The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs

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Aims The objective of this study was to estimate the risk of acute liver injury associated with individual acid-suppressing drugs and assess the role of dose and duration of treatment.

Methods We used a nested case-control study design within a cohort of over 100 000 users of cimetidine, famotidine, omeprazole and ranitidine. The primary source of information was the General Practitioners Research Database. We identified 108 981 persons aged 20–74 years who received at least one prescription for cimetidine, famotidine, omeprazole, or ranitidine during 1990–93, and we ascertained the first occurrence of clinically acute liver injury referred to a specialist or admitted to a hospital.

Results After review of medical records, 33 patients were considered eligible cases of idiopathic acute liver injury with no fatal cases. The type of liver injury was hepatocellular in almost half of the cases, and 80% of all cases presented with jaundice. Twelve cases occurred among current users of cimetidine, five among ranitidine users and one in an omeprazole user. The absolute risk of acute liver injury associated with cimetidine was estimated to be slightly greater than one per 5000 users of cimetidine. The adjusted relative risk (RRs) and 95% CI of developing acute liver injury associated with current use of cimetidine compared to non-use was 5.5 (1.9–15.9), with omeprazole 2.1 (0.2–19.2) and with ranitidine 1.7 (0.5–5.8). In the absence of concomitant use of other hepatotoxic drugs, the RR with cimetidine was 14.4 (2.8–73.7). Among users of cimetidine, the risk was especially high in the first 2 months of starting therapy (RR: 11.3, 3.7–35.1) and at daily doses of 800 mg or greater (RR: 8.8, 3.0–26.0).

Conclusions Cimetidine was the individual anti-ulcer drug with the highest risk of developing symptomatic acute liver disease. Further data are required to confirm this finding. Our study indicates that there is a dose relationship and a short latent period between cimetidine treatment and acute liver injury.

Keywords: cimetidine, anti-ulcer drugs, liver

Introduction

H_2- receptor antagonists and proton pump inhibitors have now been used by hundreds of millions of patients worldwide. As with most drugs, available information on the hepatotoxic profile of this therapeutic group of compounds is primarily based on published case reports and national spontaneous adverse drug reactions reporting systems. In a comprehensive review of the literature by Lewis *et al.* in 1987 [1], they found 12 cases reported suggesting a possible relationship between ranitidine and acute hepatitis, and nine cases reported with cimetidine. The authors concluded that hepatic injury from these drugs was similarly rare. Another review [2] also published in 1987 suggested that the comparative incidence of hepatotoxic effects of all types following ranitidine therapy in general clinical use appeared to have exceeded that for cimetidine during the early corresponding period in its history. These are discordant conclusions derived from a similar set of data. Clinical data on adverse hepatic effects of other H_2-receptor blockers to date are scanty [3].

Omeprazole is a substituted benzimidazole that inhibits gastric acid secretion by interference with the proton pump on the secretory membrane of the parietal cell. A study published in 1983 raised concern over hepatotoxicity where 10 individuals out of 32 had mild elevations in liver transaminases [4]. However, none of the subsequent clinical studies confirmed this suspicion [5].

In view of the uncertainty on the relative risk of acute liver injury associated with individual H_2-receptor blockers and omeprazole, we performed an observational study which included more than 100 000 patients in order to identify the forms of acute hepatic injury associated with

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acid-suppressing drugs. We compared the risk of clinically serious acute liver injury associated with use of cimetidine, famotidine, omeprazole and ranitidine utilizing the General Practitioners Research Database (GPRD) in the UK. A case-control study design nested within the cohort of patients exposed to the four anti-ulcer drugs was conducted to examine in more detail the relation between dose and duration of treatment, and the risk of acute hepatitis.

Methods

Source population

The GPRD database contains computerized information entered by approximately 2000 general practitioners in the UK [6]. Data on about 4 million patients are continuously recorded and sent anonymously to the Office of Population Censuses and Surveys (OPCS). OPCS organizes this information in order to be used for research projects. The computerized information includes demographics, details of every general practitioner consultation, notes of specialist referral and hospital admission, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer. A previous validation study of the GPRD database has documented that over 90% of all referrals are entered on the general practitioners' computers with a code that reflects the specialist's diagnosis [7, 8]. An additional requirement for participating practices is inclusion of the indication for all new courses of treatment. A modification of the OXMIS classification system is used to code specific diagnoses [9], and a drug dictionary based on data from the Prescription Pricing Authority is used to code drugs.

