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Adverse drug reactions and polypharmacy in the elderly in general practice

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Abstract Objectives: The risk of adverse drug reactions (ADRs) increases with the number of drugs used. Most studies refer to potential interactions; the results regarding the severity of occurring and registered ADRs are inconsistent. Therefore, we examined the relevance of drug-induced problems in the elderly in general practice and their association with polypharmacy.

Design: Retrospective cross-sectional analysis of prospectively collected data.

Setting: Three family practices participating in the medication and morbidity Registration Network Groningen (RNG).

Methods: From 2185 elderly patients (>64 years) medication and morbidity data were collected over the period of 2 years (1994 and 1995). Polypharmacy was defined as the long-term simultaneous use of two or more drugs. Adverse reactions recognised as such were coded as a separate 'diagnosis' A85. The most risky drug groups and the most prevalent diseases in relation to ADRs were studied.

Results: The incidence of ADRs in general practice was 5.7 per 100 elderly patients and the prevalence 6.1 per 100. Moderate polypharmacy was more frequent in the elderly who experienced adverse effects; no other differences in degree of polypharmacy could be found. The elderly who experienced adverse reactions used overall more different drugs (14.4 ± 7.6 , of which 1.5 ± 1.5 were used long term) than the other elderly patients (8.1 ± 5.7 , of which 1.0 ± 1.5 were long term). The incidence of ADRs increased non-significantly with the number of drugs used long term. Antibiotics, anti-

hypertensives and non-steroidal anti-inflammatory drugs were mainly responsible for gastrointestinal complaints (nausea, diarrhoea and stomach pain) and rash. In the cases of treating urinary tract infections and sleeping disorders, there was a significantly high risk of ADRs. Slightly more at risk for adverse drug reactions were older patients with coronary heart disease or asthma/chronic obstructive pulmonary disease.

Conclusion: Most of the ADRs observed in general practice turn out to be rather harmless. This is in agreement with outpatient studies, though not with hospital studies. An increased risk of adverse effects with the number of drugs used simultaneously, as reported in other studies, was not confirmed in our study. This study however is limited to actually registered effects.

Key words Adverse drug effects · Polypharmacy · Elderly

Introduction

Drug use is frequently considered to be hazardous for the elderly, because of the greater vulnerability of the elderly to drugs and to multiple drug use [1, 2, 3, 4, 5]. Recently, Bjerrum and others showed different methods of estimating polypharmacy, but he did not investigate the relationship of adverse drug reactions and polypharmacy [6]. The risks refer to side effects and interactions that may lead to hospitalisation and to morbidity, resulting from inadequate or incorrect use and from non-compliance. The importance of this problem is not disputed, but for the practising general practitioner many questions remain open. He does not know what to expect in view of the great variety in reported incidence (1.5–35% and inconsistent severity [7, 8, 9, 10, 11]). It has been shown that the risk of adverse drug reactions increases with the number of drugs used [12]. It remains unclear whether the adverse drug reactions found were due to interactions or to one of the drugs used. The problem is that most studies looking into the risks of multiple drug regimens

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refer to the *potential* for interactions, not at actually occurring adverse effects, leaving the clinical relevance in general practice uncertain [13].

In this study, we look at adverse effects actually observed in general practice, filling in the gap between theory (potential problems) and practice of registered drug problems. The focus is on the relationship with multiple drug regimens and the identification of drug groups and diseases with the highest risk of adverse reactions.

