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Bioavailability of the antiemetic metopimazine given as a microenema

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The absorption of the antiemetic metopimazine (MPZ) given as a single dose of (a) 40 mg microenema, (b) 40 mg orally and (c) 10 mg as a 60 min i.v. continuous infusion was investigated in six healthy volunteers. Blood samples were drawn and the serum concentrations of MPZ and its acid metabolite were measured. The bioavailability of MPZ given orally and as enemas was 22.3 and 19.5% respectively. Partial avoidance of hepatic first pass metabolism was seen with the enemas, which in contrast to suppositories, seems to represent a reliable form of rectal administration.

Keywords antiemetics metopimazine bioavailability enemas

Introduction

The phenothiazine derivative metopimazine (MPZ) is a dopamine D_2-receptor antagonist [1] with significant antiemetic activity in patients receiving chemotherapy [2–4]. Oral MPZ is safe in single doses of 50 mg [5] and in repeated doses of 30 mg [4].

Oral administration of drugs is generally the route of choice [6], but in patients receiving cancer chemotherapy oral absorption is often compromised by nausea and vomiting. In a pilot study, administration of 50 mg suppositories of MPZ resulted in serum concentrations below the limit of assay detection. We therefore determined the bioavailability of MPZ given orally and as a single microenema.

Methods

Six healthy volunteers (median age 37 [34–56] years, four women) participated in three trials separated by a period of at least 1 week. Subject number 1 was a smoker and subjects 2–6 non-smokers. Volunteers fasted for 8 h before and for 4 h after dosage. Blood pressure was recorded at 0 and 480 min.

Trial (a): 40 mg MPZ as a single microenema

The microenemas contained 6.67 mg MPZ, 0.67 mg ascorbic acid, 1.10 mg sodium citrate and 4.50 mg sodium chloride in 1 ml water, pH: 4.1 (adjusted). The enemas were administered in a plastic syringe mounted with a 5 cm rectal probe, thereby ensuring the correct site of application and volume (6 ml) of the enemas. Blood samples were drawn at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360 and 480 min after MPZ. The serum was stored at $-20\,^{\circ}C$ until the time of analysis.

Trial (b): 40 mg MPZ as a single, oral dose

Procedure as in Trial (a). Blood samples were drawn at 0, 15, 25, 35, 45, 60, 90, 120, 180, 240, 300, 360 and 480 min after MPZ.

Trial (c): 10 mg MPZ i.v. as a 60 min continuous infusion

MPZ 10 mg was dissolved in 250 ml 0.9% sodium-chloride and administered as a 60 min continuous infusion using the Pharmacia Deltec, CADD-1 infusion pump. Blood samples were drawn at 0, 10, 20, 30, 45, 60, 65, 75, 90, 105, 120, 180, 240, 300, 360 and 480 min after start of infusion.

Analytical method and statistics

Serum concentrations of MPZ and its acid metabolite (AMPZ) were measured by h.p.l.c. [7]. Areas under the curves to 8 h AUC (0,8 h) were calculated by the linear trapezoidal rule. C_{max} and t_{max} were obtained by direct

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inspection of the data. Subject number 6 received a 20 mg microenema, and the AUC was therefore multiplied by 2. The two-tailed Wilcoxon matched-pairs test was used. Level of significance was 5%.

Results

Figure 1 shows mean serum concentrations of MPZ and AMPZ. The bioavailability of oral MPZ (median value of $AUC_{p.o.}/AUC_{i.v.}$ ratios normalized for dose) and of MPZ given as a microenema were 22.3 and 19.5% respectively (Table 1). The relative bioavailability of the microenema compared with oral MPZ was 91% (95% CI 48–160%). AUC (MPZ) values were not significantly different for MPZ given orally and as a microenema ($P=0.69$), but for AMPZ significantly lower AUC values were obtained with the enema ($P=0.03$). The median values of the ratio of AUC (AMPZ) to AUC (MPZ) were 2.5 following intravenous, 13.7 following oral and 6.2 following rectal administration (95% CI 1.6–3.7, 3.4–15.2 and 2.1–14.5, respectively). C_{max} (MPZ) was 128 ng ml^{-1} following the microenema *vs* 59 ng ml^{-1} after oral MPZ ($P=0.06$). t_{max} (MPZ) was consistently seen at 10 min when administered as an enema. Oral t_{max} was observed significantly later (53 *vs* 10 min, $P=0.03$). For the microenema significantly lower (AMPZ) C_{max} (193.5 *vs* 296 ng ml^{-1}, $P=0.03$) and an earlier t_{max} (60 *vs* 120 min, $P=0.03$) was observed.