Study cohort definition

The study period started on 1, January 1990 and ended on 30, November 1993. Patients between the ages of 20 and 74 years, with a 'permanent' registration status and who received a prescription for cimetidine, famotidine, omeprazole or ranitidine within the study period, were identified. All subjects with one of the codes (liver injury outcomes) listed in Table 1 prior to the date of their first prescription were excluded. Persons who had a code before study entry indicating cancer, other liver disease, jaundice, gallbladder or pancreatic disease, congestive heart failure, alcoholism, rheumatoid arthritis, sarcoidosis, systemic lupus, Crohn's disease or ulcerative colitis, were also removed from the cohort. The remaining patients were followed from the date of entering the study cohort until the earliest of the following events: occurrence of liver injury codes (Table 1) or any of the clinical exclusion codes, pregnancy, death or end of the study period.

Case ascertainment

We identified among the study cohort members all those with a code suggestive of liver disorder (Table 1). Patients not referred to a specialist or not admitted to a hospital were excluded. Next, we reviewed manually the patients' computerized profiles to select those for whom we requested medical records from their general practitioners. For subjects that had recorded normal liver function tests (LFTs) or minor elevations in LFTs (less than twice the upper limit), viral infection (serologically confirmed), cholelithiasis or congestive heart failure, records were not requested. All these steps were carried out blind to drug exposure data.

Table 1 Oxmis Codes Used In Case Ascertainment.

Oxmis code	*Diagnosis*
070F	Fulminant hepatitis
570XX	Hepatitis/liver necrosis
573XX	Other liver disorders
576 A	Obstructive jaundice
785CP	Pale stools
7851XX	Enlarged liver
7852XX	Jaundice
9779PN	Drug-induced jaundice
K501XX	Liver biopsy
L1151	Bilirubin serum level
L1151NA	Bilirubin serum level abnormal
L3260	Liver function test
L3260AB	Abnormal liver function test
L3262AB	Biochemical liver dysfunction
L3263AB	Abnormal liver enzymes
L3263H	Liver enzymes raised
L3264AB	Abnormal hepatic function
L4720N	Alkaline phosphatase level
L109H	ALT raised
L110H	AST raised
L1002CR	Aspartate aminotransferase level raised

Case validation

Two of the authors and a specialist in hepatology reviewed the medical records blinded to exposure status and with patient personal identifiers suppressed. Complete agreement was reached on case status after discussion. We classified patients as non-cases when they did not present with liver injury according to our criteria or when they had other liver disorders, cancer, cholelithiasis, viral hepatitis confirmed with serologic tests, congestive heart failure, alcoholism or a well-defined systemic condition affecting the liver. The following case definition of liver injury was used [10]: an increase of more than two times the upper limit of the normal range in alanine aminotransferase (ALT), or a combined increase in aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin, provided one of them was twice the upper limit of the respective normal range. The liver injury was considered acute if the clinical and laboratory signs had lasted less than 6 months from the date of onset. The type of liver injury was designated hepatocellular when there was an increase more than twice the upper limit of the normal range in ALT alone or $R \geq 5$, where R is the ratio of serum activity of ALT over serum activity of AP, or cholestatic when there was an increase of over twice the upper limit of the normal range in AP alone or $R \leq 2$, or mixed when $2 < R < 5$.

Exposure definition

We defined three periods of exposure related to use of antiulcer drugs: current use, past use and non-use. The time window of current use encompassed the days of drug therapy prescribed by the general practitioner. Past use referred to the period up to 90 days after the end of current use. Consequently, the time window of non use started at the end of past use.

Nested case-control analysis

All confirmed cases were used in the nested case-control analysis. To all the subjects in the study cohort, we assigned a random day within the study period. A subject was accepted as an eligible control when the random date was included between her/his date of study entry and end of follow up. From the list of eligible controls, we randomly selected 1000 controls and their random day became the index date for the nested analysis [11]. Unconditional logistic regression was done to compute estimates of relative risk and 95% confidence intervals (CI) of acute liver injury associated with current use of individual antiulcer drug compared with non use. Age, sex, calendar year, gastrointestinal morbidity and use of concomitant hepatotoxic drugs were introduced in the model to control for potential confounding. Table 2 shows a group of drugs recognized to be hepatotoxic. The table was constructed using information from a recently published textbook that summarizes existing data on the hepatic effects of drugs [12]. Separate models were run to ascertain whether the risk associated with individual antiulcer drugs varied according to the presence or absence of concomitant use of hepatotoxic drugs. Additionally, we examined dose- and duration-response relationship among users of cimetidine. Estimates of relative risk for other hepatotoxic drugs were also calculated.

