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Cimetidine increases serum mebendazole concentrations. Implications for treatment of hepatic hydatid cysts

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In eight patients (five with peptic ulcer disease and three with hydatid cysts), the [^{14}C]-aminopyrine breath test (ABT) and maximum serum concentration of mebendazole following a dose of 1.5 g of mebendazole three times daily were determined before and after treatment with cimetidine (400 mg three times daily for 30 days). Serum mebendazole concentrations were measured in blood samples taken 2 h after each drug intake. Cimetidine lowered the $^{14}CO_2$ specific activity (SA) at 1 h ($P < 0.01$) and increased the maximum serum concentration of mebendazole ($P < 0.01$). A significant correlation was found between SA at 1 h and the highest concentration of mebendazole before ($r = -0.71$, $P < 0.05$) and after ($r = -0.82$, $P < 0.05$) cimetidine ingestion. Combined administration of cimetidine and mebendazole resulted in the complete resolution of previously unresponsive hydatid cysts.

Keywords cimetidine mebendazole hydatid cysts

Introduction

In a previous report (Bekhti *et al.*, 1986), we showed that mebendazole may be metabolized by hepatic monooxygenases and behaves as an enzyme inducer. Thus, the use of an enzyme inhibitor, such as cimetidine, in non or poor responder patients suffering from hydatid cysts, could reduce the biotransformation rate of mebendazole, thereby, enhancing and prolonging its therapeutic effects. The aim of this preliminary study was to assess the influence of cimetidine on serum concentrations and therapeutic effects of mebendazole in patients with liver hydatid cysts.

Methods

Eight subjects, three men and five women, aged 21–55 years (mean ± s.d. = 39 ± 12 years) agreed to participate in this study. Informed consent was obtained. The study was approved by the University Ethics Committee. None of our patients had a history of alcoholism. None was receiving or had recently received hepatotoxic drugs or an enzyme inducer. Smoking habits were kept constant during the study. Five patients suffered from peptic ulcer disease; the other three patients (3, 4, 7) had hydatid cysts of the liver (Figure 1).

The aminopyrine breath test (ABT) was performed on day 0 according to the method described by Pauwels *et al.* (1982), and repeated on day 30 of cimetidine treatment (400 mg three times daily). The test was performed after an overnight fast. Each patient received 1.5 μCi of [^{14}C]-aminopyrine diluted in 5 ml NaCl intravenously. Patients were supine during the test. One hour afterwards, the exhaled $^{14}CO_2$ was collected in a bottle containing 2 mmol of hyamine and phenolphthalein, until the disappearance of the pink coloration indicating the neutralization of hyamine by 2 mmol of CO_2. The specific activity (SA) of the exhaled $^{14}CO_2$ was measured and expressed as the percentage of the administered dose kg^{-1}.

In patients with peptic ulcer, mebendazole was given at a dose of 1.5 g three times daily on day 0 and day 30 immediately after the ABT.

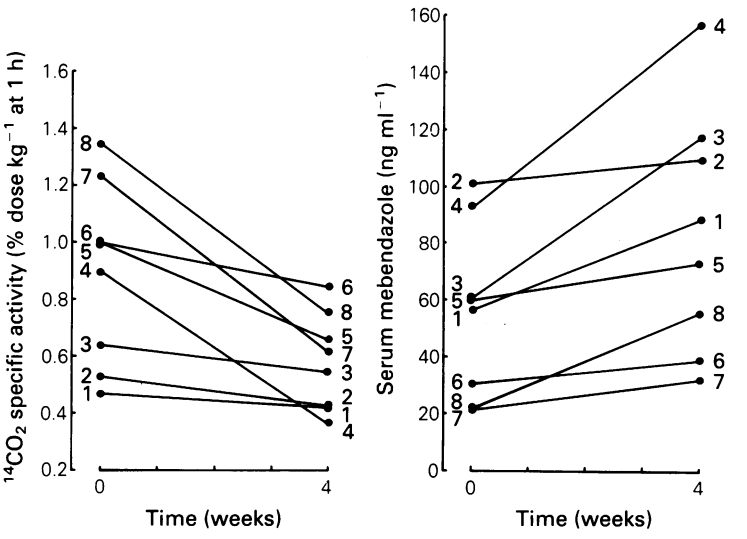

Figure 1 The effect of combined administration of cimetidine for 30 days and mebendazole on $^{14}CO_2$ specific activity at 1 h and serum mebendazole concentration in eight patients.

