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ORIGINAL REPORT

Omeprazole-Induced Hepatotoxicity? A Case Report

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SUMMARY

Case report — We observed a serious symptomatic hepatocellular liver injury in an 85-year-old man treated with omeprazole for many years. Peak values for AST, ALT and AP were 1542 U/l (normal range 14–50), 1236 U/l (11–60) and 154 U/l (30–125) respectively. Abdominal CT scan was normal and viral serologic testing was negative. Omeprazole was discontinued and liver enzymes normalized in 12 days. The patient was known to suffer from ischemic heart disease and had had a myocardial infarction 6 months previously. He was reexposed to omeprazole and the level of liver enzymes rose again and normalized after stopping omeprazole. Despite the improvement of his liver function, the patient died 5 days later due to chronic congestive heart failure.

Discussion — Five cases of omeprazole-induced liver injury have been reported to the Swiss Drug Regulatory Agency since 1990, among them two of cholestatic hepatitis and one of hepatic failure. The WHO Data Base has collected 13,630 ADRs related to omeprazole, with more than 80 cases of hepatitis, 60 of jaundice and about 40 of cholestatic hepatitis. In contrast, only one case of severe symptomatic hepatotoxicity is described in the literature. Clinical studies reported minimal increase of liver enzymes only, in 1–5% of cases.

Conclusion — This case with reexposure, together with those reported internationally, suggests that hepatitis is a possible but obviously rare complication of omeprazole treatment. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — omeprazole; anti-ulcer agents; adverse drug reactions (ADRs); liver diseases

INTRODUCTION

Acute liver injury is fairly rare in patients treated with anti-ulcer drugs.[1] With short- and long-term use the extensively prescribed hydrogen/potassium ATPase inhibitor omeprazole is generally considered not to be hepatotoxic.[2–4] Clinical studies reported only minimal increase of liver enzymes, in 1–5% of cases.[5] We present a case of serious symptomatic hepatocellular liver injury possibly related to omeprazole. Reexposure of the patient was followed by a relapse of hepatic cytolysis which normalized after omeprazole was discontinued.

CASE REPORT

An 85-year-old man was admitted to hospital because of nausea, vomiting, anorexia and general malaise of 3 weeks' duration. Physical examination showed evidence of dehydration, weight loss but no jugular distension or pedal oedema. The vital signs were a blood pressure of 140/90, regular pulse of 80/min and respiration 20/min. His past medical history was significant for non-insulin-dependent diabetes mellitus, ischemic heart disease, myocardial infarction, gastric ulcer, cholecystectomy and prostatic adenocarcinoma treated with radiotherapy and bilateral orchidectomy. He was not an alcoholic and had stopped smoking 40 years previously. Medications prior to admission and used for a long time included furosemide 40 mg 2 × /week p.o., isosorbide dinitrate 40 mg/day p.o., digoxin 0.125 mg/day p.o., omeprazole 20 mg/day

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p.o., acenocoumarol p.o. and glipizide 5 mg/day p.o. Laboratory results revealed hepatocellular liver injury with peak values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 1542 U/l (normal range 14–50) and 1236 U/l (11–60) respectively (see Table 1 and Fig. 1). Other laboratory results included haemoglobin 11.9 g/dl (14–18) and haematocrit 37.3% (40–52). Other haematologic values and serum creatinine, total serum creatinine-kinase were within the norm. Abdominal ultrasound and CT scan showed no obstruction of the common bile duct or signs of liver metastasis but did show bilateral pleural effusions consistent with congestive heart failure. Electrocardiogram showed a regular sinus rhythm and Q-waves consistent with the anterolateral myocardial infarction sustained 6 months previously, but no acute ischemia. Viral serologic testing (HIV-1, HIV-2, CMV, EBV and hepatitis A, B, C and Delta) was negative. Omeprazole, furosemide and glipizide were discontinued and liver enzymes normalized in 12 days. At that time the following medications were still being taken by the patient: acenocoumarol, digoxine and

Table 1 — Laboratory flow sheet

Liver enzymes (normal range in U/l)	Day 0*	Day 1†	Day 2	Day 4	Day 12	Day 14‡	Day 18§	Day 20	Day 28	Day 34‖
AST (14–50)	364	612	1542	290	42	65	672	235	68	—
ALT (11–60)	263	468	1236	708	111	97	400	558	132	—
AP (30–125)	—	112	—	—	—	—	—	—	184	—
LDH (187–443)	870	1641	2100	386	308	—	—	560	—	—
g-GT (0–56)	—	397	—	—	308	296	441	359	309	—
BILI tot (5–17)	—	18	—	29	34	23	33	37	23	—
BILI conj (0–3.5)	—	—	—	13	15	8	14	15	9	—
Amylase (70–235)	—	112	—	—	—	—	41	—	—	—

*Hospital admission. †Omeprazole is discontinued. ‡Rechallenge with omeprazole. §Omeprazole is discontinued. ‖Patient's death. AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; LDH, lactate dehydrogenase; g-GT, gamma glutamyl-transpeptidase; BILI tot, total bilirubin; BILI conj, conjugated bilirubin.

