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A comparison of the availability of prochlorperazine following i.m. buccal and oral administration

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Summary

The administration of prochlorperazine by the i.m., p.o. and buccal routes has been evaluated in a series of single and multi-dose pharmacokinetic studies in non-patient volunteers. Studies have indicated that the drug has an elimination half-life of 8.1 h following single i.m. injection and 9.0 and 8.6 h following multi-dose administration by the buccal and oral routes, respectively. Plasma levels following single-dose (10 mg) oral administration are too low to obtain meaningful pharmacokinetic parameters but steady-state data indicates 3 mg b.d. buccal delivery (Buccastem – trademark of Reckitt & Colman Products Ltd.) to be equivalent to 5 mg t.i.d. oral (Stemetil – trademark of May & Baker Ltd.). This observation has been confirmed in clinical evaluation in patients suffering vertigo disorders.

Introduction

Prochlorperazine is a member of the phenothiazine group of drugs and is used extensively to treat vertigo due to Meniere's disease and labyrinthitis, and for nausea and vomiting. It is commercially available for intramuscular and oral administration, but, in common with other phenothiazines, the oral bioavailability of prochlorperazine is very low (Taylor and Bateman, 1987). Unreliable oral absorption may also be a problem in cases of vomiting or when gastric emptying is delayed as often occurs with vertigo (Thompson et al., 1982). Administration of a drug via the buccal cavity avoids first-pass metabolism and poor absorption due to gastric stasis or vomiting.

This report describes single and multi-dose steady-state studies that have been undertaken to compare prochlorperazine bioavailability following oral and buccal administration.

Materials and Methods

All studies were of open randomised cross-over design for which each non-patient volunteer weighed between 60 and 80 kg and was aged between 18 and 50 years. All studies were granted Ethical Committee approval and all volunteers were fully informed of the nature of the study and the possible adverse effects. Blood was sampled into previously unused chromic acid-washed,

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silanised (trimethylchlorosilane) glass tubes, centrifuged and the plasma collected and stored in similarly treated tubes at −20 °C until analysed.

Study 1 Protocol (Single dose, n = 6). After fasting overnight, each subject received either two buccal tablets (2 × 5 mg prochlorperazine maleate), two oral tablets (Stemetil, 2 × 5 mg prochlorperazine maleate) or an intramuscular injection (Stemetil Injection, 12.5 mg prochlorperazine mesylate). The treatments were crossed over with at least 2 weeks between dosing periods. The buccal tablets were administered between the upper gingiva and cheek and held in position until dissolved. Blood samples were taken from a peripheral vein immediately prior to dosing and at 5, 15, 30, 45, 60 and 90 min and 2, 3, 4, 6 and 8 h after drug administration.

Study 2 Protocol (Multi-dose, n = 12). Each subject received either one buccal tablet (5 mg prochlorperazine maleate) at approximately 08.00 h once a day for 7 days, one buccal tablet (5 mg) every 12 h for 6 days, with a final dose at approximately 08.00 h on day 7 or one oral tablet (Stemetil, 5 mg prochlorperazine maleate) at 6, 6 and 12 h intervals for 6 days with a single dose at approximately 08.00 h on day 7. The treatments were crossed over with at least 2 weeks between dosing periods. Blood was collected immediately prior to dosing and at 1, 2, 4, 6, 8, and 12 h after drug administration on day 1, immediately before the initial dose and at 4 h post-dose on days 2–6 and immediately before the initial dose and at 4, 12, 24, 36, 48 and 72 h after the last dose of the study.

Study 3 Protocol (Multi-dose, n = 12). Each subject received either one buccal tablet (Buccastem, 3 mg prochlorperazine maleate), every 12 h for 6 days or one oral tablet (Stemetil, 5 mg prochlorperazine maleate) at 6, 6 and 12 h intervals each day for 6 days. On day 7 a single dose of either medication was administered. The treatments were crossed over with at least 2 weeks between dosing periods. Blood samples were taken from a peripheral vein immediately prior to and at 4, 8 and 12 h following the initial dose on day 1, immediately prior to and 4 h after the initial dose on days 2–6, and immediately prior to and at 2, 4, 6, 8, 12 and 24 h after the dose on day 7.

Analysis

All glassware used in the plasma extraction procedure was chromic acid-washed and subsequently silanised prior to use.

Plasma (5 ml) was mixed with an aqueous solution of promethazine hydrochloride (25 ng · ml^{-1}, internal standard). Sodium hydroxide solution (1 ml, 1 M) and diethyl ether : chloroform (4:1) mixture (8 ml) were added and the mixture vortexed. The upper organic layer was transferred into a clean 10 ml tube and evaporated to dryness under a stream of nitrogen. The organic residue was reconstituted in chromatographic mobile phase (75 μl) and an aliquot (50 μl) assayed by high-performance liquid chromatography (HPLC).

