The risk of acute pancreatitis associated with acid-suppressing drugs

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Aims To assess the risk of acute pancreatitis associated with use of acid-suppressing drugs.

Methods We conducted a retrospective cohort study with a nested case-control design within the General Practice Research Database (GPRD) in the United Kingdom. The cohort included 180 178 persons aged 20–74 years, who had received at least one prescription of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole from January 1992 to September 1997 and who did not have major risk factors for pancreatic diseases. Patients with a computerized medical history compatible with idiopathic acute pancreatitis were validated through review of medical records. For the nested case-control analysis 1000 controls were randomly selected from the study population.

Results We identified 88 potential cases of idiopathic acute pancreatitis. Medical records were available for 86. After review of these records 36 cases of acute pancreatitis were confirmed. Seven cases occurred during nonuse, corresponding to a background incidence rate (IR) of 4.4/100 000 person-years (PY). Six cases occurred during current use of ranitidine (IR 10.5/100 000 PY), five patients were current users of cimetidine (IR 13.9/100 000 PY), and three were current users of omeprazole (IR 7.8/100 000 PY). There were no cases among current users of famotidine, lansoprazole, or nizatidine. Relative risk (RR) compared with nonuse and corrected for age, gender, calendar year and use of medication known to be associated with acute pancreatitis was 1.3 (95% CI: 0.4,4.1) for ranitidine, 2.1 (95% CI: 0.6,7.2) for cimetidine, and 1.1 (95% CI: 0.3,4.6) for omeprazole.

Conclusions The results of this study do not support an association between acute pancreatitis and the use of acid-suppressing drugs, although a substantial increase in risk cannot be excluded with confidence.

Keywords: acute pancreatitis, acid-suppressing drugs, pharmacovigilance, epidemiology

Introduction

Several drugs have been implicated as possible causes of acute pancreatitis [1–3]. Most information on drug-induced acute pancreatitis is derived from anecdotal case-reports, and very little is known about the incidence and mechanisms of drug-induced acute pancreatitis.

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Cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, and omeprazole are extensively used in the treatment of peptic ulcer disease, and reflux oesophagitis. Adverse drug reactions affecting the central nervous system, kidneys, haematological system, gastrointestinal tract and the cardiovascular system have been attributed to these acid-suppressing drugs [4]. Cimetidine and ranitidine have been associated with acute pancreatitis in several case-reports [5–9]. Although a relationship was found between cimetidine and acute pancreatitis in rats [10], others have questioned this [11]. A record-linkage case-control study showed a crude significant association between cimetidine, ranitidine and acute pancreatitis,

but this association disappeared after adjustment for potential confounders [12].

In view of the controversies regarding the association between acid-suppressing drugs and acute pancreatitis, we conducted a retrospective cohort study in the General Practice Research Database (GPRD) in the United Kingdom (UK) to assess the risk of acute pancreatitis associated with the use of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, and omeprazole. A nested case-control analysis was conducted to examine in more detail the relationship between dose and duration of treatment, and the risk of acute pancreatitis.

Methods

Setting

Over 4 million residents in the UK are registered with general practitioners (GPs) who participate in the GPRD database. Medical data on these 4 million patients are continuously recorded and sent anonymously to the Office of National Statistics (ONS) for use in research projects. The computerized information contains demographic data, general practitioner consultations, referrals to consultants and hospitals, and all prescriptions issued. Indications for new courses of treatment are routinely stored in the database. In addition, the GP may record laboratory test results and other medical data in a free text comment field. A modification of the Oxford Medical Information System (OXMIS) classification is used to code specific diagnoses. Previous validation studies have found that over 90% of all referrals are recorded with a code that reflects the specialist's diagnosis [13, 14]. Drugs are coded according to a drug dictionary based on data from the Prescription Pricing Authority.

Source population

The source population consisted of all patients aged 20–74 years registered with 337 general practitioner practices with a permanent registration status during the study period January 1st 1992 and September 30th 1997.

