Risk factors for the development of adver

Vormt polyfarmacie een risico voor de patient? Dr. van den Bemt verrichtte een onderzoek naar de risicofactoren voor schadelijke bijwerkingen. De invloed van leeftijd, geslacht, soort medicijn en het aantal medicijnen werd onderzocht. De conclusie geeft een duidelijk antwoord.

Abstract

Adverse drug events in hospitalised patients lead to increased morbidity, mortality and costs. Early detection of adverse drug events could aid in the prevention of these adverse outcomes. A cost-effective system for the early detection of adverse drug events should focus on high risk patients. A study was set up with the primary aim to identify characteristics that are associated with the development of adverse drug events (ADEs) in hospitalised patients.

ADE reports were gathered from physicians and nurses (spontaneous reports) and from patients after intensive ward interviews by hospital pharmacists. All patients admitted to the internal medicine wards of two Dutch hospitals, during a two month period, were included.

The following characteristics were analysed for their potential relationship to the occurrence of ADEs: age (categorised), gender, number of drugs prescribed during hospital stay, types of drugs used and changes in drug use on admission.
Age was found to be inversely associated with the development of ADEs. Furthermore, statistically significant associations were found for the number of drugs prescribed per hospitalised patient, for newly prescribed drugs and for the cessation of drugs on hospital admission. The use of gastrointestinal drugs, central nervous system drugs and antibiotics was associated with the development of ADEs, when compared to all other drugs taken by the patients.

In this study, the most important risk factors are the number of drugs used per patient and the starting of a new drug during hospitalization. As most hospitalised patients start new drug therapies while in hospital, this seems an inappropriate focus. However, careful monitoring of patients using more than 7 drugs at a time may be possible in a cost-effective system for the early detection of ADEs.

Introduction

Adverse drug events (ADEs) frequently occur in hospitalised patients. Two recently published studies report rates of 0.7% [1] and 2.4% [2], while a recent meta analysis reports an incidence of 10.9% of both serious and non serious adverse drug events [3]. Classen et al. have shown that these ADEs lead to excess mortality, morbidity and costs [2]. Early detection of ADEs would aid in the prevention of these adverse outcomes. For this purpose, spontaneous reporting is commonly used, but it has the disadvantage of substantial underreporting. Intensive monitoring probably has overcome this problem. It is, however, not a very efficient method for the detection of ADEs. It consumes a lot of time and results in the reporting of a large number of minor ADEs. A system that focuses on certain patients who are at high risk for the development of ADEs is likely to be more efficient in the prevention of ADEs. Therefore, one would like to identify risk factors that lead to adverse drug events, but especially in Europe there is a paucity of studies on risk factors for the development of ADEs in hospitalised patients. Such a study was set up, with the objective to identify risk factors that are related to the development of adverse drug events in hospitalised patients.

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Methods

Setting

The study was conducted in the internal medicine wards of two Dutch general hospitals (in Tilburg and Delft).

Study Design

The study was of a follow-up design. The duration of the study was two months. It was conducted from October 1, 1996 to November 30, 1996 in Tilburg and from May 1, 1997 to June 30, 1997 in Delft. An ADE was defined as any noxious, unintended, and undesired effect of a drug (possibly causally related), which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. Reports of ADEs were collected from three sources, namely from doctors and nurses (spontaneous reporting) and from patients (intensive ward interview by hospital pharmacists). The use of three sources enabled us to identify adverse drug events with a relatively high degree of sensitivity.

Population and sampling

All patients admitted to the specified wards (including geriatric patients) during the two months period, were included. Exclusion criteria were not applicable to the spontaneous reporting of doctors and nurses, because adverse drug event reporting by doctors and nurses is part of daily care and therefore applies to all patients. For the collection of patiënt reports, the patients had to be interviewed by the hospital pharmacists. Patients were included in this daily ward interview, when they gave oral informed consent and when they could understand the questions.

