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Absorption rate and bioavailability of promethazine from rectal and oral dosage forms

Frits Moolenaar, Jaap G. Ensing, Ben G. Bolhuis and Jan Visser

Department of Pharmacology and Pharmacotherapeutics, State University of Groningen, Ant. Deusinglaan 2, 9713 AW Groningen, (The Netherlands)

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Promethazine is widely used as an antihistaminic, antiemetic, sedative and anaesthetic drug. Like other tertiary phenothiazines, it is readily absorbed from the gastrointestinal tract. After a single oral dose of 25 mg promethazine, absorption was found to be complete, although systemic availability of promethazine was very low ($F = 0.25$). This is consistent with an extensive first-pass effect, mainly resulting in S-oxidation of promethazine (Quinn and Calvert, 1976; Houston and Taylor, 1981). Especially its use as one of the most effective antiemetic drugs (Wood, 1979) may indicate that in the case of nausea and vomiting, rectal administration of promethazine may be valuable as a therapeutic measure. In addition, from the point of view of pharmacokinetics it is of interest to establish whether the hepatic first-pass effect will occur to the same extent as after oral dosing.

So far no detailed studies have been performed concerning rate and extent of rectal absorption of promethazine. We therefore designed a cross-over study in 6 healthy volunteers to investigate the nature of the rectal absorption process of promethazine, by measuring plasma concentrations of promethazine by means of HPLC analysis (Uges and Bouma, 1979) after administration of micro-enemas and fatty suppositories. To establish differences in rate and extent of absorption a comparison was made with orally administered solutions of promethazine-HCl (25, respectively 50 mg in 50 ml of water). Suppositories were prepared by mixing promethazine-HCl (Ph. Eur., Interpharm) with a molten base of Witepsol H15 (Interpharm), poured into brass moulds (3 ml) and stored in the refrigerator for one night before use. The weight of the suppositories was adjusted exactly to 3.0 g. They contained 25.0 mg of promethazine-HCl. The release characteristics in vitro of promethazine-HCl from Witepsol H15 suppositories were determined by the method of Schoonen et al. (1976). To maintain sink conditions the pH of the fluid in the release apparatus was kept at pH 5.0 (solubility at a higher pH range decreases very rapidly).

Coarse particles (50–100 μm) were selected to achieve an optimal release

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(Schoonen et al., 1979). About 85% of promethazine-HCl was released within 30 min. For rectal use, a solution was prepared containing 25 mg of promethazine-HCl in a 5-ml citrate/phosphate buffer (0.1 M, pH 5.0).

The in vivo experiments were initiated in the morning and the volunteers, ranging in age from 21 to 27 years, and in body weight from 58 to 84 kg, did not take in any food during the morning. No drugs were taken for two weeks prior to and during the study. Blood samples of 10 ml were taken at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 h after administration. From Table 1 and Fig. 1 it can be observed that promethazine was readily absorbed from the orally administered solutions containing 25 and 50 mg promethazine-HCl: the mean (n = 6) peak plasma concentration (C_{max}) being 11.2 and 39.2 ng · ml^{-1}, respectively, was reached within 3 h and the mean plasma half-life ($t_{1/2}\beta$) after administration of the 25 mg dose was calculated to be 12.7 ± 2.4 h. These results are in agreement with the kinetic data of Houston and Taylor (1981) following blood concentration–time profiles for promethazine and its sulphoxide metabolite after intravenous and oral administration of promethazine. We also presume an extensive first-pass effect, judging from the substantial non-linearity of the AUC–dose ratio with the two oral doses used. From Table 1 it can be calculated that the difference in $AUC_{0\text{-}24h}$ following oral administration of the 25 and 50 mg dosage forms is significantly ($P < 0.05$) more than a factor of two.

After rectal administration of the aqueous dosage form, the C_{max} of 10.2 ng · ml^{-1} was reached within 4 h; the difference was not significant as compared with oral dosing of 25 mg, nor did the half-life and the $AUC_{0\text{-}24h}$ differ significantly between these routes of administration. This indicates that rectal absorption is rather fast and fairly complete. In view of the similarity of the AUCs for both routes of administration, this also suggests that rectal dosing with promethazine dissolved in an aqueous

TABLE 1

ABSORPTION CHARACTERISTICS OF PROMETHAZINE (PMZ, MEAN ± S.D.) FROM DOSAGE FORMS AFTER RECTAL AND ORAL ADMINISTRATION OF PROMETHAZINE-HCl TO 6 HEALTHY VOLUNTEERS.

