrich-Alexander-University Erlangen-Nuremberg,
Waldstrasse 6,
91054 Erlangen, Germany

A. Neubert
School of Pharmacy, University of London,
London, UK

K. G. Gaßmann
Department of Geriatric Medicine, Waldkrankenhaus St. Marien,
Rathsberger Str. 57,
91054 Erlangen, Germany

W. Rascher
Department of Paediatrics,
Friedrich-Alexander-University Erlangen-Nuremberg,
Loschgestraße 15,
91054 Erlangen, Germany

K. Brune
Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nuremberg,
Bavaria, Germany

Introduction

Female gender appears to be a potential risk factor for adverse drug reactions (ADRs) [1–12]. Differences between male and female subjects in physical (body-water space, muscle mass, organ blood flow, organ function) [13] and physiological aspects (menopause, pregnancy and menstruation) [14] as well as differences regarding pharmacody-

namics and pharmacokinetics (bioavailability, distribution, metabolism, excretion) are purported and considered potential reasons for different ADR risks [15–17]. The clinical relevance of these gender-based differences to the occurrence of ADRs is not yet clear. Typical risk parameters for ADRs increase with age and polypharmacy [1, 3, 4, 6] for male and female subjects.

To analyse the influence of gender with respect to age and number of prescribed drugs, a prospective multicenter study was performed based on the intensive pharmacovigilance method in hospitals.

Methods

Study design

Over the past few years, a prospective multicenter study based on intensive pharmacovigilance was conducted that included 2,371 patients in several departments (pediatrics, medicine and geriatrics) at the Hadassah University of Jerusalem, the Friedrich Alexander University of Erlangen-Nuremberg, the General Hospital Waldkrankenhaus St. Marien of Erlangen and the University Hospital of Regensburg. All admissions were monitored prospectively by a pharmacoepidemiological team (PETE) for the occurrence of ADRs. The team consisted of physicians, pharmacologists and pharmacists. Patient charts were screened, and bedside visits took place on a daily basis for detection and evaluation of potential ADRs. All information on ADRs (probability, severity, preventability), their causative drugs and therapeutic consequences were entered into a specifically developed database—KLASSE [18].

Patient characteristics

Patients were evaluated according to demographic data (age and gender), body composition (BMI) and number and kind of prescribed drugs. To analyse ADR risk in different age cohorts, we classified age into five groups: 0–24, 25–54, 55–64, 65–75 and >75.

Classification of drugs according to ATC

To classify drug prescriptions, we used the Anatomical Therapeutic Chemical Classification System (ATC) [19].

ADR characteristics

Definition

ADRs were defined according to the World Health Organization's adverse reaction terminology [20]. Additionally, all ADRs were categorized into six different reactions:

Type A: Dose-related reactions, which were common, and related to the drug's augmented pharmacological action. Examples are toxic effects or side effects.

Type B: Non-dose-related reactions were uncommon and not related to a suspected drug's typical pharmacological action. Examples are immunological or idiosyncratic reactions.

Type C: Dose- and time-related reactions were uncommon effects related to the cumulative dose of a drug, such as hypothalamic pituitary adrenal axis suppression of corticosteroids.

Type D: Time-related reactions were delayed reactions that occurred some time after the use of the drug such, as teratogenesis or tardive dyskinesia.

Type E: Withdrawal symptoms that became apparent after the early withdrawal of a drug, for example, lung oedema after stopping diuretics or opiate withdrawal syndrome.

Type F: Unexpected failure of therapy was mainly due to inadequate drug dosages or the prescription of dangerously interacting drugs.

Probability

ADR probability was evaluated by PETE using the Naranjo score algorithm. Doubtful ADRs were excluded from statistical consideration [21].

Severity

Severity was assessed by applying a weighted score of the following indicators of drug induced harm: if ADRs impaired the patient's quality of life, caused temporary or permanent inability to work, led to or prolonged hospitalisation, caused temporary or permanent malfunction of an organ system or were dangerous, life threatening or fatal. An additional criterion was if drug withdrawal or introduction of a different drug therapy was necessary. A score of 1–4 indicated a mild, 5–8 a moderate and >8 a severe ADR [22]. Mild, moderate and severe ADRs were included.