As regards patients with hydatid disease, mebendazole treatment was given for 30 days. Serum mebendazole concentration was measured in blood samples taken 2 h after each drug intake, using a specific radioimmunoassay procedure (Michiels *et al.*, 1982). Only the highest concentration value obtained after the three daily determinations of mebendazole was taken into account in this study.

In patients with hydatid cysts, the therapeutic effect of the combination cimetidine-mebendazole was assessed by ultrasound and computed tomography.

Statistical comparisons were made using Student's *t*-test for paired data. Significance was assumed at $P < 0.05$.

Results

In our eight patients, the intake of cimetidine during 30 days reduced $^{14}CO_2$ specific activity (SA) at 1 h (0.57 ± 0.17 *vs* 0.89 ± 0.32% of the administered dose kg^{-1}; $P < 0.01$) and increased the maximum serum concentration of mebendazole (82.3 ± 41.8 ng ml^{-1} *vs* 55.7 ± 30.2 ng ml^{-1}; $P < 0.05$) (Figure 1). The maximum serum drug concentration was correlated with SA at 1 h before ($r = -0.71$, $P < 0.05$) and after cimetidine administration ($r = -0.82$, $P < 0.05$).

Simultaneous administration of cimetidine resulted in a complete resolution of previously unresponsive multivesicular hepatic cysts in three patients (cases 3, 4, 7). In all cases, the maximum concentration of mebendazole increased after 1 month of cimetidine treatment (Figure 1). The subsequent follow up of patient 4 showed a further rise in serum mebendazole concentrations (Figure 2).

Discussion

Cimetidine is widely used in the treatment of peptic ulcer, but because of its ligand interaction with cytochrome P-450, it impairs the biotransformation of other drugs (Somogyi & Gugler, 1982; Sedman, 1984). In this report, the use of cimetidine has led to a reduction of $^{14}CO_2$ specific activity, and a rise of serum mebendazole concentrations suggesting a decrease of *N*-demethylation rate of [^{14}C]-aminopyrine as well as impairment of the biotransformation of mebendazole.

Luder *et al.* (1986) found higher fasting serum mebendazole concentrations in seven patients suffering from *Echinococcus multilocularis* and receiving cimetidine (1 g day^{-1}) concomitantly. This observation is in accordance with our study and suggests that the inhibitory effect of cimetidine may result in higher serum concentrations of mebendazole. According to Luder *et al.* (1986), this increase of mebendazole concentrations induced by cimetidine is too small to have a therapeutic effect on *E. multilocularis*. In contrast, we demonstrated in this study that com-

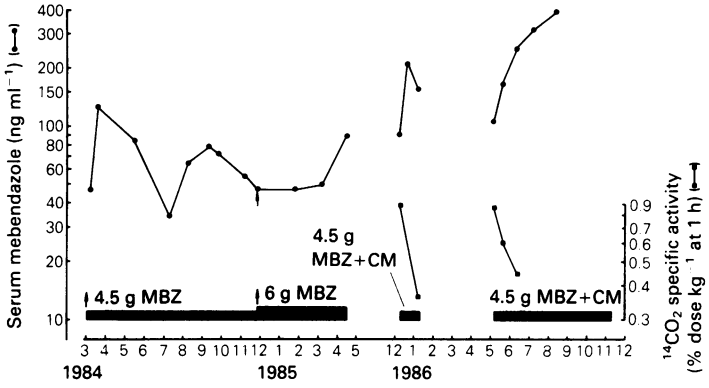

Figure 2 The effect of simultaneous treatment with cimetidine (CM) and mebendazole (MBZ) on maximum serum mebendazole concentration and the specific activity of exhaled $^{14}CO_2$ in a patient with poorly responsive multivesicular hydatid cysts of the liver (case 4).

bined administration of cimetidine and mebendazole at sufficient doses may result in therapeutic effects in patients with hydatid cysts unresponsive to mebendazole given alone. Our preliminary results suggest that addition of cimetidine to mebendazole may be of clinical benefit when the increase of mebendazole dosage does not result in a rise of serum drug concentration (Bekhti, 1985; Bekhti & Nizet, 1986). On the basis of these findings, we believe that failures of mebendazole treatment could often be due to insufficient serum and intracystic concentrations of mebendazole rather than to the use of an ineffective drug.

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