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Clinical pharmacology of prochlorperazine in healthy young males

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1 The pharmacokinetics and pharmacodynamics of prochlorperazine (PCZ) have been studied in healthy young males following single 12.5 mg i.v. and 50 mg oral doses, and during repeated doses (25 mg twice daily) for 14 days.
2 Oral bioavailability was low and an *N*-desmethyl metabolite was detected. Plasma clearance was high (0.98 l kg^{-1} h) and the volume of distribution was large (12.9 l kg^{-1}) after i.v. dosing.
3 The terminal elimination half-life of PCZ was 9 ± 1 h and 8 ± 2 h after i.v. and single oral dosing, respectively. The urinary recoveries of drug and metabolite were low.
4 Accumulation of PCZ and its metabolite occurred following repeated dosing. The half-life at the end of 14 days therapy was 18 ± 4 h.
5 Postural tachycardia, decreased salivary flow, impaired psychomotor function and a diminished level of arousal were observed after intravenous PCZ. Similar effects, but of lower magnitude were observed after single oral doses. During chronic dosing postural tachycardia and antihistaminic effects were observed, the latter not being observed after single doses.
6 After single intravenous dosing the maximal drug effects occurred 2–4 h after peak plasma drug concentrations for all measures except for plasma prolactin and self-scored restlessness
7 An antagonist action at dopamine (D_2), muscarinic-cholinergic and α-adrenoceptors is postulated after single doses, with antihistaminic effects during chronic dosing, possibly indicating the presence of an active metabolite.

Keywords prochlorperazine pharmacokinetics pharmacodynamics

Introduction

Prochlorperazine [2-chloro-10-(3-(1-methyl-piperazinyl) propyl) phenothiazine] (PCZ) was introduced into medical practice in 1956 and is widely used in the prevention and symptomatic control of nausea, vomiting, vestibular and psychiatric disorders (Lapierre *et al.*, 1969). Despite its use for more than three decades, very little is known of its human pharmacology, since early studies in the pre-regulatory era were principally designed to establish efficacy.

It has been shown from *in vitro* radioligand binding studies (Richelson, 1984) that apart from the well-known affinity for dopamine receptors, PCZ has affinity for muscarinic-cholinergic, histamine H_1 and α-adrenoceptors, but these effects have not been investigated in man. Furthermore, until the recent introduction of h.p.l.c. with electrochemical detection, the measurement of PCZ in tissues and biological fluids was difficult (Fowler *et al.*, 1986; Sankey *et al.*, 1982). A pharmacokinetic study by Taylor & Bateman (1987) suggested slow absorption and a low bioavailability following oral dosing. Of particular interest in this study was the finding of a metabolite after oral dosing in a number of the subjects studied.

We have therefore evaluated the pharmacokinetics and pharmacodynamics of prochlorperazine after intravenous and oral dosing in an attempt to determine the influence of the route of administration on the metabolite profile and the subsequent dynamic response.

Since adverse reactions to prochlorperazine, in particular Parkinsonism, seem to occur after chronic dosing (Bateman *et al.*, 1986) a repeated dosing study was then carried out in a separate group of volunteers, and pharmacodynamic measurements were also made.

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Methods

Subjects

Seven healthy young male volunteers participated in the single dose study. Ten males were recruited into the multiple dose study, of whom six completed the protocol. All subjects were normal on clinical examination and had normal electrocardiography and haematological and biochemical tests. None of the subjects was on concurrent medication or had taken any drug in the preceding month. Subjects were also asked to abstain from alcohol and xanthine-containing beverages for the evening before each study day, and not to smoke during the 3 week experimental period. Subjects were acquainted with the various test measures, and practiced to achieve steady performance on the psychotropic tests on three occasions in the week before the study commenced.

Written informed consent was obtained from all subjects and the study was approved by the Newcastle Ethics Committee.

Procedure

Single dose study Each subject was studied on 3 days, each separated by an interval of at least 1 week. On each study day one of three treatments was administered in randomised, double-blind fashion. The treatments consisted of:

(a) 12.5 mg intravenous PCZ and placebo capsules;
(b) 50 mg oral PCZ capsules and intravenous normal saline;
(c) i.v. normal saline and oral placebo capsules.