The HPLC was carried out on a 25 × 0.46 cm (i.d.) stainless steel column packed with 5 μm Spherisorb-CN (Phase Sep.,... Deeside Industrial Estate, Queensferry, Clwyd, U.K.). The mobile phase consisted of dipotassium hydrogen phosphate solution (0.1 M) adjusted to pH 6.5 with H_3PO_4, acetonitrile and methanol (7 : 6 : 4 v/v) delivered at a rate of 2 ml · min^{-1}. The eluant was monitored by an electrochemical detector housed in a Faraday cage and fitted with a glassy carbon electrode and operating with an applied potential of 0.75 V in the oxidation mode at a range of 0.5 nA. The detector output was processed by a Hewlett Packard reporting integrator.

Quantitation of the prochlorperazine content of the samples was achieved by comparison of the prochlorperazine : internal standard peak area ratio with that of the calibration curve prepared with samples of known concentration of prochlorperazine maleate.

Calculations

Mean values for elimination half-life, pre-dose and 4 h post-dose plasma concentrations were calculated from individual data. Daily maximum plasma concentration at steady-state (C_{16}) following oral dosing was calculated from the mean pre-dose steady state concentration (C_0) data from the following day using the expression:

$$C_{16} = C_0/e^{-K8}$$

where K represents the elimination rate constant (h^{-1}).

Results and Discussion

Analytical procedure

The analytical procedure is based upon that of Sankey et al. (1981). By pretreatment of all extraction vessels with chromic acid and subsequent silanisation, the irreversible binding of sub-ng · ml^{-1} levels of the drug was prevented and a lower limit of quantification of 0.15 ng · ml^{-1} was achieved. Prochlorperazine and promethazine gave retention times of 6.7 and 4.9 min, respectively. Calibration lines were constructed on a daily basis and statistical analysis of the day-to-day variation of the data at the 0.5 and 1.0 ng · ml^{-1} levels gave coefficients of variation of 12.6% and 6.1%, respectively.

Plasma levels

The single dose intramuscular, oral and buccal study was a 6-volunteer pilot investigation to determine the viability of single dose studies as a means of evaluating relative bioavailability from each of the 3 routes. Because of the low concentrations involved, definitive assay of prochlorperazine plasma levels following single oral dose (10 mg) proved very difficult and measurable plasma levels from this route were found in only one of the volunteers. The study, however, indicated bioavailability from the buccal route to be considerably greater than that from oral delivery and confirmed the validity of the assay in pharmacokinetic studies in that the i.m. data gave rise to volume of distribution, clearance and elimination half-life of 17.9 l · kg^{-1}, 2.35 l · min^{-1} and 8.1 h, respectively (Table 1), similar to those values reported by Taylor and Bateman (1987) following 6.25 mg i.v. administration.

From the limited single-dose data, a tentative prediction of multi-dose steady-state plasma levels was made and led to the 5 mg buccal, daily and b.d., versus 5 mg oral t.i.d. study.

Inspection of the pre-dose plasma concentrations on each day of this study indicates that trough levels following the oral dose regimen are significantly less than those following buccal b.i.d.

TABLE 1

Pharmacokinetic parameters in non-patient volunteers given prochlorperazine 12.5 mg i.m.

Volunteer	$t_{1/2}$ (h)	Volume of distribution (l · kg^{-1})	Clearance (l · min^{-1})
1 *	–	–	–
2	8.4	15.8	1.58
3	5.2	15.9	2.94
4	6.5	22.5	3.07
5	9.2	20.4	2.18
6	11.2	14.9	2.00
Mean	8.1	17.9	2.35
±S.E.M.	1.0	1.50	0.28

* Insufficient data points.

TABLE 2

Mean (± S.E.M.) prochlorperazine maleate levels (ng · ml^{-1}) immediately before the first dose of the day during the 5 mg buccal daily, b.i.d. and oral Stemetil 5 mg t.i.d. study

Treatment	Plasma concentration (ng · ml^{-1})					
Day:	2	3	4	5	6	7
5 mg oral t.i.d.	0.25 (±0.08)	0.21 (±0.10)	0.19 (±0.05)	0.16 (±0.04)	0.25 (±0.05)	0.33 (±0.06)
5 mg buccal daily	0.19 (±0.25)	0.22 (±0.09)	0.16 (±0.05)	0.19 (±0.06)	0.13 (±0.03)	0.19 (±0.04)
5 mg buccal b.i.d.	0.40 (±0.05)	0.37 (±0.04)	0.53 (±0.06)	0.42 (±0.05)	0.51 (±0.06)	0.52 (±0.04)

