PHARMACOKINETICS OF PROMETHAZINE AND ITS SULPHOXIDE METABOLITE AFTER INTRAVENOUS AND ORAL ADMINISTRATION TO MAN

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1 Blood concentrations of promethazine and promethazine sulphoxide have been measured following oral and intravenous administration of promethazine to seven healthy male volunteers.

2 Promethazine disposition is characterised by a large volume of distribution (1970 l) and a high blood clearance (1.14 l min⁻¹). Less than 1% of the dose is excreted unchanged in the urine, therefore total body clearance is essentially metabolic clearance. In accord with this high clearance the oral availability of promethazine is only 25%. The absorption of promethazine from the gastrointestinal tract exceeds 80% in most subjects. Minimal metabolism by the gastrointestinal mucosa is implicated.

3 Promethazine sulphoxide pharmacokinetics are consistent with a pronounced first pass effect. Although the area under the curve for this metabolite is not route dependent, there is a marked alteration in the shape of the metabolite curve when oral and intravenous data are compared. Evidence is presented to support the hypothesis that S-oxidation of promethazine is predominantly a hepatic event. The conclusions of previous investigators with regard to the role of the gut mucosa in S-oxidation of phenothiazines is critically assessed.

Introduction

Promethazine (PMZ), a member of the phenothiazine group of drugs, is commonly used in allergic conditions, as a sedative and hypnotic and as a premedicant in anaesthesia and obstetrics. Yet despite extensive application and a history of more than 30 years in clinical practice, little is known concerning its disposition in man.

DiGregorio & Ruch (1980) reported maximum blood concentrations of 22 ng/ml after intramuscular dosing of 25 mg of PMZ suggesting a large volume of distribution. In the same study peak blood concentrations after oral dosing were only 25% of those following intramuscular administration and this was attributed to first-pass metabolism. These findings are consistent with the large volumes of distribution (approximately 30 l/kg) and oral availabilities of less than unity documented for other phenothiazines (Dahl, 1976; Dahl & Strandjord, 1977; Hansen *et al.*, 1976). The elimination half-life for PMZ following oral administration has been estimated to be within the range of 12–15 h (Taylor *et al.*, 1979; Moolenaar *et al.*, 1981).

Following the observation that chlorpromazine was metabolised by an intestinal tissue preparation *in vitro* (Curry *et al.*, 1971), the importance of gut wall metabolism of orally administered phenothiazines

has been widely accepted (Curry, 1976; Lader, 1976; Cooper, 1978; Davis *et al.*, 1978). The evaluation of this hypothesis in man is difficult due to several technical and ethical problems. However, phenothiazine sulphoxides have been detected in human plasma following oral administration but not intramuscular administration of parent drug (Dahl, 1976; Dahl & Strandjord, 1977). These studies suggest that the S-oxidation of phenothiazine is limited to the gut wall and only occurs during the absorption process.

The present investigations were designed to compare the disposition of PMZ after oral and intravenous dosing to healthy human volunteers. The influence of route of administration on PMZ sulphoxide formation was also investigated in order to elucidate hepatic and intestinal contributions to the metabolism of this phenothiazine.

Methods

Subjects

The study, which was approved by an ethical committee, was carried out using seven healthy male volunteer subjects. The group had a mean weight of 72.4 kg (range 67–76 kg) and a mean age of 25.3 years

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(range 24–29 years). None had a history of renal or hepatic disease, nor were any receiving medication, and with the exception of one (subject PB) none were smokers. All gave their written consent to taking part in the study after the objectives and procedures had been fully explained to them

Protocol

Each of the subjects received 12.5 mg of promethazine hydrochloride by the intravenous route and 25 mg orally, using a balanced cross-over design with a two week interval between dosing. Subjects fasted overnight and for 2 h after dosing (at approximately 10.00 h). Alcoholic beverages were not permitted for 10 h prior to and 30 h following dosing, non-alcoholic beverages were permitted *ad libitum* except during the 1 h period immediately after dosing.

Administration and sampling

Intravenous doses consisting of 0.5 ml Phenergan injection (25 mg ml⁻¹ promethazine hydrochloride, May and Baker) diluted to 5 ml with saline (sodium chloride for injections E.P.) were infused during a 5 min period through a 23-G Butterfly Infusion Set (Abbott Laboratories) into an antecubital vein. After dosing the infusion set was flushed with 3 ml of saline and removed. Oral doses consisted of 1.0 ml of Phenergan injection from the same batch, diluted to approximately 100 ml with tap water.