Each study day commenced at 08.00 h after an overnight fast. Twenty minutes before commencement of measurements, with the subject supine, an indwelling cannula was inserted into a vein of the non-dominant forearm under local anaesthesia and kept patent with heparinised saline (2 iu ml^{-1}). The intravenous treatment (drug or normal saline) was administered into the contralateral arm over 2 min and flushed with 5 ml of normal saline. The capsules (drug or placebo) were swallowed with 200 ml water at the same time as the intravenous therapy. Blood (15 ml) was sampled prior to dosing (time 0) and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 h. A further sample was obtained by venepuncture at 24 h. The blood was placed in lithium heparin tubes in an ice bucket, plasma was separated in a refrigerated centrifuge and stored at −80°C until analysis.

All urine passed was collected in fractions of 0–4, 4–8 and 8–24 h on each study day. The volume was recorded and 40 ml aliquots stored at −80° C until analysis.

Drug effects were assessed on each study day using a range of measurements. These were heart rate, blood pressure (lying and 2 minutes standing), salivary flow (Dollery *et al.*, 1976), intradermal histamine response (Bateman *et al.*, 1983), plasma prolactin, critical flicker fusion threshold frequency, choice reaction time, letter cancellation tests and visual analogue scales of sedation, restlessness and mouth dryness. The measurements were made prior to medication, at intervals up to 8 h, and at 24 h post dosing. A standard meal was served at 3 h after dosing.

The level of plasma prolactin was measured by a double antibody binding radio-immunoassay using a commercial kit (Amersham prolactin kits). The Leeds psychomotor tester (Hindmarch, 1979) was used to determine the critical flicker fusion threshold frequency (mean of ten presentations, five each of flicker to fusion and fusion to flicker) and the choice reaction time (mean of thirty, after an initial ten run-in presentations). In the letter cancellation tasks subjects were asked to search systematically and quickly cancel 100 letter couplets or triplets randomly distributed among 1000 computer-generated letter couplets or triplets over a 3 min period. The number correctly cancelled was recorded as the cancellation accuracy.

Subjective side effects were assessed by 10 cm visual analogue scales. Eight scales were administered in order to assess restlessness (4 items), sedation (2 items), and dryness of the mouth (2 items). The pairs of extremes were:

1. Thoroughly contented/extremely discontented
2. No desire to move limbs/intrinsic desire to move limbs
3. Extremely relaxed/very tense
4. Quite calm and still/extremely restless and cannot keep still
5. Fully alert/very drowsy
6. Wide awake/nearly asleep
7. Mouth is fully moist/very dry
8. Mouth is thoroughly lubricated/parched.

Repeated dosing study The pharmacokinetics and effects of PCZ during repeated dosing were assessed in an open study in which each subject took a 25 mg oral dose at 09.00 h and at 21.00 h for a period of 14 days. The first three subjects were given 25 mg three times daily but the protocol was revised to twice daily after the first 48 h owing to excessive drowsiness, fatigue and restlessness. Blood (15 ml) was sampled pre-dose and at 2, 4, 6 and 8 h after morning dosing on days 1, 7 and 14. Further samples were obtained before the morning dose (trough concentrations) on days 3 and 11. On day 14, after the last (morning) dose of PCZ, blood was sampled at 2, 4, 6, 8, 10, 24, 32 and 48 hrs. On days 21, 24 and 28 blood samples were obtained at 09.00 h for measurement of plasma prolactin. Plasma was separated after centrifugation and stored at −80° C until analysis.

All urine passed for 8 h after the morning dose was collected on days 1, 7 and 14. On day 14, the 8–24 h and 24–32 h fractions were also collected. The urine volume was recorded and 40 ml aliquots stored at −80° C until analysis.

Pharmacodynamic effects, as in the single dose study, were assessed pre-treatment and 4 h after dosing on day 1, and subsequently before the first morning dose and at 4 h after the dose on days 7 and 14. Further assessments were done after the dosing period on days 15, 17 and 21.

Compliance was checked by return tablet count.

Plasma and urinary PCZ and N-desmethyl PCZ

In an earlier report (Fowler *et al.*, 1986) a metabolite peak was present on the chromatogram which was

believed to be due to the sulphoxide. A peak was not found in the position of the sulphoxide in the 4 h plasma in the present studies. However a peak was found which was separable from the sulphoxide standard and coincided with the *N*-desmethyl PCZ standard peak. The assay was therefore modified to optimise detection of this metabolite and the resulting solvent system described below, did not allow detection of the sulphoxide.