Study cohort

The study cohort comprised all patients who received at least one prescription for cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole during the study period. We excluded all subjects with a history of acute pancreatitis or assessment of amylase before the date of the first prescription of a study drug. Patients with a diagnosis of cancer, alcoholism, biliary-or pancreatic diseases, and biliary or pancreatic surgical procedures within 5 years before study entry were also removed from the cohort. The remaining patients were followed from the date of the first prescription of one of the study drugs to the earliest of the following events: development of acute pancreatitis, assessment of amylase, one of the above mentioned clinical exclusion criteria, death, or end of the study period.

Case ascertainment

With a computerized search, we identified all study members who had a code for acute pancreatitis or a code for assessment of amylase. Subsequently, the complete computerized patient profiles blinded to drug exposure were manually reviewed to exclude all patients who were not referred to a specialist or hospital, all patients with a diagnosis of cancer, alcoholism, cholelithiasis, postoperative pancreatitis, other pancreatic disorders, and all patients in whom the diagnosis of acute pancreatitis was clearly excluded. Potential cases were those for whom the information in the patient profiles was compatible with idiopathic acute pancreatitis.

Case validation

We requested the medical records of all potential cases ($n = 88$) from the GPs. Received records were, independently and blinded to exposure, validated by all four authors. Based on this information, we excluded all individuals who had any evidence of alcohol abuse, cholelithiasis, chronic pancreatitis, malignant neoplasms, any other well-defined condition associated with the development of acute pancreatitis, or if symptoms of acute pancreatitis started before start of follow-up. Consensus was reached on all cases. The diagnosis was accepted when acute pancreatitis was explicitly mentioned in the discharge letter or when there was a clinical picture compatible with acute pancreatitis together with one of the following criteria: an increase in serum amylase or lipase of > 2 times the upper limit of normal, confirmatory evidence of acute pancreatitis at imaging procedures or at laparotomy or autopsy.

Cohort analysis

Person-time contributed by the study participants was divided into three mutually exclusive categories: current use, past use and nonuse. Current use was defined as the person time experienced during the length of an acid-suppressing drug prescription and 6 days thereafter. Past use included the period up to 365 days after the end of current use. Consequently, the time window of nonuse started at the end of past use. Incidence rates were calculated by dividing the total number of cases of acute pancreatitis by the corresponding total amount of person-

Table 1 Age and gender distribution: all numbers refer to number of acid-suppressing drug prescriptions.

	Total	*Male*	*Female*	*20–59years*	*60–74years*
Overall	1 545 921	52%	48%	51%	49%
Cimetidine	382 767	52%	48%	51%	49%
Famotidine	16 797	52%	48%	50%	50%
Lansoprazole	54 554	51%	49%	57%	43%
Nizatidine	49 079	51%	49%	51%	49%
Omeprazole	439 104	50%	50%	51%	49%
Ranitidine	603 620	53%	47%	49%	51%

time experienced. Ninety-five percent confidence intervals (95% CIs) were calculated based on a Poisson distribution.

Adjusted estimates of relative risks and its 95% CIs associated with current and past use as compared with nonuse were computed using a Poisson regression model with age, sex, and calendar year included in the model.

Nested case-control analysis

In order to explore dose and duration effects we performed a nested case-control analysis within the study cohort. All confirmed cases were used in the nested case-control analysis. The index date for the cases was the date of start of symptoms compatible with acute pancreatitis (same index date as used in the cohort analysis). In order to ascertain controls, a random date during the study period was generated for all study participants. A subject was an eligible control when the random date was included in his or her follow-up time. All exclusion criteria applied to the selection of the cases were also applied to the controls. From the list of eligible controls, we randomly selected 1000 controls and their random date was defined as the index date.

A participant was defined as a current user of one of the study drugs if the index date fell within the prescription period or when the end date of the last prescription fell within 6 days preceding the index date. A person was defined as a past user when the end date of the last consecutive prescription period fell within 7 to 371 days before the index date. A person was defined as a nonuser when none of the study drugs were used in the 371 days preceding the index date. Estimates of the odds ratios and their 95% CIs were calculated by logistic regression analyses comparing current and past use with nonuse of the individual acid-suppressing drugs. Age, sex, calendar year, and presence of other drugs associated with acute pancreatitis [3] (ACE-inhibitors, aminosalicylates, NSAIDs, oestrogens, frusemide, thiazide diuretics, valproic acid, and azathioprine) were included in the model to control for potential confounding.