Venous blood samples were taken for assay as follows: predose, 0.25 (intravenous dose only), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, (via an indwelling catheter (Viggo, Sweden)) 23.0, 25.0 and 27.0 h (by venepuncture) after dosing. The samples were placed in heparinised polycarbonate tubes and frozen at -20°C until assay. A predose sample of urine was obtained and collections during the following periods after dosing were undertaken: 0–24 h, 24–48 h and 48–72 h. The urine was protected from light during each collection period, at the end of which the volume was measured and an aliquot taken for assay and stored at -20°C.

Chemical analysis

Concentrations of promethazine (PMZ), promethazine sulphoxide (PMZSO) and monodesmethyl-promethazine (Nor₁PMZ) were determined using a reverse-phase high performance liquid chromatographic procedure described elsewhere (Taylor & Houston, 1982). Minimum detectable concentrations for PMZ, Nor₁PMZ and PMZSO were 0.2, 0.2 and 1.0 ng ml⁻¹ respectively.

Data analysis

Total areas, under the blood concentration-time curves (AUC) and under the first moment curves (AUMC) were calculated using linear trapezoidal summation together with appropriate extrapolations (Gibaldi & Perrier, 1975; Benet & Galeazzi, 1979) using half-lives regressed from terminal blood concentration data. Areas were calculated for both the parent drug (AUC, AUMC) and its sulphoxide metabolite (AUC_m, AUMC_m) following both oral and intravenous routes of administration.

The fraction of the oral dose available to the systemic circulation was calculated from the ratio of the AUCs and the ratio of the cumulative renal excretion of PMZ for the two routes. The fraction of the dose absorbed from the gastrointestinal tract was calculated from the ratio of the AUC_ms and the cumulative renal excretion of PMZSO (Houston, 1981). Dose normalised data was used.

The total clearance and renal clearance of PMZ was obtained by dividing the intravenous dose and the cumulative renal excretion of PMZ, respectively, by the AUC for PMZ. The renal clearance of PMZSO was calculated from the ratio of the cumulative renal excretion of PMZSO and the AUC_m. Intravenous data was used for these clearance calculations and the measurement of steady-state volume of distribution (V_{ss}) (Benet & Galeazzi, 1979):

$$V_{ss} = \text{AUMC} \cdot \text{Dose} / (\text{AUC})^2$$

The mean residence time for PMZSO was calculated from the ratio of AUMC_m and AUC_m for the appropriate routes of administration (DeVane & Jusko, 1981).

A biexponential equation was fitted to the promethazine blood concentration data following i.v. dosing and values for distribution half-life ($t_{1/2,\alpha}$) elimination half-life ($t_{1/2,z}$) and the volume of the initial dilution space (V_1) were calculated using standard procedures (Gibaldi & Perrier, 1975).

Statistical comparisons of disposition parameters were made using the paired *t*-test and the 95% level of significance.

Results

Promethazine blood concentrations

Typical blood concentration-time profiles for promethazine (PMZ) following intravenous and oral dosing are illustrated in Figure 1. Following intravenous dosing, PMZ blood concentrations are low due to a large volume of distribution (970 l) and decline in a biexponential manner ($t_{1/2,\alpha}$ —1.4 h, $t_{1/2,z}$

Figure 1 Blood concentration-time profiles for promethazine in a human volunteer (GL) following administration of 12.5 mg of promethazine intravenously (O) and 25 mg of promethazine by the oral route (●).

Table 1 Disposition parameters for promethazine following intravenous dosing in man

Subjects	$t_{1/2,\alpha}$ (h)	$t_{1/2,z}$ (h)	Initial dilution volume (l)	Steady-state volume of distribution (l)	Clearance (l min ⁻¹)
PB	1.3	10.6	919	1346	1.66
DG	1.5	11.6	512	655	0.72
EH	0.3	15.6	319	713	0.53
GL	1.7	9.4	497	868	1.51
JR	1.6	13.1	283	1146	1.17
GT	1.1	10.8	463	863	1.08
ST	2.2	14.1	664	1196	1.30
Mean	1.4	12.2	522	970	1.14
s.d.	0.59	2.19	216	262	0.41

Table 2 A summary of the availability of promethazine following oral dosing in man

Subject	Fraction available		Fraction absorbed		Predicted hepatic blood flow (l min ⁻¹)
	F (b)*	F (u)+	f _A (b)	f _A (u)+	
PB	0.13	0.16	0.94	0.63	1.93
DG	0.36	0.32	0.57	0.72	1.95
EH	0.39	0.37	0.74	0.62	1.12
GL	0.19	0.21	0.99	1.51	1.87
JR	0.25	0.28	0.96	0.80	1.58
GT	0.14	0.07	1.18	0.65	1.22
ST	0.26	0.12	0.80	0.88	1.93
Mean	0.25	0.22	0.88	0.83	1.66
s.d.	0.10	0.11	0.20	0.31	0.36

* Calculated from blood data

+ Calculated from urine data

12.2 h). The PMZ disposition parameters for each subject are summarised in Table 1.