PCZ and *N*-desmethyl PCZ were measured by h.p.l.c. with electrochemical detection. Plasma (2 ml i.v. or 4 ml oral) was placed in acid washed sialinised glassware (with glass stoppers) and desipramine (150 μg in 60 μl methanol) was added as internal standard. The mixture was made alkaline with 0.8 ml of 5M NaOH and extracted by mixing for 15 min with 3% v/v isopropyl alcohol in hexane (10 ml). After centrifugation for 10 min, a 6 ml aliquot of the supernatant was transferred into an acid washed Sovirel® tube, and evaporated to dryness at 30° C under a gentle stream of nitrogen. The residue was reconstituted in 100 μl of mobile phase (65% v/v acetonitrile, 35% v/v 0.1 M potassium dihydrogen orthophosphate containing 25 mg EDTA, at pH 6.5) and 40 μl was injected onto the chromatographic column.

The chromatographic system comprised a Waters Model 510 pump (Northwich UK), a Spherisorb 5 μ nitrile normal phase column, 250 mm × 4 mm i.d. (Technicol, Cheshire, UK) and a Bioanalytical Systems Electrochemical Detection Unit (West Lafayette, IN, USA). An oxidising potential of 0.85 V was used, with a solvent flow of 1.4 ml min^{-1}. The retention times were 5.4 min (desipramine), 7 min (*N*-desmethyl PCZ) and 9.5 min (PCZ). The limit of assay was 0.5 ng ml^{-1} for both PCZ and *N*-desmethyl PCZ and the interassay coefficients of variation were 11.8% and 12.3% at 1 ng ml^{-1}, and 8.3% and 10.0% at 5 ng ml^{-1}, respectively. The interassay coefficients of variation were 8.9% and 7.5% for PCZ and *N*-desmethyl PCZ, respectively.

Pharmacokinetic analysis

The area under the plasma drug concentration-time curve (AUC) was determined by the linear trapezoidal rule with extrapolation to infinity.

The plasma clearance (CL) and apparent volume of distribution *V* were calculated from Dose/AUC and CL/λ_z, respectively.

The oral bioavailability was calculated from the ratio of AUC after oral and i.v. administration normalised for dose. A biexponential function was fitted to the i.v. data by least squares regression analysis.

The renal clearance of PCZ was calculated from the ratio of the 24 h urinary recovery and AUC after i.v. administration.

During repeated dosing the steady-state plasma concentrations of PCZ and its *N*-desmethyl metabolite were estimated from the areas under the plasma concentration time curves between the dosing interval on days 7 and 14. Since samples were only collected to 8 h after dosing the 12 h values were extrapolated by regression of the log plasma concentration-time curves.

Linear regression analysis was used to estimate the terminal elimination rate constant and half life from the log concentration-time curve after stopping the drug on day 14.

Data are expressed as mean ± s.e. mean. A two way analysis of variance with corrections for repeated measure was used to analyse the variables at each time point and the differences in visual analogue scores were analysed using Friedman's ANOVA. Further analyses of significant means was done using the Wilcoxon rank sum test, Statistical significance was taken to be $P < 0.05$.

Results

Single dose study

Pharmacokinetics The calculated pharmacokinetic parameters and mean plasma drug concentrations after i.v. dosing are shown in Table 1 and Figure 1, respectively.

Following intravenous administration, the plasma concentration of PCZ declined biexponentially with a terminal half-life of 9.3 ± 1.2 h (range 5.3–14.6 h). The plasma clearance averaged 0.98 ± 0.1 l h^{-1} kg^{-1} and the apparent volume of distribution was 12.9 ± 1.6 l kg^{-1}. Concentrations of *N*-desmethyl PCZ were below the limit of assay in all subjects after i.v. PCZ.

