Omeprazole, other antiulcer drugs and newly diagnosed gout

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Aims Case-reports describing patients who developed a first episode of acute gout while being treated with the proton pump inhibitor omeprazole led us to compare incidence rates of newly diagnosed gout cases among omeprazole, ranitidine and cimetidine users.

Methods We conducted a cohort study with a nested case-control analysis using the UK-based General Practitioner Research Database (GPRD). The study encompassed a cohort of more than 53 000 subjects who received some 185 000 prescriptions for the three study drugs.

Results Neither current omeprazole *vs* recent use (age- and sex-adjusted relative risk 1.1, 95% CI 0.5–2.1), nor current omeprazole use in comparison with current use of the two histamine H_2-receptor blockers was associated with an increased risk of developing newly diagnosed gout. Higher age (RR 2.4, 95% CI 1.5–3.9), male gender (RR 5.4, 95% CI 2.8–10.3), high body mass index (OR 3.3, 95% CI 1.0–10.9) and hypertension (OR 4.5, 95% CI 1.6–12.9) were all important risk factors for gout.

Conclusions While other known risk factors were significantly associated with gout, current omeprazole use was not materially associated with an increased gout incidence.

Keywords: omeprazole, ranitidine, cimetidine, gout

Introduction

Two recent case-reports of first-time acute gout during use of the proton pump inhibitor omeprazole have raised concern over a possible causal association [1]. Both patients developed gout within the first 2 weeks of omeprazole treatment. In addition to these reports, the manufacturer has received 21 spontaneous reports over the last 10 years of patients suffering from gout during omeprazole treatment [2].

No formal studies have been published evaluating the frequency of newly diagnosed gout among users of omeprazole or other ulcer healing drugs. We therefore sought to evaluate the possible relation of omeprazole to the occurrence of acute gout using the large UK-based General Practitioner Research Database (GPRD). We conducted a retrospective cohort study with a nested case-control analysis to assess and compare incidence rates of first-time diagnoses of gout in omeprazole, ranitidine and cimetidine users, three antiulcer drugs which are used for similar gastrointestinal diseases associated with hyperacidity.

Methods

Over four million people in the UK are enrolled with selected general practitioners who use office computers provided by Value Added Medical Products and who have agreed to provide data for research purposes. General practitioners have been trained to record medical information in a standard manner and to supply it anonymously. The information recorded includes demographics, medical diagnoses, and all drug prescriptions, since the doctors generate prescriptions directly with the computer. Hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. A modification of the Oxford Medical Information System classification is used to enter medical diagnoses. For the purpose of this study, OXMIS- codes have been mapped onto ICD-codes. The recorded information on drug exposure and on diagnoses in the GPRD is of high quality and is satisfactory for drug safety studies [3–7].

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Cohort definition

Subjects with a first-time prescription for either omeprazole, ranitidine or cimetidine between January 1, 1992 and March 31, 1995, who were (1) 20 to 60 years old at the time of their first prescription for a relevant study drug, (2) permanent patients in the practice, and (3) had a prescription history of at least 1 year were eligible to be cohort members. Subjects with a history of gout or any rheumatic diseases, cancer, AIDS, cystic fibrosis, chronic heart disease, chronic renal disease, renal transplantation, chronic alcoholism or some other drug abuse, or severe liver disease were excluded.

Exposure definition

Based on the number of tablets prescribed and the number of tablets to be taken per day according to the GP, we calculated 'current' and 'recent' exposure time for each of

the three study drugs. Person time was accumulated as current exposure for the length of the prescription plus an additional 7 days, separately for each of the three study drugs. Time from day 8 after the length of the prescription was accumulated as recent exposure time, until the first of the following occurred: a new prescription for a study drug was recorded (then current exposure began again), the subject became a case, died, left the practice, or the predefined, arbitrarily chosen follow-up time of a maximum of 360 days ended. We accumulated all recent exposure time into one person-time stratum, regardless of the most recently taken antiulcer drug. We arbitrarily chose this approach under the assumption that the risk of developing gout would be—if present at all—strongest among current users, and that the risk would decline after stopping the therapy, regardless of the most recently taken study drug. We calculated incidence rates of gout attacks among current users of each of the three study drugs, and an incident rate for all cases combined in the recent exposure time. To make sure that we did not overlook an association between recent use of a particular study drug and the risk of developing gout, we also evaluated the distribution of cases which occurred in the recent use period (with regard to timing and most recently taken study drug).