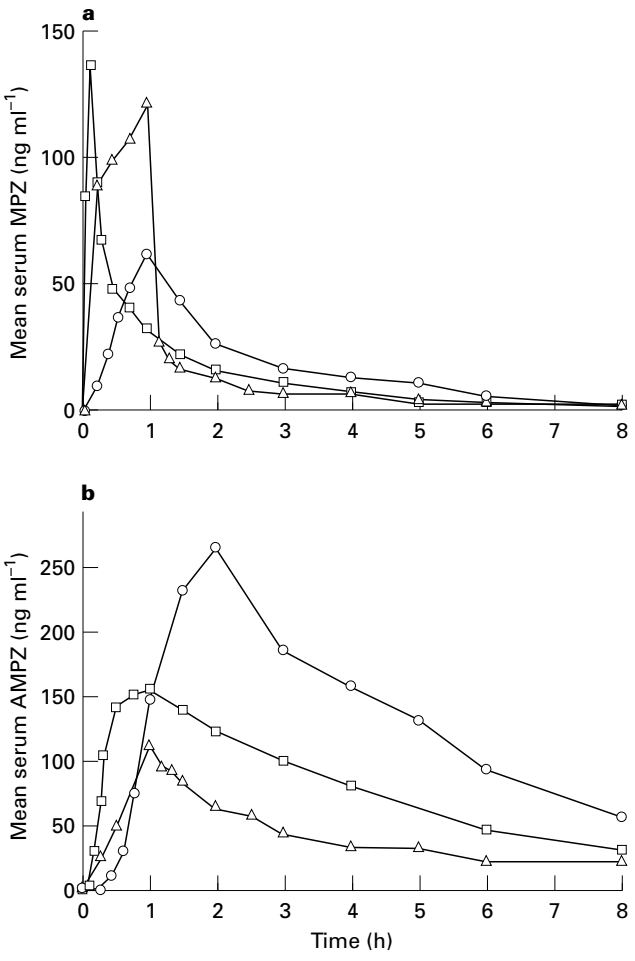

Figure 1 Mean serum concentrations of a) metopimazine (MPZ) and b) the acid metabolite (AMPZ) in six healthy volunteers receiving oral MPZ 40 mg (○), a microenema of MPZ 40 mg (□), and a continuous 1 h i.v. infusion of MPZ 10 mg (△).

Adverse events

The enemas did not cause local irritation in any of the volunteers. One subject felt uncomfortable 10 min after the 40 mg enema and had to lie down. The blood pressure was unchanged in the supine position, but decreased from 110 to 90 mmHg systolic in the standing position. Symptoms disappeared and blood pressure normalized within 20 min. Another case sensed moderate sedation after 40 mg orally. No other adverse events were reported.

Discussion

The extent of bioavailability of oral MPZ is reported to be 19% [5]. In another study based on urinary excretion, an oral bioavailability of 34% was obtained [8]. In our study the bioavailability of oral MPZ was 22.3% and of MPZ given as microenemas 19.5%. The absorption of drugs administered rectally has been the subject of several studies [6, 9]. Passive transport is the primary mechanism of rectal drug uptake. The solubility and partitioning properties of drugs given rectally are therefore of paramount importance [10].

MPZ is a high-clearance drug with a mean plasma clearance of 853 ml min^{-1} and a considerable first pass metabolism [5]. Rectal administration has the potential of partly avoiding hepatic first pass metabolism. There are, however, only a few studies reporting reduced hepatic clearance. The best example is lignocaine hydrochloride in microenema [11]. In our study AUC (MPZ) did not differ significantly after rectal and oral administration, while AUC (AMPZ) was significantly lower with the microenema. Furthermore the ratio of AUC (AMPZ) to AUC (MPZ) for the microenemas was 6.2, which is lower than the oral (13.7) but higher than the intravenous ratio (2.5). This is an indication of partial avoidance of first pass metabolism in the liver and/or gut wall. The absorption of a water-soluble drug from a microenema can be faster and of higher extent than from a suppository [11]. In a study comparing suppositories and oral MPZ 15 mg, the relative bioavailability of suppositories was only 46% and C_{max} only 10% of oral concentrations [12]. Furthermore, in a pilot study administration of 5 and 50 mg suppositories resulted in non-measurable serum concentrations of MPZ (unpublished observation). This is of concern because the commercially available 5 mg suppositories have been used as antiemetics for several years, although no randomized trials have investigated the antiemetic effect of this formulation. In addition the antiemetic effect of oral MPZ 5 mg is not different from placebo

Table 1 Median values (95% CI) of C_{max}, t_{max} and AUC of MPZ and AMPZ and dose normalized bioavailability

	Oral (40 mg)	*Rectal (40 mg)*	*i.v. (10 mg)*
MPZ			
C_{max} (ng ml^{-1})	59 (28–182)	128 (69–218)	108 (74–193)
t_{max} (min)	53 (25–90)	10 (10–10)	60 (45–60)
AUC (0,8 h) (ng ml^{-1} h)	91.5 (63.0–271.7)	118.5 (44.9–181.0)	139.6 (76.3–188.2)
Bioavailability (%) (dose normalized)	22.3 (11.8–38.1)	19.5 (14.1–29.8)	—
Relative bioavailability (%) (rectal/oral)	91 (0.48–1.60)		—
AMPZ			
C_{max} (ng ml^{-1})	296 (128–369)	194 (44–271)	106 (75–180)
t_{max} (min)	120 (90–300)	60 (30–120)	60 (60–80)
AUC (0,8 h) (ng ml^{-1} h)	1055.4 (744.6–1347.8)	671.1 (267.8–1154.1)	344.3 (228.1–386.5)

MPZ = metopimazine, AMPZ = acid metabolite, CI = confidence intervals.

[3], whereas doses of 10–30 mg result in significant antiemetic effect [2–4]. Microenemas, on the other hand, appear to represent a reliable form of rectal administration with a bioavailability comparable with that of oral MPZ (91%), and rapid absorption. The dose limiting adverse effect of MPZ given as enemas is, as with other formulations, orthostatic hypotension. The incidence is not correlated to high serum concentrations of MPZ or AMPZ, but is due to an interperson variability in the sensitivity to this drug event.

We conclude that rectal administered MPZ should be given as a microenema which could represent an especially appropriate administration form in nauseated patients and in patients where a rapid onset of antiemetic effect is required.

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