Methods

The study is based on data from three general practices participating in the Registration Network Groningen (RNG). The study population is representative for the patient population in other general practices in the north of the Netherlands [14]. Data cover all patients of 65 years or older in 1994 and 1995. In the database, all patient contacts have recorded the diagnosis (ICPC-code), prescribed drugs (ATC-code) and referrals [15, 16]. Adverse reactions recognised as such by the general practitioner are coded as a separate 'diagnosis' with ICPC-code A85. The actual adverse effect and the drugs responsible were available from the information in the computerised medical records. Polypharmacy has been defined as the long-term simultaneous use of two or more drugs; long term is 480 days or more in 2 years. Minor (2–3 drugs), moderate (4–5 drugs) and major (>5 drugs) polypharmacy were distinguished. Data are being compared with other registration projects in Dutch general practice with comparable data [8, 17]. The incidence of adverse drug reactions was calculated as the number of episodes per 100 elderly patients per year, based on data from 1994 and 1995.

The five most frequent drug groups causing adverse effects were identified, based on the highest incidence. The risk for adverse effects related to polypharmacy was assessed for the ten diseases with the highest prevalence, covering 50% of all diseases. Repeat prescriptions written by the practice assistant were included [18].

Analysis

To identify the risk of adverse effects in relation to polypharmacy for repeat prescribing, we compared elderly patients with and without adverse effects. Odd's ratios were calculated. In order to test the significance of the difference between consulting frequencies of patients with and without adverse effects the student's *t*-test was used. By means of a logistic regression analysis, we assessed the risk of adverse drug effects for the ten most prevalent diseases in this group of elderly patients, drug use without a clear indication and the number of long-term drugs used.

Results

The cohort consisted of 2185 people 65 years and older, of whom 60% were female and 74% were covered by public health insurance; over half of the group (55%) was between 65 years and 74 years of age. During the research period of 2 years, 90% of this cohort of elderly used at least one drug, while 51% used one drug or more on a long-term basis. Adverse reactions (A85) were recorded for 195 people with a total of 247 episodes; the incidence amounts to 5.7 per 100 elderly patients (Table 1). The majority of adverse reactions occurred in women (69%) and in the younger (<75 years) age group (50%), while only 9% of the recorded episodes were in the very old (over 85 years). The average age of the elderly with adverse reactions was 75.2 years (CI 95% 74.2–76.2)

compared with 74.8 years (CI 95% 74.5–75.1) for those with no adverse effects. The elderly who experienced adverse effects were more frequently on moderate polypharmacy; no other differences in the degree of polypharmacy could be found (Table 2). Although the elderly with adverse reactions overall used more different drugs (14.4 ± 7.6 , of which 1.5 ± 1.5 were long term) than the other elderly patients (8.1 ± 5.7 , of which 1.0 ± 1.5 were long term), the correlation between number of drugs prescribed and number of encounters with the doctor because of adverse effects (A85) was only modest ($r = 0.28$, $P = 0.0002$); the correlation was even lower and not significant for long-term medication ($r = 0.06$, $P = 0.42$). The same picture emerges when looking at the incidence of adverse drug effects for the different levels of polypharmacy; the confidence intervals overlapped (Table 3).

Further analysis was limited to 185 patients (95%) with 215 episodes of an adverse effect because of inadequate data available for the other ten patients. Most adverse effects were caused by antibiotics (15%), followed by antihypertensives (13%) and non-steroidal anti-inflammatory drugs (NSAIDs) (8%) (Table 4). The top five drug groups with identified adverse effects described in Table 4 covered 47% of all drugs causing adverse drug reactions and 45% of all adverse effects. Antibiotics caused mainly gastrointestinal complaints and rash as side effects; antihypertensives caused a wide range of adverse effects and NSAIDs mainly caused stomach pain. The adverse effects observed by the general practitioner were mainly minor complaints. Nausea was the most frequently occurring adverse effect, caused in the first place by antibiotics and antidepressants and for the rest by 11 different drug groups. Headache was caused by calcium-channel blockers in three cases, and in three other cases by nitroglycerine derivatives (not shown in table). The other 108 side effects included a variety of mainly minor complaints of the skin ($n = 20$), general and unspecified ($n = 18$), digestive system ($n = 16$) and respiratory system ($n = 9$), etc.