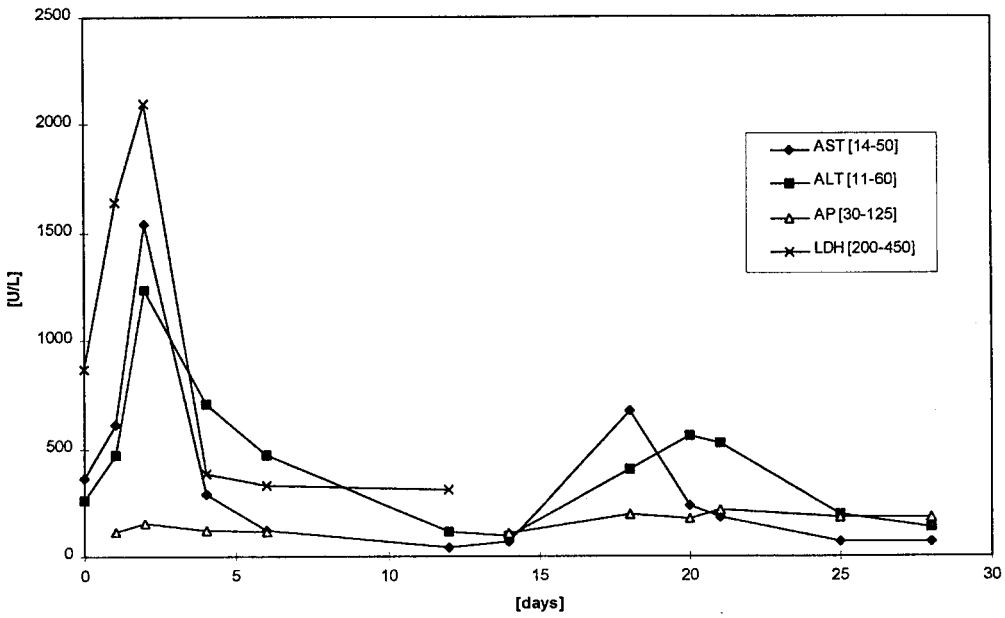

Fig. 1 — Liver enzyme values. Day 1, omeprazole is discontinued; day 14, reexposure to omeprazole; day 18, omeprazole is discontinued

isosorbide dinitrate. Omeprazole was again prescribed to the patient. Nausea, vomiting and moderate icterus reappeared within 48 h. Laboratory results performed 4 days after reexposure to omeprazole revealed a relapse of hepatic cytolysis. Omeprazole was therefore discontinued and a cardiology consultation requested to evaluate the possibility of a cardiac origin for the liver dysfunction. The cardiologist who examined the patient 5 days after reexposure to omeprazole (and 1 day after its discontinuation) observed no clinical signs of arrythmia, major hypotension or myocardial infarction. Echocardiography showed left ventricular dilatation with a giant aneurysm but no signs consistent with significant increase of right ventricular pressure. Ten days after discontinuation of omeprazole, liver enzymes were almost back to the normal range (see Table 1 and Fig. 1). Despite the improvement of his liver function, the patient died 2 weeks after discontinuation of omeprazole in acute congestive heart failure. An autopsy was performed the next day and revealed cardiomegaly and a left ventricular myocardial infarction estimated by the pathologist to have occurred 24 h before death; hepatic endofibrosis and stasis were noted and malignancy and metastatic disease were excluded.

DISCUSSION

We observed a symptomatic hepatocellular liver injury possibly related to omeprazole in a man treated with this drug for several years. A reexposure showing recurrence of the clinical symptoms and an increase of liver enzyme activity support this hypothesis. One might suggest that the observed liver cytolysis could be due to concurrent cardiac dysfunction because of the patient's known ischemic heart disease and the history of myocardial infarction 6 months previously. At the time of the hospital admission however, no clinical symptom of major hypotension, heart failure or arrythmia were observed. Blood pressure was normal (140/90), there was no jugular distension or pedal oedema and electrocardiogram confirmed regular sinus rhythm with no sign of ischemia. At the time of the reexposure to omeprazole the patient's heart condition was stable, with no change in blood pressure and pulse noted. The cardiologist, on the basis of his examination and echocardiography, performed 5 days after reexposure to omeprazole, specifically stated that a cardiac origin to the hepatic cytolysis seemed improbable. The patient's death occurred 2 weeks after omeprazole was discontinued and was due to a left ventricular myocardial infarction sustained within 24 h of death. It seems unlikely that the observed acute liver dysfunction was due to the patient's cardiac disease, although in the absence of continuous cardiac monitoring this cannot be totally excluded. The autopsy results also ruled out the diagnosis of malignancy or metastatic disease as a cause of the observed symptoms.