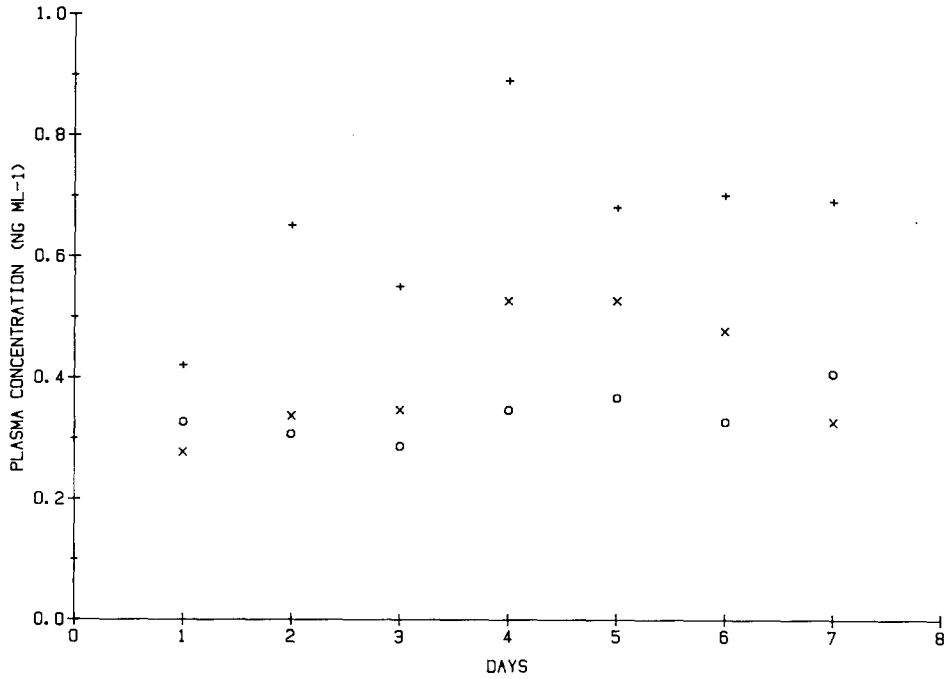

Fig. 1. Mean ($n = 12$) plasma prochlorperazine levels 4 h after the first dose of the day following 5 mg oral t.i.d. (o), 5 mg buccal daily (×) and buccal b.i.d. (+).

treatment (Table 2). This observation, confirmed by comparison of the 4 h post-dose plasma levels (Fig. 1), supports the single-dose study to show that bioavailability from the buccal route is significantly greater than that from the oral. Moreover, the ratio of the 4 h post-dose levels, which approximate to peak concentration, to the pre-dose levels which were calculated at steady-state to be 1.63, 3.63 and 2.33 for the buccal b.i.d., daily and oral routes respectively, indicate the fluctuation in plasma concentration following buccal b.i.d. dosing to be less than that from the other dose regimens.

From this multi-dose study it was calculated that 3 mg buccal prochlorperazine maleate in a twice daily dosage regimen would be equivalent to the standard 5 mg oral dose given 3 times daily and this was investigated in the second multi-dose study: plasma prochlorperazine concentrations were monitored over the 7 day dosing period and following the last dose on day 7 for each of the two dose regimens (Fig. 2). Mean individual peak levels occurred at 4.9 (±0.9, S.E.M.) h following Buccastem administration and at 4.0 (±0.8 S.E.M.) h after Stemetil. The elimination half-life of prochlorperazine was estimated to be 9.0 and 8.6 h for Buccastem and Stemetil, respectively, in reasonable agreement with the i.m. data of Taylor and Bateman (1987), such that steady-state (> 95%) would be predicted to be achieved for either treatment within 48 h of the first dose. A comparison of the mean steady-state pre-, 4 and 16 h post-dose plasma levels for the two treatments (day 3 onwards) is given in Table 3. No differences in trough levels at steady-state were observed between treatments, but Buccastem gave consistently higher levels 4 h after the first dose of each day, the difference in treatments being significant on days 4, 6 and 7. For Buccastem, for which an even 12 h dosing schedule was used, the 4 h post-dose level approximates to the peak concentration. Stemetil, however, was administered by a 6/6/12 h daily regimen, since this fitted with established clinical practice, and for this regimen daily peak levels would not occur until 4 h after the final dose on each day. Calculation of these