Before the study started, the doctors and nurses of the specified wards were given instructions regarding the procedure for reporting adverse drug events. They were asked to report all adverse drug events (both serious and non serious) on special forms. Data on this report form include gender and date of birth of the patient involved, information about the suspected medicine (name, dose, frequency, route of administration), concomitantly used medication, and other available information considered relevant by the reporter (including diseases, factors possibly related to the event and laboratory findings).

All reporting forms were sent to the hospital pharmacy. The investigator (a hospital pharmacist) then responded to the reporter by giving information or advice concerning the reported adverse drug event.

Patient reports were collected during a daily ward round by the investigator. The investigator asked the patient whether he/she experienced an adverse drug event. If so, the investigator asked information about the time relationship. Both questions were printed on a special form (different from the doctor/nurse form), which also contained patient characteristics such as age and gender. Adverse drug events were only recorded when the patient could link it to a suspected drug, when the time relationship between drug and adverse drug event was appropriate and when it had occurred during hospital stay. Four investigators (hospital pharmacists) participated in the daily visits in the wards. By using the above mentioned form, the investigators made sure to collect the necessary information in a consistent manner.

Age and gender of the patients admitted to the specified wards were recorded, as well as their length of hospital stay. Adverse drug events were classified according to the World Health Organization (WHO) code, which classifies adverse drug events into system-organ classes and into preferred terms for the ADE [4]. The drugs prescribed to the patients before (by using the records of the community pharmacies of the patients) and during admission (by using the records of the hospital pharmacies) were recorded. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) code [5]. The changes in drug use on admission to the hospital were also recorded (again by using the records of the community pharmacies of the patients).

The study was approved by the medical ethics committees of the participating hospitals.

Data Analysis

The following variables were analysed for their potential relationship to the occurrence of ADEs: age, gender, number of drugs prescribed during hospital stay, types of drugs used (both before and during hospital stay; classified according to the ATC code; only the five most frequently prescribed classes of drugs were analysed for their relationship with the reporting of adverse drug events, because these

five classes contained 80% of all prescribed drugs and the other 20% of drugs belonged to 11 classes) and changes in drug use. Changes in drug use were defined as the cessation of drugs used before hospital admission or the prescription of new drugs on hospital admission or during hospital stay.

The data were analysed using Statistical Package for Social Sciences (SPSS) version 9.0.
Logistic regression analysis was used to determine the relationship between the development of an adverse drug event and age, gender, number of drugs prescribed during hospital stay, classes of drugs used before and during hospital stay (compared to all other drugs the patient used) and changes in drug use on admission. By using multiple logistic regression an adjustment was made for possible confounders (e.g. the relationship between age and the development of an adverse drug event was corrected for gender, length of hospital stay and number of drugs prescribed).

Logistic regression analysis was used to be able to estimate the magnitude of the association between individual risk factors and the probability of developing an ADE. This is a follow-up study and therefore these associations could also have been expressed as risk ratio's instead of odds ratio's by means of simple 2x2 table analysis. However, we also wanted to adjust for several possible confounding variables, ie perform a multivariate analysis, so we chose to use logistic regression analysis. This is a convenient and the most common used approach in such instances.

Results

Nine patients refused to participate in the study and were therefore excluded. The remaining 538 patients were included in the study, of which 149 (27.7%) experienced one or more adverse drug events. Most adverse drug events were reported during the intensive ward visit (85%) and the remaining 15% of the adverse drug events was reported by doctors and nurses. There was a small overlap in ADEs reported by the three sources (11 reports). Table 1 shows some general characteristics of the study population. A total of 460 patients received newly prescribed drugs on hospital admission or during hospital stay, while 211 patients had one or more of their medications cessated on hospital admission. The five classes of drugs that were most frequently prescribed before and/or during hospital stay were: gastrointestinal drugs (396 patients), central nervous system drugs (376 patients), cardiovascular drugs (312 patients), drugs acting on the blood (294 patients) and antibiotics (183 patients).

The type of adverse drug events, classified by system-organ class, can be found in table 2. Most adverse drug events were gastro-intestinal effects, followed by psychiatric disorders and central & peripheral nervous system disorders and disorders of skin and appendages.