Additionally, all serious ADRs were classified according to the WHO definition as follows: 0=no severe ADRs, 1=results in death, 2=life threatening, 3=results in persistent and severe invalidity, 4=results in invalidity, 5=results in congenital anomaly or congenital defect, 6=requires inpatient hospitalisation and 7=prolongs existing hospitalisation [23].

Because some patients had several ADRs simultaneously or successively, the total number of reactions was greater than the total number of patients having a reaction. If more

Table 1 Distribution of age, gender, adverse drug reaction (ADR) rate, number of prescribed drugs in defined age groups

	Gender	Age groups				
		1 (0–24)	2 (25–54)	3 (55–64)	4 (65–75)	5 (>76)
Patients		423 (17.8)	467 (19.7)	381 (16.1)	491 (20.7)	609 (25.7)
No. (%)	Female	185 (18.3)	142 (14.0)	109 (10.8)	198 (19.6)	378 (37.4)
No. (%)	Male	238 (17.5)	325 (23.9)	272 (20.0)	293 (21.6)	231 (17.0)
Age (mean ± SD	Female	7 (26.9)	42 (68.9)	60 (22.8)	70 (53.2)	83 (25.0)
	Male	7 (97.5)	43 (28.5)	59 (92.9)	69 (93.2)	82 (25.0)
No. of drugs (median, range)	Combined	4 (2/6)	7 (4/11)	10 (6/15)	12 (7/16)	13 (10/17)
	Female	3 (2/6)	8 (4/14)	9 (6/14)	13 (9/18)	14 (10/18)
	Male	4 (2/7)	7 (4/11)	10 (5/15)	11 (6/15)	12 (9/17)

than one drug was supposed to be responsible for an ADR, the most probable drug was used for analysis and statistics.

Statistical Analysis

Data were first analysed using descriptive statistical methods. Depending on the scale used, the (variable) mean value, together with the corresponding standard deviation (SD) or median with range (Q25/Q75) is given. We used the *t* test or the Mann–Whitney and Wilcoxon's *U* test to compare the distribution of continuously distributed variables, and the chi-square test for categorical variables. Multivariate logistic regression analyses were conducted using ADRs as the outcome and gender, age, number of prescribed drugs, body weight, height or BMI in kg/m^2 as independent variables. Body weight and height were fitted in one model. We employed the SAS system version 9 (SAS Institute, Inc., Cary, NC, USA). An age-stratified analysis was carried out to assess gender-specific differences depending on age group. We report odds ratios (OR) from the logistic regression models with 95% confidence intervals (CI).

Results

Patient characteristics

Altogether, 2,371 patients were involved in the study. Of these patients, 1,012 (42.7%) were female subjects. Age distribution differed between female and male subjects. Whereas female gender was more prevalent in the older age group (>76), male gender was more evenly spread. The attribution of the study population to defined age groups is shown in Table 1.

Mean BMI in adults (>18 years) was 24.7±5.5 standard deviation (SD) kg/m^2 in female subjects and 25.1±5.0 SD kg/m^2 in male subjects

Drugs

A total of 25,532 drugs were prescribed for the study population. The median number of drugs prescribed per patient was nine (5/15). Increasing age was positively correlated with the number of drugs prescribed. The median number of drugs prescribed for female subjects was 11 (6/16) and for male subjects nine (5/14). This, however, could be due to different age distributions within the two groups.