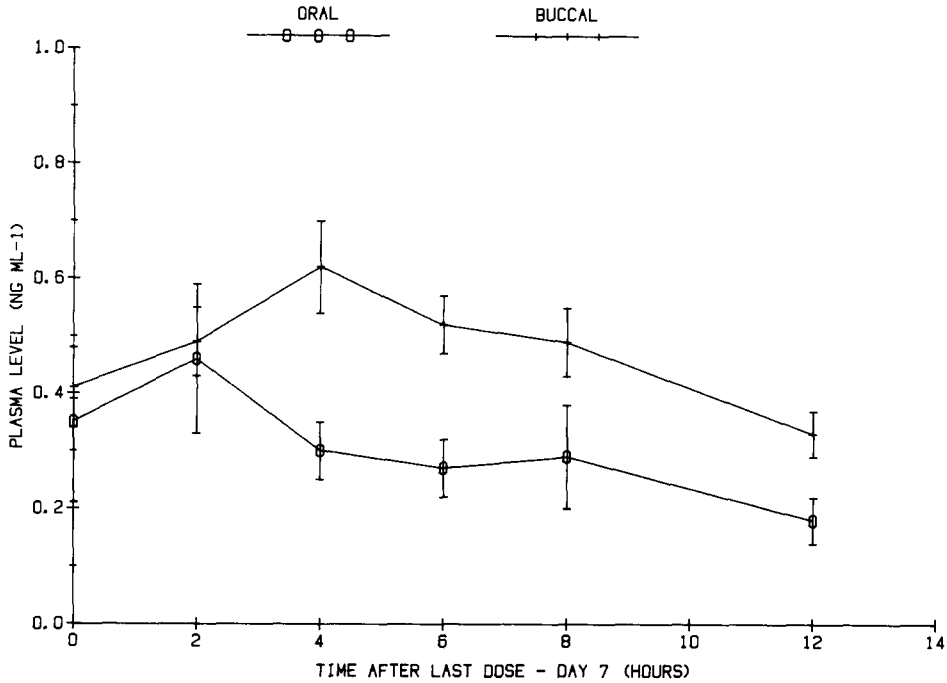

Fig. 2. Mean ± S.E.M. ($n = 12$) plasma levels of prochlorperazine on day 7 following dosing with 5 mg oral t.i.d. and 3 mg buccal b.i.d.

TABLE 3

Mean (± S.E.M.) prochlorperazine plasma levels ($ng \cdot ml^{-1}$) pre-dose and 4 and 16 h post-dose following Buccastem (3 mg b.i.d.) and Stemetil (5 mg t.i.d.) administration

Day	Buccastem ($ng \cdot ml^{-1}$)	Stemetil ($ng \cdot ml^{-1}$)	*P*-value
Prior to the first dose of the day			
3	0.20 ± 0.04	0.19 ± 0.05	NS
4	0.42 ± 0.06	0.25 ± 0.06	NS
5	0.38 ± 0.06	0.25 ± 0.03	NS
6	0.35 ± 0.04	0.24 ± 0.05	NS
7	0.41 ± 0.07	0.35 ± 0.14	NS
4 h after the first dose of the day			
3	0.55 ± 0.10	0.36 ± 0.05	NS
4	0.56 ± 0.09	0.31 ± 0.04	0.05
5	0.57 ± 0.06	0.46 ± 0.12	NS
6	0.62 ± 0.06	0.36 ± 0.06	< 0.02
7	0.62 ± 0.08	0.30 ± 0.05	< 0.02
16 h after the first dose of each day			
3	0.55 ± 0.10	0.67 ± 0.05	NS
4	0.56 ± 0.09	0.48 ± 0.06	NS
5	0.57 ± 0.06	0.46 ± 0.03	NS
6	0.62 ± 0.06	0.67 ± 0.05	NS

NS = not significant

values indicated no significant difference between treatments in peak levels.

Demonstration of bio-equivalence of the two dosage forms in a single-dose study would have been ideal but such a study would require administration of an unacceptably high dose of drug, an impractical proposition for buccal dosing.

To reaffirm the equivalence of the two dose regimens a clinical evaluation (Ward, 1988) of the buccal tablet in patients suffering from vestibular disorders was undertaken. In a single blind parallel group study involving a total of 160 patients comparing Buccastem (3 mg b.d.) plus oral placebo tablet with oral Stemetil (5 mg t.i.d.) plus placebo buccal tablet, the relief of symptoms was equivalent over the 2 week assessment periods.

The results obtained in these studies indicate the buccal route to be a viable means of delivering phenothiazine drugs such as prochlorperazine allowing reduction in both the dose and dosing frequency over oral administration as well as avoiding possible poor absorption due to associated gastric stasis or vomiting (Thompson et al., 1982).

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