To our knowledge only one case of symptomatic hepatotoxicity is reported in the literature. This report described fulminant hepatic failure in a 62-year-old man 17 days after omeprazole was introduced.[6] Other short- and long-term clinical studies report only mild elevations of hepatocellular liver enzyme activity, even with high dose omeprazole.[4,5]

In contrast, a significant number of hepatic ADRs related to omeprazole are mentioned in national and international data bases. Three other cases of omeprazole-induced liver injury with a positive dechallenge have been reported to the Swiss Drug Regulatory Agency since 1990: one case of cholestatic hepatitis with jaundice, one of cholestatic hepatitis and one of hepatic failure. No rechallenge was performed in these patients. The time of exposure varied from 2 days to 9 months. In all these cases, other hepatotoxic drugs were used and stopped at the same time making the causal relationship more dubious. Of 13,630 ADR reports related to omeprazole recorded in the WHO Data Base, about 6.5% consist of hepatic and/or biliary dysfunction. More than 80 cases of hepatitis, 60 of jaundice and about 40 of cholestatic hepatitis have been reported (see Fig. 2).

Serious hepatic reactions are obviously rare events considering the frequency with which omeprazole is used around the world. In contrast with the results of clinical studies and with the number of published cases, the significant number of spontaneously reported cases seem to indicate that omeprazole hepatotoxicity is a possible complication of omeprazole treatment. A closer analysis of these cases would be necessary in order to have a complete understanding of the role of omeprazole in these hepatotoxic reactions.

Indeed, the mechanism of omeprazole-induced hepatotoxicity remains unclear. The cases reported to the Swiss Drug Regulatory Agency occurred at quite low doses. An idiosyncratic mechanism seems most likely but a dose-related ADR cannot be excluded. All these cases appeared in patients over

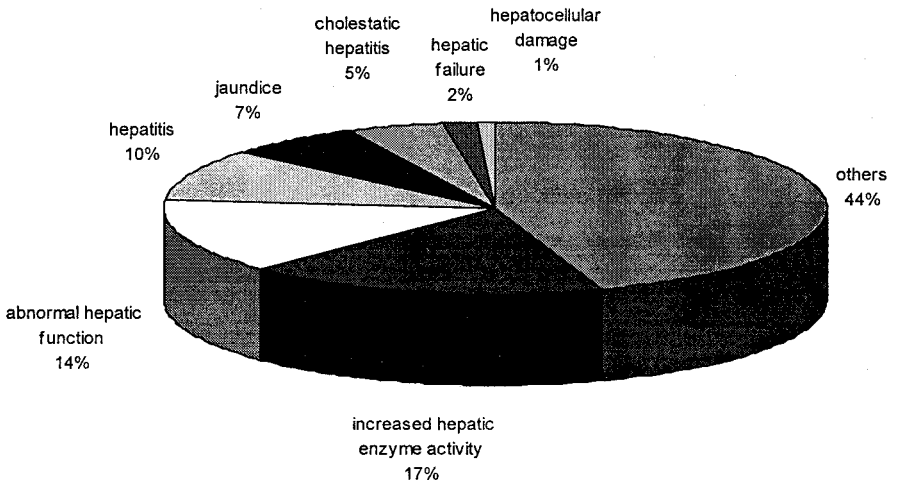

Fig. 2 — Hepatic ADRs ($n = 897$ cases) related to omeprazole reported in the WHO Data Base through March 1997

60 years of age and who were concurrently taking other potentially hepatotoxic drugs. A recent case–control study showed that age was not an independent risk factor for anti-ulcer drug-induced acute liver injury but that concurrent use of potentially hepatotoxic drugs could increase the risk by 3. The estimated adjusted relative risk of acute liver injury associated with omeprazole was 2.1.[1] However, this result is not significant when considering the 95% confidence interval (95% CI 0.2–19.2) and is not in favour of omeprazole-induced hepatotoxicity. Others studies will be necessary to assess the exact risk of omeprazole-induced hepatic reactions.

In our geriatric institution, 11% of the patients are treated with omeprazole. Polymedication with potentially hepatotoxic drugs and multiple co-morbidities are frequent in this very elderly population placing these patients at greater risk of hepatic adverse events. In this setting, adverse drug reaction is high on the list of potential causes of liver dysfunction and the clinical decision as to which drugs to stop can be very challenging as illustrated by this unusual case involving omeprazole in an elderly cardiac patient.

CONCLUSION

This case with relapse of hepatic cytolysis after reexposure to omeprazole suggests that hepatitis is a possible complication of omeprazole treatment. A significant number of cases are reported internationally but unfortunately, these reports do not allow definite conclusions as to the precise role of omeprazole in the reported hepatic reactions. Serious hepatic reactions are obviously rare events considering the frequency with which omeprazole is used around the world. Elderly patients may be at higher risk of adverse drug hepatic reactions due to the high frequency of polymedication with potentially hepatotoxic drugs and multiple comorbidities. Pharmacovigilance is important in recognizing unsuspected rare and serious ADRs, but can be very challenging in the geriatric population.

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