Table 3 shows the association between the development of an adverse drug event and the characteristics age (categorised), gender, number of drugs prescribed during hospital stay (categorised), newly prescribed drug, cessation of drug on hospital admission and class of drugs, as well as their confidence intervals, both without adjustment for possible confounding factors (odds ratio's) and with adjustment for possible confounders (adjusted odds ratio's). Age was found to be inversely associated with the development of ADEs. Furthermore, statistically significant associations were found for the number of drugs prescribed per hospitalised patient, for newly prescribed drugs, for the cessation of drugs on hospital admission and for the use of gastrointestinal drugs, central nervous system drugs and antibiotics. Gender and use of drugs acting on the blood and cardiovascular drugs were not statistically significantly associated with the development of ADEs, but after adjustment for possible confounders the use of drugs acting on the blood was statistically significantly associated with ADEs.

Discussion

When the incidence of adverse drug events in this population is compared with the results of the meta analysis of Lazarou et al. [3], it is rather high: 27.7% versus 10.9% in the meta analysis. Three reasons can explain this result. First, all possible adverse drug events were included, while Lazarou et al. included probable and definite adverse drug events only. Secondly, most of the reports were obtained by asking the patient for any adverse drug events that he or she had noticed (i.e. intensive monitoring). It has been shown in older studies that this increases the number of reports [6]. This study aimed to collect adverse drug events with a high degree of sensitivity, so three sources of reports were used (doctors, nurses, patients), without applying a formal causality assessment. In this manner, adverse drug events were collected with a high degree of sensitivity, but the method lacks specificity. Because risk factors were studied that can possibly lead to adverse drug events in hospitalised patients, a high degree of sensitivity seemed more important than a high degree of specificity. However, even this method of asking patients for any experienced ADEs still results in some underreporting, because patients are of course unable to

Table 1:General characteristics of the study population (n=538)

Gemiddelde leeftijd	68.7 jaar
Geslacht:	
Man	43.5 %
Vrouw	56.5%
Aantal medicijnen voorgeschreven:	
<4	21.0 %
4-6	27.9 %
7-9	23.8 %
>9	27.3 %
Gemiddelde opnameduur	16.5 dagen

Table 2:Type of adverse drug events, classified by system-organ class (WHO)

system-organ class:	**number of ADE's (%)**
gastro-intestinal system disorders	108 (43.5)
psychiatric disorders	28 (11.3)
skin and appendages disorders	22 (8.9)
central & peripheral nervous system disorders	22 (8.9)
body as a whole - general disorders	20 (8.1)
platelet,bleeding & clotting disorders	9 (3.6)
other	39 (15.7)

Table 3:Association of the development of adverse drug events with the characteristics age, gender, number of drugs prescribed, newly prescribed drug, cessation of drug on hospital admission and type of drug

characteristic	**Odds Ratio (95% C.I. b))**	**Adjusted Odds Ratio a) (95% C.I. b))**
age		
< 60 years	1 (ref.c))	1 (ref.c))
60 74 years	0.69 (0.42 1.11)	0.70 (0.43 1.14)
75 80 years	0.56 (0.31 1.02)	0.54 (0.30 0.99)
> 80 years	0.36 (0.21 0.61)	0.34 (0.20 0.59)
gender	1.20 (0.82 1.76)	1.30 (0.89 1.92)
number of drugs prescribed		
< 4	1 (ref.c))	1 (ref.c))
4 6	2.61 (1.32 5.18)	4.00 (1.91 8.39)
7 9	3.50 (1.76 6.96)	5.55 (2.62 11.76)
10 or more	5.01 (2.58 9.76)	8.50 (4.03 18.19)
newly prescribed drug	6.65 (2.63 16.81)	8.17 (3.16 21.13)
cessation of drug on hospital admission	1.50 (1.02 2.20)	1.84 (1.23 2.76)
Type of drug		
gastrointestinal drugs	2.13 (1.32 3.45)	2.38 (1.44 3.91)
central nervous system drugs	1.66 (1.07 2.57)	1.88 (1.19 2.95)
cardiovascular drugs	0.70 (0.48 1.03)	1.02 (0.65 1.60)
drugs acting on the blood	1.33 (0.91 1.95)	1.73 (1.14 2.62)
antibiotics	2.44 (1.65 3.60)	2.71 (1.81 4.06)