Table 2 List of recognized hepatotoxic drugs.

Allopurinol
Amoxicillin-clavulanic acid
Azathioprine
Carbamazepine
Chlorpromazine
Cloxacillin
Cotrimoxazole
Dextropropoxyphene-paracetamol
Erythromycin
Flucloxacillin
Haloperidol
Hydralazine
Imipramine
Isoniazid
Ketoconazole
Mesalazine
Methotrexate
Nitrofurantoin
NSAIDs
Olsalazine
Phenobarbitone
Phenytoin
Prochlorperazine
Quinine
Rifampicin
Sulphasalazine
Tetracycline
Thioridazine
Trimethoprim
Valproate

Results

We initially identified 108 981 members of the study cohort who received 746 670 prescriptions of the four antiulcer drugs during the study period (Table 3). Men received 54% of the total number of prescriptions and the sex distribution was similar among the four antiulcer drugs, as was the age distribution. The average number of acid-suppressing prescriptions was 6.9 per user. The use of omeprazole was for shorter duration (four prescriptions per user). There were 185 patients who had a computerized history compatible with a potential episode of acute liver injury, and for whom medical records were requested from the GPs. In 12 subjects, either no information was received, or it was insufficient to ascertain case status. Seventy seven patients had normal LFTs or minor elevations and 63 presented some co-morbidity partly responsible for the liver disorder such as chronic liver disease, infectious hepatitis, cancer or high alcohol consumption. There remained 33 patients who met all our criteria for case definition.

There were 21 men (64%) out of 33 cases and the median age of all cases was 60 years (range 27–73). Eight patients (24%) were admitted to hospital. No case resulted in a fatal outcome. About 80% (26 patients) presented with jaundice. The remaining seven patients had abdominal pain, general malaise and/or nausea and vomiting. The main clinical and laboratory features of the 33 cases are summarized in Table 4. The pattern of liver injury was cholestatic in eight cases, mixed in 10, and hepatocellular in 15. There were six cases of acute liver injury during the period of no use of antiulcer drugs, resulting in a crude background rate of 5.4 per 100 000 person-years.

The adjusted estimates of relative risk and 95% CI of acute liver injury were 5.5 (1.9–15.9) for current cimetidine, 2.1 (0.2–19.2) for current omeprazole and 1.7 (0.5–5.8) for current ranitidine (Table 5). Adjusting for the same factors, the risk of acute liver injury was increased by three with use of potentially hepatotoxic drugs. Age was not an independent risk factor and men had a slightly greater risk than women. Severity of gastrointestinal morbidity did not alter the risk of developing acute liver injury.

Table 3 Distribution of users and prescriptions by antiulcer drug.

Antiulcer drug	*Subjects* (n)	*Prescriptions* (n)
Cimetidine	52,820	261,224
Famotidine	2,524	15,390
Omeprazole	23,175	92,082
Ranitidine	55,988	377,974
Total*	108,981	746,670

*23% of patients received two or more individual antiulcer drug.

Table 4 Clinical and laboratory findings and exposure status of 33 cases.

Pattern⋆	*ALT*†	*AlkPh*†	*Exposure*‡	*Latency*§
C	2.2	1.9	Non use	–
C	9.0	6.4	Non use	–
C	3.8	10.4	Non use	–
M	13.3	5.5	Non use	–
M	12.7	3.5	Non use	–
M	3.7	1.4	Non use	–
C	5.0	3.0	Cimetidine	732
C	3.6	1.8	Cimetidine	13
M	3.3	1.1	Cimetidine	85
M	20.0	8.0	Cimetidine	8
M	24.1	5.6	Cimetidine	47
M	6.9	2.2	Cimetidine	15
H	19.9	3.0	Cimetidine	174
H	23.2	1.3	Cimetidine	41
H	43.2	2.1	Cimetidine	6
H	6.6	1	Cimetidine	4
H	8.7	1.3	Cimetidine	10
H	6.6	0.4	Cimetidine	3
H	9.5	1.1	Omeprazole	359
C	2.9	2.5	Ranitidine	97
M	3.5	1.7	Ranitidine	38
M	10.0	2.1	Ranitidine	5
H	18.2	1.4	Ranitidine	103
H	10.0	1.8	Ranitidine	3
M	5.7	2.1	Multiple	–
H	2.1	0.3	Multiple	–
C	1.5	3.2	Past use	–
C	2.7	3.0	Past use	–
H	21.3	2.5	Past use	–
H	30.3	2.8	Past use	–
H	8.5	1.1	Past use	–
H	41.5	3.0	Past use	–
H	7.4	1.0	Past use	–