Most patients in this cohort (159 of 185) suffered only one episode of adverse effects, 22 patients had two episodes, two had three episodes, one had four and one had seven episodes. Looking at the health problems of patients, it appeared that only patients with urinary tract infections, sleeping disorders and known coronary ischaemic diseases and asthma/chronic obstructive pulmonary disease (COPD) were more at risk with regard to adverse drug reactions (Table 5).

The elderly suffering from adverse reactions consulted their general practitioner more often than the other elderly patients (Table 2). Repeat prescribing was lower for patients with adverse drug reactions (Table 2).

Discussion

The incidence of adverse drug reactions in the elderly in this study corresponds with what has been found in

Table 1 Incidence and prevalence of adverse drug reactions in the elderly in Dutch general practice (percentages per year)

	Incidence	Prevalence	Prevalence 65–74 years	Prevalence >75 years
RNG (this study)	5.7	6.1	5.4	6.8
Meyboom-de Jong (autonomie) [8]	4.9	4.7	4.4	5.1
Lamberts (transitie) [17]			5.7	6.9

Table 2 Characteristics of the elderly with and without adverse drug reactions in 1994/1995 (percentages and 95% confidence intervals)

	Elderly with adverse drug reaction (<i>n</i> = 195)	Elderly without adverse drug reaction (<i>n</i> = 1895)
No long-term drug	34.6 (27.8–41.9)	52.1 (49.7–54.4)
1 Drug	25.4 (19.4–32.4)	21.6 (19.7–23.6)
2–3 Drugs	28.1 (21.8–35.3)	19.8 (18.4–22.1)
4–5 Drugs	10.3 (6.5–15.4)	4.5 (3.6–5.6)
>5 Drugs	1.6 (0.04–5)	2.0 (1.4–2.8)
Mean consulting frequency*	10.6 (SD 8.8)	5.4 (SD 5.2)
Mean house-call frequency**	8.1 (SD 12.1)	4.7 (SD 9.5)
Proportion of repeat 50 prescribing #		57

* *t*-value 11.9; *P* < 0.001/***t*-value 4.5; *P* < 0.001
#Odds-ratio 0.76

other studies in general practice in The Netherlands (Table 1) [7, 17]. Most of the adverse effects observed in general practice turn out to be rather harmless. This is in agreement with outpatient studies, but in contrast with hospital studies [13, 19, 20, 21]. The incidence found in this study is low compared with many general practice related or outpatient studies in other countries (10–14%) [22, 23]. This may be explained by differences in methods, in particular in the study populations and in registration or selection criteria for adverse effects. In this

Table 3 Incidence of adverse drug reactions (A85) per category of long-term drug use (*n* = 1993; missing codes 143) (percentages and 95% CI)

Long-term drug use	A85
No drug	6.6 (5.2–8.4)
1 Drug	10.6 (7.9–13.9)
2–3 Drugs	12.4 (9.5–16.1)
4–5 Drugs	18.6 (11.9–27.8)
>5 Drugs	7.7 (1.8–18.6)

Table 4 The five drug groups that caused adverse effects most frequently in 215 episodes

	Stomach pain (24)	Nausea (27)	Headache (9)	Erythema (16)	Diarrhoea (12)	Other ^a (108)
Antibiotics (33)	9.1%	24.2%	–	15.2%	15.2%	36.4%
Antihypertensives (28)	7.1%	13.6%	10.7%	3.6%	3.6%	71.4%
NSAIDs (17)	70.6%	5.9%	–	11.8%	11.8%	–
Antidepressants (12)	–	41.7%	–	8.3%	8.3%	41.7%
Diuretics (11)	9.1%	9.1%	–	9.1%	–	72.7%

^a These other side effects include a variety of mainly minor complaints

Table 5 Risk of adverse drug reactions in elderly patients with the ten most prevalent diseases and with drug use without a clear indication (in Odds-ratios with 95% CI)