Table 2 Adverse drug reaction (ADR) distribution rate and risk ratio

Population	Male *n*[a] (%)	Female *n* [a](%)	OR[b] 95% CI	*P* value
Overall (adjusted to age)	361 (26.6)	413 (40.8)	1.60 (1.31–1.94)	<0.0001
1 (0–24)	37 (15.6)	25 (13.5)	1.07 (0.59–1.96)	0.8215
2 (25–54)	70 (21.5)	41 (28.9)	1.21 (0.74–1.97)	0.4572
3 (55–64)	77 (28.3)	42 (38.5)	1.67 (0.97–2.79)	0.0631
4 (65–75)	85 (29.0)	104 (52.5)	2.32 (1.54–3.48)	<0.0001
5 (>76)	92 (39.8)	201 (53.2)	1.60 (1.13–2.26)	0.0085

OR odds ratio, *CI* confidence interval
[a] Number of patients with at least one ADR
[b] Adjusted to number of prescribed drugs

As shown in Table 1, for age groups 1–3, the median number of drugs prescribed was identical (not significant) for both genders. In age group 4 ($p<0.0001$) and 5 ($p=0.02$), female subjects received significantly more drug prescriptions than did their male counterparts (Table 1).

ADRs

In 782 out of 2,371 patients, at least one ADR was found by PETE, for a total of 1,773 observed ADRs in all patients. With increasing age, an increasing number of ADRs/patient was observed ($p<0.001$). Except for age group 1, a higher ADR rate for female subjects was detected in all age groups. This varied from 13.5% to 53.2% (Table 2) depending on age. There was a significant difference for age groups 4–5: female subjects showed more ADRs than did male subjects.

Using the so-called Naranjo score, ADRs were considered possible in 40.7% of female subjects and 36.8% of male subjects, probable in 54.2% and 59.7%, and highly probable in 5.1% and 3.6%, respectively. The degree of severity was mild in 56.2% of female subjects and 57.5% of male subjects, moderate in 42.0% and 39.8%, and severe in 1.8% and 2.7%, respectively. In serious ADRs, no difference was seen between genders. The relationship between gender and the different types of ADR categories is shown in Table 3.

A gender-based distribution of ADRs based on the six most common body systems and organ classes [24] of the study population is presented in Table 4. CV disorders, for example, were observed in 51 female patients (13.1% of all ADR-positive female patients) and 24 male patients (7.3% of all ADR-positive male patients).

Using an unadjusted regression model, out of all system and organ classes observed, cardiac disorders showed a significantly increased incidence in female subjects (OR 1.92, CI 1.15–3.19; $p=0.012$).

Multivariate regression analysis

In the multivariate regression analysis including age, gender, weight, height, BMI and number of prescribed drugs, female gender (OR 1.596, CI 1.31–1.94; $p<0.0001$), age (per 15 years: OR 1.115, CI 1.045–1.191; $p<0.001$) and number of prescribed drugs (OR 1.145, CI 1.13–1.17; $p<0.001$) showed a significant influence on ADR occurrence. Weight, height and BMI had no significant impact. In the age-stratified analysis, female gender turned out to be a significant risk factor in age groups 4 (OR 2.32, CI 1.54–3.48; $p<0.0001$) and 5 (OR 1.60, CI 1.13–2.26; $p=0.008$). In age group 3, the same trend (OR 1.6 CI 0.97–2.78; $p=0.06$) could be observed but not to a significant extent.

Table 3 Gender-specific adverse drug reactions (ADRs)

Type of ADR	Female (%)	Male (%)
Type A: Dose-related	268 (51.8)	170 (39.8)
Type B: Non-dose-related	69 (13.4)	72 (16.9)
Type C: Dose- and time-related	149 (28.8)	150 (35.1)
Type D: Time-related	30 (5.8)	34 (7.9)
Type E: Withdrawal	0	0
Type F; Unexpected failure of therapy	1 (0.2)	1 (0.2)

Table 4 Frequency of prescribed drugs classified according to gender

System and organ classes	Female (%**)	Male (%**)
Skin and appendage disorders	25 (6.4)	11 (3.4)
Central and peripheral nervous system disorders and psychiatric disorders	34 (8.7)	33 (10.1)
Gastrointestinal system disorders	133 (32.2)	96 (26.6)
Liver and biliary system disorders	80 (20.6)	53 (16.2)
Metabolic and nutritional disorders	142 (36.6)	110 (33.5)
Cardiovascular disorders *	51 (13.1)*	24 (7.3)*
Blood cell disorders	52 (13.4)	60 (18.3)

