Contraindicated NSAIDs are frequently prescribed to elderly patients with peptic ulcer disease

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Aims To establish the frequency with which NSAIDs were prescribed to elderly patients after admission to hospital for serious gastrointestinal complications and to study which factors are determinants of the prescription of these contraindicated drugs.

Methods A retrospective cohort study of patients from The Rotterdam Elderly Study, a prospective population-based cohort study of people older than 55 years of age was carried out. Elderly patients with a hospital admission for serious gastrointestinal complications were followed until prescription of an NSAID, death, removal to another area or end of the study period, whichever came first. The following baseline determinants for receiving a contraindicated prescription were studied: gender, age, presence of rheumatoid arthritis or osteoarthritis, presence of cardiovascular risk factors, number of GP visits, number of visits to a medical specialist, cognitive function and the prescriber being a GP or a medical specialist.

Results Prescriptions of an NSAID after discharge from hospital, were identified in 73 patients (73%). Fifty-one percent were prescribed aspirin of whom the large majority used it as an antithrombotic agent, and 49% were prescribed a nonaspirin NSAID after discharge from hospital. Twenty percent of the patients used more than one NSAID on one or more occasions after discharge. For patients who were prescribed NSAIDs before admission as well as after discharge, the proportion of contraindicated prescriptions with concomitant use of antiulcer drugs rose significantly from 0.19 before discharge to 0.60 after discharge for aspirin and from 0.11 to 0.61 for nonaspirin NSAIDs. In the multivariate analysis the only remaining factor with prognostic influence on prescription of NSAIDs was a history of NSAID use before cohort enrolment. A history of rheumatoid arthritis or osteoarthritis was not associated with NSAID prescription after discharge.

Conclusions Contraindicated NSAIDs are prescribed to a great extent in elderly patients, despite their greater vulnerability for life-threatening gastrointestinal blood loss. It is remarkable that a history of rheumatoid arthritis or osteoarthritis is no significant determinant for receiving a contraindicated prescription, which suggests that these drugs are mainly prescribed for uncomplicated arthralgia.

Keywords: contraindication, drug prescription, elderly patients, NSAIDs, peptic ulcer disease

Introduction

Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of hospitalization and death from gastrointestinal bleeding and perforation [1–4].

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Numerous studies have established the association between NSAIDs and gastrointestinal toxicity. All NSAIDs cause a full range of gastrointestinal adverse effects, although they vary in frequency and severity [3, 5–7]. Several patient- and drug-related factors have been identified that increase the risk of NSAID-associated gastrointestinal complications. Almost all deaths from NSAID-related gastrointestinal adverse effects occur in elderly persons [8] and elderly women seem particularly susceptible [9–11]. Patients with a *Helicobacter pylori*

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infection have an increased risk of bleeding from NSAID-associated peptic ulcers [12]. Higher doses [6, 10–13] and concomitant use of oral anticoagulants [7, 14] and corticosteroids [7, 15, 16] are frequently noted as drug-related risk factors. Worldwide, 30 million patients use prescription NSAIDs on a daily basis [17, 18]. Half of these patients are beyond 60 years of age [18]. The US Food and Drug Administration (FDA) estimated that 2–4% of chronic NSAID users will develop upper gastrointestinal bleeding, a symptomatic ulcer, or an intestinal perforation each year [19], despite the fact that 26% of NSAID users are prescribed antiulcer therapy [20, 21]. The mortality rate among patients who are hospitalized for NSAID-induced upper gastrointestinal bleeding is about 5–10% [22]. Deaths from gastrointestinal toxic effects of NSAIDs are assumed to be the 15th most common cause of death in the United States [1, 23]. Yet these toxic effects remain largely a 'silent epidemic', with many physicians being unaware of the magnitude of the problem [23]. These complications also occur in patients taking over-the-counter NSAIDs [24–26]. The high exposure prevalence raises the question whether patients are receiving NSAIDs unnecessarily and whether NSAID-related adverse effects are adequately managed. In the present study, we established the frequency with which NSAIDs were prescribed to elderly patients after they had been admitted to hospital for serious gastrointestinal complications. Furthermore, we studied which patient- or physician-related factors are determinants of the prescription of these contraindicated drugs.

Methods

Setting

Data were obtained from The Rotterdam Study. This study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly. All inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, aged 55 years or over and living in the district for at least 1 year were invited in 1990–93 to participate in the study. The rationale, ethics approval and design of this study have been described elsewhere [27]. The cohort encompasses 7983 individuals who were all interviewed and investigated at baseline. For all participants, all hospital discharge records from 1 January 1991 through 31 December 1998, were obtained from the Dutch Center for Health Care Information. These records include detailed information concerning the primary and secondary diagnoses, procedures and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases (ICD-9-CM [28]). More than 99% of participants fill their drugs at seven pharmacies which are fully computerized. The pharmacy data include the Anatomical Therapeutical Chemical (ATC)-code [29], date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, and product name of the drugs.