⋆Pattern of liver injury; C, cholestatic: M, mixed: H, hepatocellular.
†Multiplier of upper limit of normal value of ALT (alanine aminotransferase) or AlkPh (alkaline phosphatase).
‡Cimetidine, omeprazole and ranitidine mean that the patient was currently exposed to one of these drugs. Multiple indicates that the patient was currently exposed to an antiulcer drug with a prescription for another antiulcer drug whose supply overlapped with the current one. See methods for remaining definitions.
§Interval in days since the beginning of treatment among current individual antiulcer drug users.

Table 5 Relative risk of acute liver injury associated with use of anti-ulcer drugs and other factors.

	Cases (n = *33*)	*Controls* (n = *1000*)	*Relative risk (95% CI)*
Anti-ulcer drug			
non-use	6	371	1.0
current cimetidine	12	112	5.5 (1.9–15.9)
current omeprazole	1	26	2.1 (0.2–19.2)
current ranitidine	5	154	1.7 (0.5–5.8)
multiple and past use	9	337	1.6 (0.6–4.7)
Age (years)			
20–59	15	599	1.0
60–74	18	401	1.2 (0.6–2.5)
Sex			
Male	21	551	1.0
Female	12	449	0.6 (0.3–1.2)
Hepatotoxic medication			
non-use	17	791	1.0
current use	16	209	3.1 (1.5–6.5)
Gastrointestinal morbidity			
dyspesia or other ill-defined			
GI disorders	19	501	1.0
peptic ulcer disease	14	499	0.7 (0.4–1.5)

⋆Estimates derived from a logistic regression model that included age, sex, calendar year, gastrointestinal morbidity and use of antiulcer drug and hepatotoxic medication.

Table 6 Influence of duration and daily dose of cimetidine on the risk of acute liver injury.

	Cases	*Controls*	*Relative risk (95% CI)*⋆
Daily dose of cimetidine†			
<800 mg	0	40	– 0.0–6.2
≥800 mg‡	11	64	8.8 3.0–26.0
Duration of cimetidine therapy			
First 2 months	9	43	11.3 3.7–35.1
After 2 months	3	69	2.1 0.5–9.0

⋆Estimates derived from logistic regression models that included age, sex, calendar year, and use of antiulcer drugs and hepatotoxic medications. Risk with cimetidine compared with non-use.
†Data on daily dose of cimetidine could not be calculated for one case and eight controls.
‡All 11 cases and 61 out 64 controls were receiving 800 mg.

The crude incidence rate (IR) and 95% confidence interval (CI) for acute liver injury associated with cimetidine was 2.3 (1.3–4.0) per 10 000 users, or 1 case in 4100 users (95% CI: 1 in 2400 to 1 in 7000). In the absence of concomitant use of other hepatotoxic drugs, the relative risk associated with cimetidine use was 14.4 (95% CI, 2.8–73.7) compared with non-use. The adjusted relative risk and 95% CI for current cimetidine compared with current use of all the other antiulcer drugs studied was 3.4 (1.2–9.4). Table 6 shows that among cimetidine users, there was an increase in risk with higher daily doses. Users of 800 mg and above had an almost nine-fold increased risk compared with non users. Also, the relative risk was much greater at the beginning of therapy (11.3: 95% CI, 3.7–35.1) than subsequently (2.1: 95% CI, 0.5–9.0). Among the list of other hepatotoxic medications, use of amoxycillin/clavulanic acid, chlorpromazine, flucloxacillin and trimethoprim presented a relative risk greater than the one observed with use of cimetidine (data not shown). Also, there were 86 persons in the study cohort who took rifampicin and/or pyrazinamide as antituberculous treatment. Of these, one patient went on to develop overt hepatitis.