Variables	Odds ratio (CI 95%)
Number of long-term drugs	1.0 (0.9–1.1)
Urinary tract infection (<i>n</i> = 404)	2.5 (1.8–3.5)
Sleeping disorder (<i>n</i> = 224)	2.4 (1.7–3.6)
Coronary heart disease (<i>n</i> = 388)	1.8 (1.2–2.5)
Astma/COPD (<i>n</i> = 190)	1.8 (1.1–2.7)
Depression (<i>n</i> = 94)	1.7 (1.0–3.1)
Heart failure (<i>n</i> = 198)	1.6 (0.9–2.2)
Atrial fibrillation (<i>n</i> = 134)	1.3 (0.8–2.3)
Hypertension (<i>n</i> = 735)	1.3 (1.0–1.8)
Diseases of the stomach (<i>n</i> = 123)	1.2 (0.7–2.1)
Diabetes (<i>n</i> = 226)	0.8 (0.5–1.3)
Drug use without clear indication (<i>n</i> = 472)	1.3 (0.9–1.9)

study, as well as in the other Dutch primary care studies mentioned, adverse effects are restricted to those observed and registered as such by the general practitioner. This probably implies an underestimation of ‘true’ adverse effects occurring. However, studies looking at potential adverse effects may overestimate true incidence of adverse effects [24].

Heerdink, for example, found for drug-using patients of 60 years and older an 18–20% risk of interactions due to undesirable combinations of drugs [25]. Such data do not reveal whether the potential interactions actually manifested themselves clinically. In some studies, hospitalisation due to interactions is hardly found [26, 27].

An increased risk of adverse effects with the number of drugs used simultaneously, as reported in other studies, was not confirmed in our study [28, 29]. This may be explained by the fact that polypharmacy was measured based on long-term drug use. Most methods used to study polypharmacy have been based on interviews and questionnaires. The validity of these data may be influenced by recall bias. Methods for estimating polypharmacy from prescription data and computerised databases have, however, not been evaluated in detail. Recently, Bjerrum e.o. concluded that a 3-month period was a valid point prevalence for polypharmacy.

However, he did not investigate adverse drug reactions in patients with polypharmacy [6].

In our study, we defined polypharmacy as the simultaneous use of two or more long-term drugs. Since most adverse effects occur within 4 days after taking a new drug, these drugs are most probably not included in our measurement of polypharmacy [7]. Another factor may be that the general practitioners participating in this study were using computer programmes with reminders about the risk of interactions. This may prevent or at least decrease the prescribing of undesirable combinations of drugs. If such combinations are prescribed despite the warning, the general practitioner may have good reasons to do so, for example that the patient is not showing any symptoms of an adverse effect. Moreover, pharmacists are also actively involved in medication surveillance, checking for possible drug-related problems and warning the general practitioner if such problems occur. It is interesting that people taking more than five drugs showed an incidence of ADR lower than that of other long-term treated subjects. The difference is, however, not significant. The group was small ($n=39$) and it possibly concerned elderly people with extensive care and monitoring.

This study was limited to actually occurring and registered adverse effects. It is known that, in many cases, the elderly do not visit their general practitioner with suspected adverse effects, because either they do not think them serious enough or they expect and accept that the drugs they need have minor side effects [13, 30]. Inadequate surveillance, because of repeat prescribing without face-to-face consultation, does not seem to play a role. In fact, patients with adverse effects are seen more often in face-to-face contacts. The adverse effects actually observed occur with the ten most presented problems in general practice by the elderly but seem fortunately limited to minor and reversible ailments.

Patients with urinary tract infections and sleeping disorders are more at risk of adverse drug reactions. The prescribing of antibiotics for urinary tract infections is probably responsible for the adverse drug effects. The higher risk associated with sleeping disorders is not quite clear. With regard to chronic diseases, older patients with coronary heart disease or asthma/COPD are more at risk of adverse drug reactions. For determining the cause of this result further research is indicated.

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