Case definition and ascertainment

We identified all people in the study with a first-time clinical diagnosis of gout (ICD-code 274.0) during current or recent drug use. In addition to the clinical diagnosis recorded on computer, they had to have either a recorded increased abnormal high serum urate level, or a newly started drug treatment for gout (allopurinol, colchicine, probenecid, indomethacin or other potent non-steroidal anti-inflammatory agents), or both. We categorized cases into 'confirmed', if they had both a recorded elevated abnormal urate level and new drug treatment for gout, and into 'probable', if only the clinical diagnosis and new prescriptions for drugs to treat gout were recorded, but not the blood urate level.

In order to validate the computer recorded diagnoses of gout, we sent for medical records for a sample of 38 antiulcer drug exposed subjects who had an entry of a first-time diagnosis of gout in the computer record. Among 'confirmed' and 'probable' cases, 10/10 and 24/28, respectively, were confirmed through medical records and laboratory results. This led to an overall acceptance rate of 34/38 (90%) which was considered satisfactory for the purpose of this study. We also did the nested case-control analysis for 'confirmed' and 'probable' cases separately, which resulted in a closely similar finding.

Any information with regard to the study drugs was suppressed in the computerized patient profiles when we identified potential cases.

Cohort analysis

To obtain incidence rates, we aggregated person-time for all cohort subjects across age-and gender-strata, using the above defined definitions for current and for recent drug use. We performed Poisson regression with the generalized linear interactive modeling (GLIM) package [8], taking recent use as the reference group and controlling for gender and age (<50, $>=50$ years).

Nested case-control analysis

A nested case-control analysis was carried out in order to further evaluate covariates such as body mass index (<25, 25–29.9, $30+$ kg m^{-2}, or unknown), smoking status (non-, ex-, current smoker, or unknown), the presence of a diagnosis of hypertension, having a past history of use of one of the three study drugs other than the one currently used at the index date, use of diuretics, and indication for the antiulcer drug (functional disorders, oesophagitis, peptic ulcer or gastritis, duodenal ulcer or duodenitis, hiatus hernia, irritable bowel syndrome, or other).

This part of the analysis was restricted to cases and controls who were current users of one of the three study drugs at the 'index date' (date when the first gout diagnosis was recorded for the case). Up to eight controls per case from the base population, matched on age, sex and calendar time (by using the same index date as we identified for the corresponding case), were selected at random from the same set of practices from which the cases were derived. The same exclusion criteria for cases were also applied to controls. We used conditional logistic regression (SAS) to estimate relative risks (OR) and 95% confidence intervals of current omeprazole and current ranitidine use as compared with the arbitrarily chosen reference group of current cimetidine use.

Results

Cohort analysis

The entire cohort encompassed 53 588 subjects who filled 65 329 prescriptions for omeprazole, 63 498 for ranitidine, and 56 225 for cimetidine. We identified 63 cases with a first-time diagnosis of gout, 24 among current drug users, and 39 among recent users. There were 10 cases in 5731 person-years of omeprazole exposure, nine cases in 6721 person-years of ranitidine exposure, five cases in 6546 person-years of cimetidine exposure, and 39 cases in 27 607 person-years of recent exposure across all three study drugs, resulting in age- and sex-adjusted relative risks (RR) of 1.1 (95% CI 0.5–2.1) for omeprazole, 0.8 (95% CI 0.4–1.7) for ranitidine, and 0.5 (95% CI 0.2–1.3) for cimetidine, as compared with recent use.

There was no substantial pattern of distribution among the 39 cases which occurred in the common recent use person-time strata across all study drugs, neither with regard to timing, nor with regard to the most recently taken study drug.

Higher age ($>=50$, as compared with <50 years) resulted in a RR of 2.4 (95% CI 1.5–3.9), adjusted for sex- and drug exposure to the study drugs. The risk of developing gout was significantly higher for males as compared with females with a RR of 5.4 (95% CI 2.8–10.3), adjusted for age- and drug exposure to the study drugs (Table 1).