Discussion

In this large cohort study, we observed that use of acid-suppressing anti-ulcer drugs was associated with an increased risk of acute liver injury and that patients exposed to cimetidine presented the highest risk among individual anti-ulcer drugs. The risk during cimetidine treatment was about

six times greater than during non-use and persisted after control for a number of risk factors. Cases of acute liver injury occurred only at high daily doses of cimetidine (800 mg), and its occurrence was frequently related to the beginning of cimetidine treatment. We did not find age and sex to be important independent risk factors. Adjustment for other potential confounders did not materially alter the increased risk with cimetidine. The incidence rate was slightly greater than one per 5000 users of cimetidine. In an outpatient postmarketing surveillance study that enrolled approximately 10 000 patients on cimetidine treatment soon after FDA approval, no liver disorders were reported [13, 14]. However, selection bias could have compromised the validity of those results. Physicians were contacted and asked to select from their practice lists 10 patients. Furthermore, patients already receiving cimetidine prior to the data of enrollment were recruited into the study provided that they had not been hospitalized during the preceding course of treatment.

The background incidence rate during non use of 5 per 100 000 person-years in our study was close to the rate of 4 per 100 000 person-years observed in a recent study in Canada [15].

The three major limitations in epidemiological studies are selection bias, information bias and confounding. The identification of the cohort population through the computer files of the GPRD database with a sampling method unrelated to the outcome renders selection bias an improbable explanation for the observed estimates of risk. Recall bias was not present as data on drug use was recorded on computer files before the onset of disease. The possibility of referral bias and diagnostic suspicion bias is unlikely because of the following considerations. As the large majority of cases presented with jaundice (both exposed and non-exposed to anti-ulcer therapy), it seems reasonable to assume that such patients would have been recognized and referred independently of the individual drug used, as liver dysfunction is listed in the product information of all four anti-ulcer agents. Moreover, the review of the limited literature on hepatic injury associated with anti-ulcer drugs did not single out any one drug in particular as more hepatotoxic than the others [1, 16]. Nor do UK spontaneous ADR reporting data signal this possibility: the proportions of all ADRs which have affected the hepatobiliary system are 2.9% for cimetidine, 2.7% for ranitidine and 1.6% for omeprazole, marketed a decade later (Committee on Safety of Medicines, personal communication). A case could be made that some of the patients developing liver injury straight after the start of anti-ulcer therapy had been treated with anti-ulcer drugs for prodromal signs of hepatic injury. However, such protopathic bias should work in a similar manner across all study drugs. When we restrict cases to those with a latency greater than 1 week among current users, there remain 9 out of 12 (75%) for cimetidine and 4 out of 6 (66%) for the other anti-ulcer drugs. Actually, the analysis of this subset of cases would further accentuate the increased risk observed with cimetidine compared to other anti-ulcer drugs. Neither peptic ulcer disease nor other acid-suppressing treatment indication nor other co-morbidities that we examined proved to be independent risk factors for hepatic injury. Hence, these conditions could not materially confound the association between anti-ulcer drugs and liver injury, and confounding by indication of anti-ulcer therapy was not apparent in our study population.

The mechanism of hepatic injury induced by H_2-receptor blockers and omeprazole is not known. Clinical trials performed with cimetidine and ranitidine showed an increasing trend of elevations in serum aminotransferase levels with higher intravenous doses of both drugs [1, 17]. Apart from one study [4], users of omeprazole have been found to experience a low frequency of abnormal liver enzyme elevations [5, 18]. In our study the relative risk of acute liver injury with anti-ulcer drugs was highest with cimetidine, and was significantly different from all other anti-ulcer drugs combined ($P=0.019$). However, there was no prior hypothesis of such a difference. It is therefore uncertain whether cimetidine has greater potential than other anti-ulcer drugs to induce hepatic injury or whether this finding has occurred by chance.

In conclusion, this study provides further evidence of an association between anti-ulcer drugs and acute liver injury, and has raised the hypothesis that the risk may be greater with cimetidine than other acid-suppressing drugs. Of particular interest was the finding of a dose relationship and a short latent period in cimetidine users. Clearly, clinical acute liver injury is fairly rare in patients treated with anti-ulcer drugs, and more data are required to confirm whether cimetidine carries a greater risk than that of other acid-suppressing drugs [19].

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