Cohort definition

All patients with serious gastrointestinal complications such as gastrointestinal haemorrhage, a symptomatic ulcer, an intestinal perforation or a gastric outlet obstruction (primary or secondary discharge diagnosis codes ICD-9-CM 531 through 535, and ICD-9-CM 578) in the study period between 1 January 1991 and 31 December 1998 were identified from the hospital discharge records. The date of the first hospital discharge for any of these diagnosis codes was defined as the first day of follow-up. Patients were followed until the prescription of an NSAID, death, removal to another area or end of the study period, whichever came first. Patients with a history of less than 1 year of follow-up after enrolment, because of death, removal or end of the study period, were excluded.

Outcome definition

We defined all NSAIDs used as antirheumatics, analgesics or platelet-inhibiting drugs (ATC-codes M01A, N02BA, B01AC06 and B01AC08) as potentially contraindicated drugs. We assessed the use of drugs which might increase the risk of gastrointestinal bleeding when combined with NSAIDs: coumarins (ATC-code B01AA) and oral glucocorticosteroids (ATC-code H02A and H02B). Furthermore, we assessed the use of antiulcer H_2-antihistamines (ATC-code A02BA), prostaglandins (ATC-code A02BB and M01AB55), and proton pump inhibiting (ATC-code A02BC) antiulcer drugs. All exposure data were obtained from computerized records of prescriptions filled at the community pharmacies which has been proven to be highly compatible with actual drug use in The Rotterdam Study [30]. For every drug of interest, the legend duration (prescription length) was calculated by dividing the number of dispensed units by the prescribed daily number of units per day.

In a first analysis, we defined the outcome of interest into five mutually exclusive classes: no NSAIDs; a NSAID alone; a NSAID in combination with a coumarin or an oral glucocorticosteroid without antiulcer therapy; a NSAID in combination with an antiulcer drug; a NSAID in combination with a coumarin or an oral glucocorticosteroid and an antiulcer drug. If NSAIDs were prescribed after the first discharge date, the mean time between the discharge date and the first prescription for the contraindicated drug were separately calculated for aspirin and nonaspirin NSAIDs. For patients who were

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prescribed NSAIDs before as well as after their first hospitalization, the following variables were compared per person for the time periods before admission and after discharge: the duration of the last prescription before admission and the first prescription after discharge; the mean duration of all contraindicated prescriptions and the mean dosage, calculated as the prescribed daily dose (PDD) divided by the defined daily dose (DDD) (PDD/DDD ratio). The DDD is a standard dose unit which is defined as the recommended adult dose for the main indication. For patients who were prescribed nonaspirin NSAIDs, we calculated the proportion of prescriptions for the alleged safer agents (ibuprofen, naproxen, diclofenac with misoprostol and the newer selective COX-2 inhibitors [6, 7, 31–34]). In this study, selective inhibitors of the COX-2 isoenzyme were considered as NSAIDs with a safer profile. Furthermore, the proportion of contraindicated prescriptions with concomitant use of a coumarin or an oral glucocorticosteroid and the proportion of contraindicated prescriptions with concomitant use of an antiulcer drug were compared per person before admission and after the first discharge date for patients who received contraindicated prescriptions during both time periods.

Patient- and physician-related factors

The following baseline patient characteristics were tested as potential determinants for receiving a contraindicated prescription: gender, age, a history of rheumatoid arthritis or osteoarthritis, the presence of cardiovascular risk factors (a history of stroke or myocardial infarction; prevalent angina pectoris, hypertension, or claudicatio intermittens) at the time of cohort enrolment, a history of NSAID use, the number of visits to a general practitioner as well as the number of visits to a medical specialist during 1 year before cohort enrolment, an impaired cognitive function at the time of cohort enrolment, defined as a score of 25 or below on the Mini-Mental State Examination (MMSE) [35]. As potential physician-related determinant were considered: the prescriber being a general practitioner or a medical specialist.

Statistical analyses

Paired *t*-tests were used to compare paired data from the time periods before the first admission date and after discharge. These tests were done with rejection of the null hypothesis at a level of significance of $P<0.05$. Multivariate analysis with potential determinants for receiving a prescription for aspirin as antithrombotic agent or an NSAID as analgesic after the first discharge date, were separately performed with the Cox proportional-hazards regression method. Apart from gender and age, factors were included in the model if they changed the point estimate by more than 5%.