* Odds ratio 1.92, confidence interval 1.15–3.19; $p=0.012$
** Percentages refer to all adverse drug reaction-positive female/male patients

Discussion

The question as to whether ADR occurrence depends on gender is controversially and ambiguously discussed in the literature [3, 4, 6, 10, 25]. Gender-specific differences in drug susceptibility are often assumed [26–29], but the evidence is limited. Our data confirm the higher risk of experiencing an ADR for the female gender compared with a male cohort. The risk increases with age and increased number of drugs prescribed. These risk factors have also been observed by other investigators [1, 3, 4, 6, 10, 30–36]. However, in our study, weight, height and BMI did not explain the prevalent susceptibility among female subjects. Again, this is in line with other publications [1, 3, 4, 34].

Alternatively, gender differences in drug metabolisation and elimination have been suggested. Some investigations report a modified phase I metabolism (oxidation, reduction and hydrolysis via CYP450 1A, 2D6, 2E1) and phase II conjugative metabolism (glucuronidation, conjugation, glucuronyl transferases, methyltransferases, dehydrogenases) by gender. Whereas metabolism by CYP2C9, CYP2C19, and N-acetyltransferase appears to be similar for both genders, female subjects have an increase in CYP3A4 and a variable decrease in CYP2D6, CYP2E1 and CYP1A2 [13, 16, 37–39]. Nevertheless, clinical investigations reveal no conclusive evidence with respect to the role of these

pharmacokinetic differences [11, 40–43]. In addition, body constitution (body size, body fat), age, polypharmacy and changing hormonal levels may also influence the probability of experiencing ADRs. However, there is no conclusive evidence that, for example, hormonal status plays a major role [28, 44, 45].

Some drugs (e.g. antidepressants) seemed to be more effective in female subjects than in male subjects at the same dosage and plasma concentration [39, 45]. However, an increased risk of ADRs for female subjects from these drugs is not evident [5]. Female subjects, for example, are at higher risk for CV ADRs (e.g. antiarrhythmics), but male subjects are more likely to develop more severe and clinically relevant ADRs than female subjects with CV-active drugs [46, 47]. In contrast, female patients are at a higher risk for torsade de pointes induced by antipsychotics, antihistamines, antiarrhythmics or antibiotic treatment [7, 47, 48].

In our analysis, female gender as an influential factor on the occurrence of ADRs was verified in a multivariate analysis. We observed this higher incidence within all age classes, except for children and younger adults. The higher rate was particularly prominent for the age group 55–76 years. To detect potential confounders, we looked into the number of drug prescriptions within all age classes and both genders. Only at the age of >65 years was a significantly higher drug prescription rate verifiable for women. However, the differences were small. Consequently, a 1.5-times higher ADR rate for the female gender is difficult to explain.

Our detailed evaluation shows that age and number of prescribed drugs are not obvious confounding factors to explain the higher incidence of ADRs among female subjects. In general, female subjects are similar to male subjects with respect to age and are almost identical with respect to the number of drugs prescribed.

With reference to ADRs according to SOC, in the unadjusted regression model, we observed a higher incidence of CV ADRs in female subjects, as well as skin and gastrointestinal system disorders and dose-related ADRs. This corresponds to the observation made by other investigators [9, 49, 50]. A higher risk for female subjects was particularly clear with respect to cardiovascular ADRs. Again, no relationship with regard to age or number of drugs prescribed was obvious. This lack of relationship must be considered with caution, as our sample size and number of patients in these subgroups was small.

Conclusion

This is the first study based on intensive pharmacovigilance demonstrating that female patients (aged between 55 and 100 years) have a higher ADR risk compared with male subjects, with the exception of children and young adults. Neither age nor number of prescriptions is related to the distinctly higher incidence of ADRs in female subjects. Other gender-specific risk factors must therefore exist. More attention must be paid to other potential risk factors, not only in relation to social and psychological aspects, but also in pharmacogenetics and pharmacodynamics.

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