Results

The study cohort consisted of 180 178 subjects who received at least one prescription of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole. Overall 1 545 921 prescriptions of these acid-suppressing drugs were written during the study period. The age and gender distribution of users of individual acid-suppressing drugs is presented in Table 1. There were 88 patients who had a computerized history compatible with an idiopathic

Table 2 Incidence rates of and relative risks of acute pancreatitis for individual acid-suppressing drugs.

	Person-years	*Cases*	*IR/10^5*	*Crude RR (95% CI)*	*RR (95% CI)*⋆
Non-users†	160430	7	4.4		
Current-use‡	141738	14	9.9	2.3 (0.9,5.6)	1.6 (0.6,4.2)
cimetidine	35966	5	13.9	3.2 (1.0,10.0)	2.3 (0.7,7.7)
famotidine	1551	0	–		
lansoprazole	4567	0	–		
nizatidine	4262	0	–		
omeprazole	38430	3	7.8	1.8 (0.5,6.9)	1.3 (0.3,5.3)
ranitidine	56961	6	10.5	2.4 (0.8,7.2)	1.7 (0.6,5.4)
Past use§	196356	15	7.6	1.8 (0.7,4.3)	1.6 (0.6,4.0)

⋆ Age, gender and calendar year were included in the Poisson regression model. † No use of an acid-suppressing drug in the 371 days preceding the index date. ‡ Use of an acid-suppressing drug on the index date or the 6 days preceding the index date. § Use of an acid-suppressing drug in days 7–371 before the index date.

episode of acute pancreatitis and for whom medical records were requested from the GPs. No information was received for two patients. Of the remaining 86 patients, 36 (42%) were classified as cases. The remainder were excluded because of alcohol abuse ($n=11$), cholelithiasis ($n=10$), cancer, other pancreatic disorders and post-operative pancreatitis in 11 patients. The diagnosis of acute pancreatitis was not confirmed in 11 patients. In the remaining seven patients onset of symptoms was before the start of follow-up.

The overall incidence rate of idiopathic acute pancreatitis during current use of acid-suppressing drugs was 9.9 (95% CI: 4.7,15.1) per 100 000 person years (PY), 7.6 (95% CI: 3.8,11.5) per 100 000 PY for past users, and 4.4 (95% CI: 1.1,7.6) per 100 000 PY for nonusers. After adjustment for age, gender and calendar year the RR was 1.6 (95% CI: 0.6,4.2) for current use and 1.6 (95% CI: 0.6,4.0) for past use of an acid-suppressing drug. Incidence rates and RRs for individual acid-suppressing drugs are given in Table 2.

Table 3 shows the results of the nested case-control analysis. Out of the 36 cases, 20 (56%) were male and the mean age was 61 years. Use of acid-suppressing drugs, gender and calendar year were not significantly associated with acute pancreatitis. The RR among current users of medications suspected to be associated with acute pancreatitis was 2.0 (95% CI: 1.0,4.2). Age was the only factor that was significantly associated with the occurrence of acute pancreatitis. Although not significant, the risk of acute pancreatitis was higher in the first month of acid-suppressing therapy: 2.3 (95% CI: 0.5,9.5) *vs* 1.1 (95% CI: 0.4,3.3) for long-term users. Exclusion of all current users of medications thought to be associated with acute pancreatitis did not change the risk estimates considerably (data not shown). A dose–response relationship was not observed in users of cimetidine or ranitidine (Table 4).

Discussion

In this large cohort study, we observed no significant increased risk of acute pancreatitis in users of acid-suppressing drugs. Cimetidine was the only individual acid-suppressing drug with a significantly increased risk of acute pancreatitis, but this association was no longer present after adjustment for potential confounders. There was a tendency towards an increased risk in the first month of treatment. The daily dosage of acid-suppressing drugs had no effect on the risk of acute pancreatitis.

The validity of epidemiological studies may suffer from selection bias, information bias or confounding. The presence of selection bias in this study is unlikely as identification of the study population was based on prerecorded prescriptions of acid-suppressing drugs, and therefore unrelated to the outcome of interest. Since drug

Table 3 Relative risk of acute pancreatitis associated with use of acid-suppressing drugs and other factors.