Results

Of the 7983 patients, 163 were admitted to the hospital for one or more serious gastrointestinal complications during the study period. Sixty-three patients were excluded from the analysis, 18 because they died shortly after or during the admission, and 45 because they had a history of less than 1 year of follow-up after enrolment. Hundred patients were enrolled in the cohort, seven of them were admitted more than once for the diagnoses under study. The total observation time was 148.6 person years, which equals an average of ($\pm$s.e. mean) of 1.5 ± 0.2 years of follow-up per patient. The patients in the cohort had an average age of 75 years. The majority was female (56%). Prescriptions of contraindicated drugs, i.e. an NSAID after the index date, were identified in 73 patients (73%). Fifty-one percent were prescribed aspirin of whom the large majority used it as an antithrombotic agent, and 49% were prescribed a nonaspirin NSAID after the first discharge date. Twenty percent of the patients used more than one NSAID on one or more occasions after discharge from hospital. The numbers in the five mutually exclusive classes of outcome were as follows: 27% received no prescriptions for NSAIDs after the first discharge date, 26% received a prescription for an NSAID alone, 4% received a prescription for an NSAID in combination with a coumarin or an oral glucocorticosteroid without antiulcer drug, 35% received a prescription for an NSAID in combination with an antiulcer drug and 8% received a prescription for an NSAID in combination with a coumarin or an oral glucocorticosteroid and an antiulcer drug. Of the 43% who received an antiulcer drug in combination with the contraindicated drug, 28% received H_2-antihistamines, 12% prostaglandins and 60% proton pump inhibiting drugs. The mean time ($\pm$s.e. mean) between the discharge date and the first prescription for aspirin was 467 ($\pm$82) days and for nonaspirin NSAIDs 519 ($\pm$88) days. Of the 51 patients who were prescribed aspirin after discharge, 34 received also one or more prescriptions for aspirin before admission to the hospital. The mean duration of the last prescription before admission was 75.0 days in these patients and declined to 55.6 days after discharge (Table 1). In course of time after discharge the duration of a prescription for aspirin increased and the difference in duration before admission and after discharge disappeared. The mean dosage of aspirin was significantly higher after discharge than before. The PDD/DDD ratio rose from 0.84 before admission to 0.97 after discharge. After discharge significantly more prescriptions for aspirin were prescribed in combination with antiulcer drugs: the mean proportion of prescriptions

Table 1 Characteristics of contraindicated prescriptions before admission and after discharge.

	Before admission	*After discharge*	*95% CI of the difference*
Aspirin ($n=34$)			
Mean duration of 1 prescription (days)	75.0	55.6	5.4, 33.4
Mean duration of prescriptions (days)	66.5	67.0	−10.5, 9.5
Mean PDD/DDD ratio	0.84	0.97	−0.2, −0.02
Mean proportion of prescriptions with concomitant use of risk increasing drugs	0.10	0.17	−0.2, 0.02
Mean proportion of prescriptions with concomitant use of antiulcer drugs	0.19	0.60	−0.6, −0.2
Non aspirin NSAIDs ($n=38$)			
Mean duration of 1 prescription (days)	20.1	14.2	−1.8, 13.7
Mean duration of prescriptions (days)	23.7	19.4	−1.7, 10.3
Mean PDD/DDD ratio	1.29	1.20	−0.1, 0.3
Mean proportion of less toxic NSAIDs	0.30	0.66	−0.2, −0.6
Mean proportion of prescriptions with concomitant use of risk increasing drugs	0.20	0.18	−0.1, 0.2
Mean proportion of prescriptions with concomitant use of antiulcer drugs	0.11	0.61	−0.7, −0.3