	Oral, 50 mg/ Sol., 50 ml	Oral, 25 mg/ Sol., 50 ml	Rectal, 25 mg/ Sol., 5 ml	Rectal, 25 mg/ Suppos., 3 ml
Plasma conc. PMZ (ng · ml^{-1}) at t =				
0.5 h	3.0 ± 1.9	1.3 ± 0.6	4.0 ± 1.2	1.0 ± 0.6
1.0 h	20.1 ± 7.1	3.1 ± 1.4	5.5 ± 1.7	1.5 ± 0.7
1.5 h	29.3 ± 7.3	7.0 ± 1.7	6.9 ± 1.9	2.9 ± 1.1
2.0 h	36.1 ± 5.8	10.0 ± 2.7	8.2 ± 1.8	4.1 ± 1.3
Number	6	6	6	6
C_{max}(ng · ml^{-1})	39.2 ± 8.2	11.2 ± 2.6	10.2 ± 2.4	7.5 ± 2.7
t_{max}(h)	2.5 ± 0.6	2.7 ± 0.6	3.4 ± 0.7	5.2 ± 0.9
$t_{1/2\beta}$(h)	13.7 ± 2.1	12.7 ± 2.4	14.5 ± 2.0	14.8 ± 3.4
$AUC_{0\text{-}24h}$(ng · ml^{-1} · h)	333.3 ± 45.9	111.7 ± 17.2	128.3 ± 14.8	78.0 ± 18.4

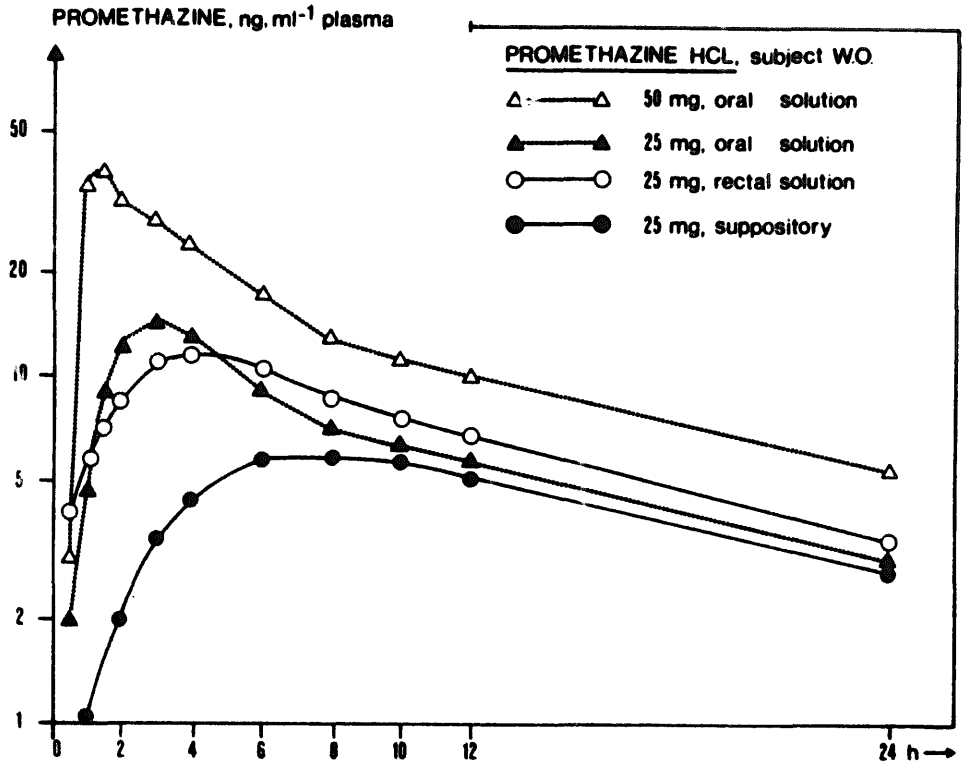

Fig. 1. Typical plasma concentration–time profiles for promethazine after oral and rectal administration in a human subject.

micro-enema does not guarantee a more pronounced by-pass of first-pass metabolism, as compared with oral dosing.

Another point of interest is the route-dependent absorption profile after oral and rectal administration of 25 mg promethazine-HCl: comparing the plasma concentrations 30 min after administration it appeared that the rectal solution did produce a significantly ($P < 0.05$) higher plasma level of promethazine when compared with oral dosing. A possible explanation for the less favourable oral absorption conditions during that first period of time may be that, apart from a possible anticholinergic action of promethazine on gastric emptying, protonation of the drug in the acid medium of the stomach will be more pronounced when compared with the rectal solution (pH 5.0). Since the pK_a of promethazine is 9.1, it is likely that oral absorption conditions are unfavourable for an initial fast transport.