	Cases (n = *36*)	*Controls* (n = *1000*)	*OR (95% CI)*
Acid-suppressing drug			
Non-use†	7	306	
Current use‡	14	263	1.4 (0.5,3.6)
cimetidine	5	65	2.1 (0.6,7.2)★
omeprazole	3	69	1.1 (0.3,4.6)★
ranitidine	6	129	1.3 (0.4,4.1)★
Past users§	15	431	1.3 (0.5,3.3)★
Age			
20–59 years	12	639	
60–74 years	24	361	3.1 (1.5,6.4)
Gender			
Male	20	486	
Female	16	514	0.6 (0.3,1.2)
Year category‖			
1992–94	16	400	
1995–97	20	600	0.9 (0.5,1.8)
Pancreatoxic medication			
Non-use	21	760	
Current use	15	240	2.0 (1.0,4.2)

★Adjusted for age, gender, calendar year, and current use of other pancreatoxic medication.

† No use of an acid-suppressing drug in the 371 days preceding the index date.

‡ Use of an acid-suppressing drug on the index date or within the 6 days preceding the index date.

§ Use of an acid-suppressing drug in days 7–371 before the index date.

‖ End of study in September 1997.

Table 4 Influence of duration of acid-suppressing drug therapy on the risk of acute pancreatitis.

	Cases (36)	*Controls (1000)*	*OR (95% CI)**
Duration of antiulcer therapy†			
≤ 30 days	3	47	2.3 (0.5–9.5)
>30 days	11	234	1.1 (0.4–3.3)
Daily dose of cimetidine†, ‡			
<800 mg	2	22	2.2 (0.4–12.6)
≥ 800 mg	3	41	1.7 (0.4–7.7)
Daily dose of ranitidine†, §			
<300 mg	2	26	1.9 (0.3–10.3)
≥ 300 mg	4	100	1.1 (0.3–4.2)

*Adjusted for age, gender, calendar year, and current use of other pancreatoxic medication.
† Current use compared with nonuse.
‡ Data on daily dose of cimetidine was not available for two controls.
§ Data on daily dose of ranitidine was not available for three controls.

exposure was recorded before the onset of disease, recall bias is not present. Case histories concerning the relationship between H_2-receptor blockers and acute pancreatitis have been published since the late seventies, some of them proven by recurrence of symptoms after restart of treatment [6, 9]. Physicians may therefore diagnose acute pancreatitis more easily in patients using these H_2-receptor blockers. This diagnostic bias might therefore explain the nonsignificant increase in RR of cimetidine and ranitidine seen in this study. Patients with gastric acid related diseases will pay more visits to gastroenterological consultants and may therefore have acute pancreatitis more easily detected. However, as none of the acute pancreatitis diagnoses was made during routine check-ups of antiulcer treatment we expect diagnostic bias to play a minor role, if any, in explaining the results. Misclassification of outcome was limited due to review of the medical records of potential cases. Misclassification of exposure, for instance by noncompliance or dispensing of acid-suppressing drugs in hospital was probably nondifferential and would therefore have biased the risk estimates towards null. By restricting the study to people without major risk factors for acute pancreatitis we tried to control for confounding by these factors.

A recent study on the association between H_2-receptor antagonists and acute pancreatitis reported a nonsignificant RR of 3.7 for cimetidine and a nonsignificant RR of 3.1 for ranitidine [12]. In patients without risk factors for acute pancreatitis these figures were 2.0 and 2.5, respectively. The authors concluded that the higher RRs might be due to residual confounding. Prescribing of acid-suppressing drugs for prodromal symptoms of acute pancreatitis, sometimes referred to as protopathic bias could be an alternative explanation for the small increased risk seen in the former study and in our study. We tried to reduce the role of protopathic bias by taking the day of onset of symptoms as index date for patients with acute pancreatitis. The risk in the first 30 days of therapy was somewhat higher than the risk thereafter, albeit nonsignificantly. This could indicate either an acute effect or imperfect control of protopathic bias. However, protopathic bias cannot explain the different risk estimates for the different acid-suppressing drugs as this form of selection bias would affect all the acid-suppressing drugs alike.

In conclusion, the results of this study do not support an association between acute pancreatitis and the use of acid-suppressing drugs, although a substantial increase in risk cannot be excluded with confidence.

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