for aspirin with concomitant use of antiulcer therapy rose from 0.19 before admission to 0.60 after discharge. Of the 49 patients who were prescribed nonaspirin NSAIDs after discharge, 38 received also one or more prescriptions for these drugs before admission. The mean duration of the first prescription for a nonaspirin NSAID after discharge was shorter than the duration of the last prescription before admission, although the difference was not significant (Table 1). This also applies to the mean duration of all prescriptions for nonaspirin NSAIDs before admission and after discharge. The PDD/DDD ratio declined from 1.29 before admission to 1.20 after discharge, a non-significant difference. After discharge a significantly higher proportion of all prescriptions for nonaspirin NSAIDs were for less toxic agents. The mean proportion of less toxic NSAIDs rose from 0.30 before admission to 0.66 after discharge. As with aspirin prescriptions, the mean proportion of nonaspirin NSAID prescriptions with concomitant use of antiulcer therapy rose significantly after discharge. A proportion of 0.11 of these prescriptions were prescribed together with an antiulcer drug before admission, against a proportion of 0.61 after discharge. The results of the univariate analysis revealed two determinants which were significantly associated with the prescription of aspirin as antithrombotic agent, namely a history of aspirin use before cohort enrolment (RR = 3.6 (95% CI 2.0, 6.6)) and the presence of cardiovascular risk factors (RR = 3.8 (95% CI 1.2, 12.4)). In the multivariate analysis, the only remaining factor with prognostic influence on prescription of aspirin was a history of aspirin use before cohort enrolment (RR = 3.2 (95% CI 1.7, 5.9)). For nonaspirin NSAIDs, the results of the univariate and multivariate analysis revealed a history of nonaspirin NSAID use before cohort enrolment as the only significant determinant (RR adjusted = 4.9 (95% CI 1.9, 12.7)). Sixty-one percent of the first aspirin prescriptions after discharge originated from a general practitioner and 39% from a medical specialist. Eighty-six percent of the first nonaspirin NSAID prescriptions after discharge were prescribed by a general practitioner and 14% by a medical specialist.

Discussion

The major finding of this study is that contraindicated NSAIDs are prescribed to a great extent in elderly people despite the fact that this group is more vulnerable to gastrointestinal complications. Our study population had serious peptic ulcer disease as exemplified by the fact that 11% of the eligible population died during the admission before cohort enrolment. Almost three-quarters of the remaining high-risk group received a contraindicated NSAID. Of these individuals, 34 and 38% had had serious gastrointestinal haemorrhage after aspirin and nonaspirin NSAIDs, respectively.

Our study has two potential limitations. Firstly, the prevalence of the use of contraindicated drugs is probably slightly underestimated in this study. Pharmacy records are usually considered as the most complete resources for drug exposure [36–38], but most over-the-counter drugs are not recorded in computerized data bases. However, our primary goal was to study the frequency with which NSAIDs were prescribed by doctors in patients with serious contraindications for these drugs. Secondly, we excluded persons with less than 1 year of follow-up because of death, removal or end of the study period, because they were too shortly eligible for receiving a contraindicated drug. If we include this group, however, the percentage of persons receiving a contraindicated drug decreased from 73 to 58, which is still substantial. The association between gastrointestinal toxicity and NSAIDs is widely known, for aspirin especially in analgesic doses.

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Although low doses of aspirin have been shown to effectively inhibit the production of thromboxane A_2 in platelets and are associated with less gastrointestinal toxicity than high doses [39–41], a recent study suggests that also patients on low doses of aspirin have a high incidence of gastrointestinal mucosal injury [42].

Why do doctors prescribe NSAIDs to patients with a history of peptic ulcer disease? Prescribing contraindicated NSAIDs is only acceptable if there is a very strong indication, and if the drug is prescribed in combination with gastroprotective drugs (e.g. secondary prevention of myocardial infarction with aspirin). In our study only 39% of the patients who received aspirin after hospitalization received their first prescription in combination with an antiulcer drug. Reasons for prescribing NSAIDs could be that physicians did not assess contraindications for use of NSAIDs because they lacked knowledge of the relevant risks, underestimated the importance of these risks, or simply forgot to assess these risks [43]. The mean dose of the nonaspirin NSAIDs was above the recommended level, and did not decrease significantly after discharge because of gastrointestinal complications. Physicians seem to be aware of the fact that there are NSAIDs with a safer profile as they doubled the proportion of these agents after hospitalization. The proportion of contraindicated prescriptions which were used in combination with antiulcer drugs increased significantly after hospitalization to 60%. Although a critical note seems appropriate because 28% of the patients who received gastroprotection, received H_2-antihistamines, for which there is very little evidence from the literature [44, 45].

Considering the above, it seems most likely, that prescribers are often aware of the adverse effects of NSAIDs but underestimate the importance of the risks despite the fact that they are explicitly mentioned in the product information. The alternative explanation may be that they lack other treatment options. Evaluation of the appropriateness of drug treatment decisions is hardly possible in our study because indications for therapy were not documented. It is remarkable that a history of rheumatoid arthritis or osteoarthritis is no significant determinant for receiving a contraindicated prescription. Apparently, these drugs are mainly prescribed for uncomplicated arthralgia.

The most prudent approach to prescribing NSAIDs is to scrutinize for possible contraindications, to consider carefully if the benefit outweighs the risk and to use NSAIDs only after potentially safer alternatives have been tried. If an NSAID must be used, the lowest effective dose of the least toxic drug should be taken for the shortest possible period and appropriate concomitant antiulcer therapy should be prescribed with every prescription of an NSAID, especially in those who have several risk factors for serious gastrointestinal complications.

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