Oral administration resulted in maximum concentrations of PMZ within the range of 2.4–18.0 ng ml⁻¹ which were achieved between 1.5 and 3 h after dosing. Dose normalised PMZ concentrations for the oral route were considerably less than those resulting from intravenous dosing. The mean fraction available to the systemic circulation was 0.25 (Table 2) and this was in accord with the systemic blood clearance (1.14 l min⁻¹).

Metabolite blood concentrations

Typical blood concentration-time profiles for promethazine sulphoxide (PMZSO) following intravenous and oral dosing with PMZ are shown in Figure 2. Maximum blood concentrations of PMZSO were attained between 4 and 10 h following intravenous administration but consistently earlier following oral PMZ dosing. After both routes of administration, peak and post-peak PMZSO concentrations exceeded those of the parent drug. The total areas under the PMZSO blood concentration-time profile following each dosing route (Table 3) were not significantly different.

The peak PMZSO concentrations were route of administration dependent (Table 3). This was particularly evident when the peak concentrations were normalised for the fraction of the oral dose absorbed. Mean residence times for PMZSO were measured in preference to times to peak concentration in view of the broad peaks in the PMZSO blood concentration-time profiles in certain subjects. This parameter which measures the mean persistence time for this metabolite in the body was significantly reduced after oral administration (16.9 h) compared to the intravenous route (20.2 h). Low concentrations of monodesmethylpromethazine (Nor₁PMZ) were detected in most of the subjects following both intravenous and oral PMZ dosing. Maximum concentrations exceeded 1 ng ml⁻¹ in only two of the subjects after oral dosing and only one of these after

Figure 2 Blood concentration-time profile for promethazine sulphoxide in a human volunteer (EH) following intravenous (○) and oral (●) administration of promethazine. The oral data has been dose normalised to aid comparison with the intravenous data.

Table 3 Disposition parameters for promethazine sulphoxide following intravenous and oral dosing with promethazine

Subject	Mean residence time (h)		Maximum plasma concentration (ng ml ⁻¹)			Area under metabolite concentration-time curve (ng ml ⁻¹ h)	
	i.v.	p.o.	i.v.	p.o.*	p.o./f _A *	i.v.	p.o.*
PB	15.9	14.1	5.0	13.0	13.8	5677	5216
DG	33.6	29.8	13.4	9.8	17.2	28851	16530
EH	20.5	14.4	14.7	21.5	29.0	22881	16933
GL	13.7	16.6	10.1	11.0	11.1	9647	9552
JR	18.3	15.3	7.9	7.8	8.1	9000	8618
GT	18.4	12.1	7.0	13.9	11.8	9182	10812
ST	20.9	16.2	11.6	15.5	19.4	16203	12814
Mean	20.2	16.9+	10.0	13.2	15.8+	14466	11511
s.d.	6.4	5.9	3.5	4.5	7.0	8548	4230

* Normalised to the intravenous dose

+ Statistically different from i.v. route by paired *t*-test (*P* < 0.05)

intravenous dosing. Post-peak concentrations of Nor₁PMZ declined at a slower rate than those of the parent drug, this together with the low concentrations prevented further analysis of the Nor₁PMZ data.

Urinary excretion of PMZ and metabolites

The renal clearance of PMZ (5.9 ml min⁻¹) was found to be a very minor contributor to its overall disposition (Table 4). The urinary excretion of Nor₁PMZ accounted for only a very small fraction of the PMZ dose (0.02–2.02% of the i.v. PMZ dose). Due to the low circulating concentrations of Nor₁PMZ, estimation of renal clearance was possible in only two of the subjects studied. The mean renal clearance in these subjects was 28.0 ml min⁻¹. Urinary excretion of PMZSO accounted for an average of 10% of the PMZ dose. The renal clearance of this metabolite (90.4 ml min⁻¹) was considerably higher than either PMZ or Nor₁PMZ.

The estimates of *F* and *f_A* from urinary PMZ and PMZSO data, (Table 2) were not significantly different from those estimated using blood concentration data (paired *t*-test).

Discussion

The results of this investigation indicate that PMZ, in common with other phenothiazine drugs, has a large volume of distribution, is highly cleared and has an oral availability (*F*) markedly less than unity. Within the panel of healthy volunteers studied the above disposition parameters varied 2 to 3 fold. There is a significant positive correlation between blood clearance and volume of distribution at steady-state (*r* = 0.778, *P* < 0.05) which explains the relative similarity in terminal half-lives of the blood concentration-time curves.