In contrast to oral dosing the plasma concentration profile after rectal administration declined markedly after that first period of time (Table 1). A likely explanation may be that in view of the pH differences between the micro-enema used (pH 5.0) and the physiological pH in the human rectum lumen (pH 7.5–8.0), this pH deviation from the physiological value may be overcome by secretion of water and electrolytes (Crommelin et al., 1979; Moolenaar et al., 1981). Since it was observed in vitro that precipitation of promethazine from an acidic solution started above a pH of 6.2, it is evident that a possible secretion of neutralizing agents may lead to unfavourable rectal absorption conditions.

Support for this hypothesis can be found in the results presented in Fig. 2 showing that during the first 60 min a substantial difference in absorption rate occurred when 25 mg of promethazine-HCl was rectally applied in aqueous vehicles at different pHs.

In spite of a fast release in vitro, rectal absorption of promethazine-HCl from a fatty suppository resulted in a sustained absorption profile: the mean C_{max} value was significantly ($P < 0.05$) lower, whereas the mean t_{max} was reached later. A likely explanation for this hampered transport may be that due to the weakly alkaline pH conditions at the absorption site, the released HCl salt is partly converted into the poorly soluble promethazine base, resulting in less favourable absorption conditions.

As a result of the saturable metabolism of promethazine, it can be expected that the extent of first-pass metabolism will be more pronounced when the rate of absorption is slow. It is therefore not surprising that the relative bioavailability 24 h after administration of the fatty suppository differs significantly ($P < 0.05$) when compared to the oral and rectal solutions containing 25 mg of promethazine.

It is important to mention here that some discomfort was reported by the healthy volunteers, due to the irritating character of rectal dosing with 25 mg promethazine. This gastric disturbance occurred independent of the rectal dosage form chosen (micro-enema or suppository) and chemical quality (salt of base) used. In this respect it is important to note that a rectal dose of 50 mg was highly irritating for the volunteers.

From a therapeutic view-point it is concluded that promethazine, in principle, can be rectally applied. An aqueous micro-enema should be chosen, if a rapid ther-

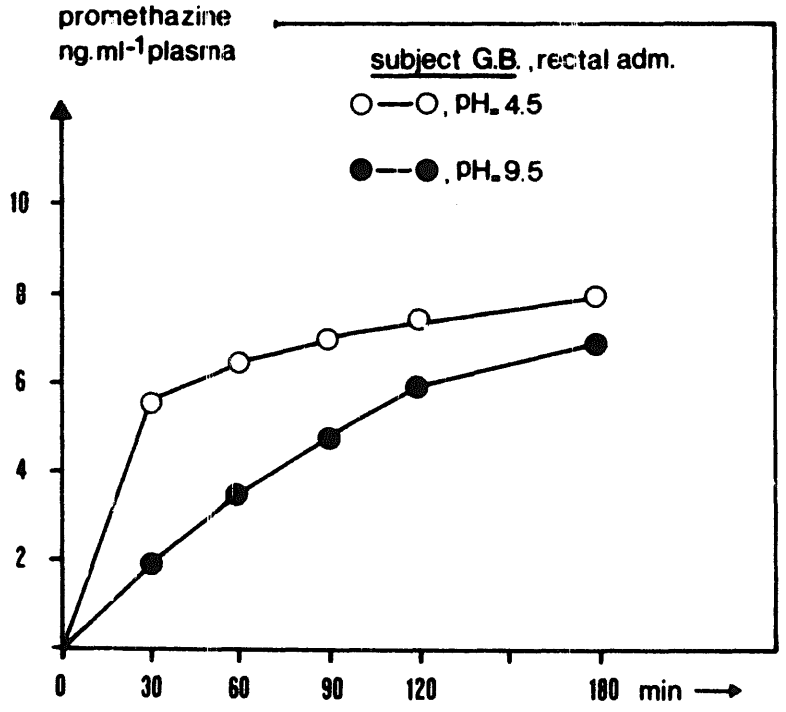

Fig. 2. Effect of the pH of the rectal aqueous dosage form on the absorption rate of promethazine.

apeutic effect is required. The similar bioavailability of promethazine after oral and rectal administration adds to the many other examples (benzoic acid, acetylsalicylic acid, paracetamol) that rectal dosing does not lead to a by-passing of liver first-pass elimination (Moolenaar and Schoonen, 1980). Although rectal administration of 25 mg did not give rise to severe local irritation it remains to be established whether multiple dosing will be possible in practice. In any event, single doses of promethazine should not exceed 25 mg for this reason.

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