a) Adjusted for possible confounding factors (age, gender, number of drugs prescribed, length of hospital stay)
b) C.I. = Confidence Interval
c) ref. = reference category
d) For each drug class the reference category was the total of all other drug classes

recognize e.g. laboratory abnormalities and because they may forget to tell certain ADEs. This may result in selection or recall bias.
Thirdly, the length of hospitalization in this study was relatively long, so there may have been simply more time for ADEs to occur. The length of hospitalization in this study can be explained by the inclusion of geriatric patients. In the Netherlands they often have to wait for admission to a nursing home; time they unjustly spend in a hospital bed.

Though it is generally stated that the incidence of adverse drug events increases with increasing age, there is still much debate about age as an independent risk factor for adverse drug events in literature [7-15]. Factors such as the number of drugs used per patient, the number of clinical diagnoses and the length of hospital stay are considered to be responsible for the increase in adverse drug reactions with increasing age. Carbonin et al. showed that age was not an independent risk factor for adverse drug events in hospitalised patients [16]. In a recent study of Moore et al. patients with an adverse drug event during hospital stay were not older than those without an adverse drug event [17]. In this study an inverse relationship was found between age and adverse drug events. Patients older than 80 years of age were significantly less likely to have adverse drug events than younger patients. This may be due to underreporting by both health care professionals and patients, which has been stated to increase with increasing age [10]. A study of reporting rates of adverse drug events to the Committee on Safety of Medicines showed that reporting rates were highest in the fifth and sixth decades and declined thereafter [18]. In this study, the decline in ADEs with increasing age may have been partly due to problems of comprehension and hearing in communicating verbal ADE reports.

Adverse drug events were reported in slightly more women than men in this study, although this difference did not reach statistical significance. In general, adverse drug events are stated to occur more often in women than in men [7,9,17,19].

This study showed two risk factors that were strongly associated with the reporting of adverse drug events. The first of these, the number of drugs used per patient during hospitalization, is a well known risk factor from literature [7-15]. The second one has not been described before, but seems very logical from a pharmacological point of view. The starting of newly prescribed drugs during hospitalisation was strongly associated with the reporting of adverse drug events. This can be explained by the pharmacological actions of newly started drugs: most adverse drug events will occur shortly after starting a drug.

Thereafter, either tolerance for the adverse drug event develops or the patient discontinues the medication.

The cessation of a drug on hospital admission was also found to be associated with the reporting of adverse drug events. In this case, there may very well have been a causal relationship. The drug may have been stopped because it was thought to be the cause of an adverse reaction.

This study showed that patients who used gastrointestinal drugs, central nervous system drugs and antibiotics were more likely to report an adverse drug event. After adjustment for age and gender this was also found for drugs acting on the blood. It is worth noting, however, that the association between ADEs and the five most prescribed classes of drugs (as compared to all other classes of drugs the patients used) was determined. The fact that these classes are prescribed so often may be related to the occurrence of ADEs.

Finally, the overlap in the three sources (doctors, nurses, patients) could have influenced the results. However, this overlap was very small (11 reports) compared to the total number of ADE's, so the influence is probably not substantial.

Conclusion

Adverse drug events in hospitalised patients lead to excess morbidity, mortality and costs [2,3,17]. Therefore, measures to prevent these adverse drug events are likely to have a positive influence on patient care, both directly (less morbidity and mortality due to adverse drug events) and indirectly (cost savings). By focusing a system for the detection of ADEs on patients with risk factors the early detection and prevention of ADEs may be possible in a cost effective manner. In this study, the most important risk factors are number of drugs used per patient and the starting of a new drug during hospitalisation. As most hospitalised patients start new drug therapies while in hospital, this seems an inappropriate focus. However, careful monitoring of patients using more than 7 drugs at a time may be possible in a cost-effective system for the early detection of ADEs. Future studies should look into the effect of interventions, aiming at reducing the number of drugs used per patiënt, on the frequency of adverse drug events in hospitalised patients.

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