Table 1 Incidence rates and relative risks for gout in the study population ($n = 53,588$).

Exposure	*Person-time*	*Cases*	*Crude incidence rates*	*RR (95% CI)* ⋆
Recent use ⋆⋆	27 607 years	39	1.4/1000 years	1.0
Current use				
Omeprazole	5731 years	10	1.7/1000 years	1.1 (0.5–2.1)
Ranitidine	6721 years	9	1.3/1000 years	0.8 (0.4–1.7)
Cimetidine	6546 years	5	0.8/1000 years	0.5 (0.2–1.3)

⋆RR adjusted for age (<50, $>=50$) and gender ⋆⋆Reference group.

Nested case-control analysis

The mean age of the 24 cases and 182 controls was 48.5 years. The relative risk estimates for current omeprazole and current ranitidine use, as compared with current cimetidine use, were 1.5 (95% CI 0.4–5.1) and 1.4 (95% CI 0.4–5.3), respectively, adjusted for age, sex and calendar time (by matching) as well as for body mass index and presence of hypertension in the regression analysis (Table 2). Subjects in the highest body mass index category were at a significantly higher risk of developing gout as compared with those in the lowest body mass index category, yielding an adjusted RR estimate of 3.3 (95% CI 1.0–10.9). Having a diagnosis of hypertension was also significantly associated with the risk of developing gout with an adjusted RR estimate of 4.5 (1.6–12.9) (Table 2). Current smoking, indication for the ulcer healing drug, current use of diuretics and 'switching between study drugs in the past' were not associated with the outcome in univariate models and therefore not included in the final regression model.

We also evaluated the possibility of a duration effect among omeprazole users. Short-term exposure of less than 30 days, as compared to longer-term use, did not result in an elevated RR estimate (OR 0.4, 95% CI 0.1–2.4).

Discussion

Current short-term omeprazole use has been associated in two published case-reports [1] as well as in 21 spontaneous adverse drug event reports to the manufacturer [2] with the onset of acute gout. (The manufacturer estimates a total number of about 200 million prescribed treatment courses. [2]) Our results do not indicate that current omeprazole use is associated with a substantially increased risk of developing gout, either in comparison with recent use, or in comparison with current use of the two histamine H_2-receptor blockers ranitidine or cimetidine. In addition to a comparison between current omeprazole and recent antiulcer drug use, we also compared current omeprazole use to current use of the two histamine H_2-receptor blockers, since these drugs are used for similar indications. We have chosen this study design to minimize the risk of observing a spurious association between omeprazole use and gout, which in fact could be a reflection of a potential relation of the underlying gastrointestinal disease to the occurrence of gout ('confounding by indication').

The incidence rate of newly treated gout in our large cohort of users of ulcer healing drugs was relatively low. Despite this fact, there is no evidence to assume that the lack of an omeprazole effect on the gout incidence in previously healthy subjects was due to small statistical power, since four previously known risk factors, namely 'higher age' and 'male gender' (in the cohort analysis), as well as 'hypertension' and 'overweight' (in the nested case-control analysis), could in fact be identified as important risk factors for gout in our study population.

While there is no substantial evidence to support the hypothesis that omeprazole use is consistently associated with an increased risk of developing gout, we cannot exclude the possibility that omeprazole may rarely cause or trigger gout in particular individuals, although there is no obvious plausible biological mechanism.

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Table 2 Relative risk estimates (OR) for current drug exposure, body mass index and hypertension.

		Cases	*Controls*	*OR (95% CI)* ⋆
Cimetidine⋆⋆		5	50	1.0
Omeprazole		10	72	1.5 (0.4–5.1)
Ranitidine		9	60	1.4 (0.4–5.3)
Body mass index	<25 kg m^{-2}⋆⋆	6	61	1.0
	25–29.9 kg m^{-2}	8	60	1.4 (0.4–5.3)
	30+ kg m^{-2}	8	21	3.3 (1.0–10.9)†
	Unknown	2	40	—
Hypertension	No⋆⋆	15	167	1.0
	Yes	9	15	4.5 (1.6–12.9)†

⋆Adjusted for all the other variables in the table ⋆⋆Reference group †$P<0.05$.

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