The renal clearance of PMZ was found to be low

Table 4 Renal excretion of promethazine and promethazine sulphoxide

Subject	PMZ		PMZSO	
	Fraction excreted unchanged	Renal clearance (ml min ⁻¹)	Fraction excreted unchanged	Renal clearance (ml min ⁻¹)
PB	0.25	4.6	7.78	127.0
DG	0.95	8.7	8.62	61.6
EH	1.58	7.9	17.57	73.1
GL	0.46	7.5	4.19	60.8
JR	0.25	3.1	10.44	117.7
GT	0.30	2.4	10.66	99.7
ST	0.72	6.9	12.78	92.8
Mean	0.64	5.9	10.29	90.4
s.d.	0.49	2.5	4.20	26.4

Based on urinary excretion over 0–72 h with the exception of DG whose data refer to 0–24 h.

whilst that of its sulphoxide metabolite was considerably higher. The unbound fraction of PMZ in blood has been estimated as 0.22 (DiGregorio & Ruch, 1980). Using this estimate a mean corrected renal clearance of 26.7 ml min^{-1} may be calculated. This indicates considerable tubular reabsorption and this is consistent with previous findings of pH dependent fluctuations in urinary excretion of this basic drug (Taylor *et al.*, 1979). The renal clearance of the sulphoxide metabolite approaches the normal glomerular filtration rate indicating that unless the metabolite is actively secreted, the fraction bound in blood must be considerably less than that of the parent drug. Krieglstein *et al.* (1972) have reported that albumin binding of sulphoxide metabolites is appreciably less than their parent phenothiazines; however, there is no published information available on sulphoxide binding in whole plasma or blood. Reduced tubular reabsorption of PMZSO compared with PMZ would be expected due to the lower lipophilicity of the metabolite.

The fraction of the PMZ oral dose which is systemically available (F) will be dependent on the fraction of the oral dose absorbed (f_A), the fraction escaping gut wall first-pass metabolism (f_G) and the fraction escaping hepatic first-pass metabolism (f_H). That is:

$$F = f_A \cdot f_G \cdot f_H \quad (1)$$

The combined information obtained by the PMZ and PMZSO blood concentration data strongly suggests that first-pass metabolism is the predominant determinant of the low availability. Comparison of the dose normalised AUCm indicates that in five of the seven volunteers the extent of absorption is greater than 80%. The reasons for the apparent lower extent of absorption in subjects EH and DG are unknown.

We propose that the extensive first-pass metabolism of PMZ occurs primarily in the liver. Since PMZ is essentially completely metabolised (renal excretion < 1% of dose) the parameter f_H may be calculated from intravenous blood clearance (CL) and the hepatic blood flow (Q) using the following relationship (Rowland, 1973):

$$f_H = 1 - (CL/Q) \quad (2)$$

However, the major limitation in the use of this equation is the intersubject variability in Q which within normal healthy volunteers may range from 1–2 l/min. Consequently we have substituted equation (1) into equation (2) and rearranged to enable calculation of Q for each subject:

$$Q = \frac{CL}{1 - (F/f_A \cdot f_G)} \quad (3)$$

When f_G is assumed to be unity, predicted values of Q for each subject (Table 2) are within the normal range. However, substituting values appreciably less than unity for f_G , results in Q values beyond the physiological limits. These observations indicate a lack of appreciable metabolism of PMZ by the gut wall. Furthermore they are consistent with the finding of similar fractions available following oral and intraportal dosing with PMZ in the rabbit (Taylor & Houston, 1983).

Although the dose normalised AUCm for oral PMZ did not differ appreciably from intravenous administration in the majority of subjects, there was a consistent route of administration effect in the shape of these metabolite profiles (Figure 2). PMZSO blood concentrations peaked relatively earlier (as reflected in the decreased mean residence times) and higher following oral administration relative to the intravenous route. This phenomenon has been observed for metabolites of other drugs which are subjected to extensive hepatic first-pass metabolism (Alvan *et al.*, 1977; Gram & Christiansen, 1976; Walle *et al.*, 1980). After oral dosing with these types of drugs a large proportion of the dose is delivered to the general circulation as a direct result of first-pass metabolism. After parenteral dosing however, whilst the fraction of the dose metabolised remains the same (Houston, 1981), metabolite production is much slower since only approximately 25% of the cardiac output perfuses the liver. This results in peak metabolite concentrations which are lower and attained at later times, than those resulting from oral dosing.

Sulphoxides of chlorpromazine and methotrimeprazine have been detected in the plasma following oral but not intramuscular dosing (Dahl, 1976; Dahl & Strandjord, 1977). In view of the present results with PMZ it is unlikely that S-oxidation of chlorpromazine and methotrimeprazine is limited to the gut mucosa during absorption. The combination of slow absorption from a parenteral route and the administration of a lower dose (50% of the oral dose) would be expected to result in a much reduced metabolite accrual than would be evident from the oral route. Thus it is feasible that after intramuscular dosing of these phenothiazines, sulphoxide concentrations are below the analytical detection limits.

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