After oral dosing the results for one of the subjects were lost owing to a technical problem during analysis. PCZ was detected in plasma in five of the remaining six subjects, and *N*-desmethyl PCZ in four. The mean plasma

Table 1 Pharmacokinetic parameters describing the fate of prochlorperazine after 12.5 mg i.v. and 50 mg oral doses to seven healthy males

			i.v.			Oral			
Subject	*Age (years)*	*Weight (kg)*	$t_{½,z}$ *(h)*	V *(l kg^{-1})*	*CL (l kg^{-1} h)*	C_{max} *(ng ml^{-1})*	t_{max} *(h)*	$t_{½}$ *(h)*	F *(%)*
1	21	85.0	12	12.5	0.74	2	5.0	11	4.8
2	21	56.0	7	8.7	0.91	ND	ND	ND	ND
3	20	82.0	5	5.8	0.75	4	9.9	14	19.8
4	21	76.4	9	13.7	1.13	8	4.3	7	25.3
5	20	75.6	15	16.8	0.80	ND	ND	ND	ND
6	21	78.2	10	15.8	1.09	4	3.4	4	7.8
7	21	68.1	8	17.1	1.46	3	4.4	4	4.9
Mean	20.7	74.5	9	12.9	0.98	4*	5.4*	8*	12.5*
± s.e. mean	0.2	3.7	1	1.6	0.10	1	1.2	2	4.2

ND – Not detectable.
* – Data for five subjects only.

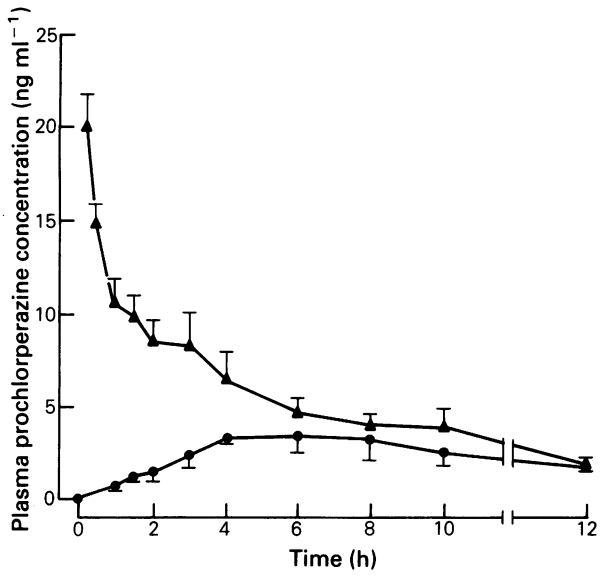

Figure 1 Mean plasma prochlorperazine concentrations (ng ml^{-1} ± s.e. mean) following single doses of 12.5 mg intravenously (▲) ($n = 7$) and 50 mg orally (●) ($n = 5$) in healthy male volunteers.

drug concentrations in the five subjects in whom PCZ was measured are shown in Figure 1 and pharmacokinetic parameters are listed in Table 1. Peak plasma concentrations (C_{max}) of PCZ and *N*-desmethyl PCZ were 3.9 ± 1.0 ng ml^{-1} ($n = 5$) and 3.1 ± 0.8 ng ml^{-1} ($n = 4$) and occurred at 5.4 ± 1.2 h and 5.0 ± 1.0 h, respectively. In the five subjects in whom PCZ was measurable the oral bioavailability was 12.5 ± 4.3% (range 4.8–25.3%).

Table 2 summarises the urinary recoveries of PCZ and *N*-desmethyl PCZ after intravenous (12.5 mg) and oral (50 mg) dosing. Recovery of parent drug in urine was extremely low amounting to 0.04% and 0.005% of the dose after intravenous and oral dosing, respectively. Renal clearance was 23.6 ± 3.0 ml h^{-1}. Negligible amounts of *N*-desmethyl PCZ were detected after i.v. administration, but recovery of this metabolite exceeded that of the parent drug after oral dosing.

Adverse effects One subject had a dystonic reaction (oculogyric crisis) at 7 h after the i.v. dose, which quickly resolved after procyclidine (10 mg) i.v. Pharmacodynamic data obtained beyond this time were excluded from the analysis. Another three subjects complained of intense restlessness characterised by vague discomfort, inability to remain still, impaired concentration and an unwillingness to take part in further studies. Five subjects after i.v., and three after oral dosing, felt drowsy or fell into a sleep from which they were easily roused. No other adverse effects were reported.

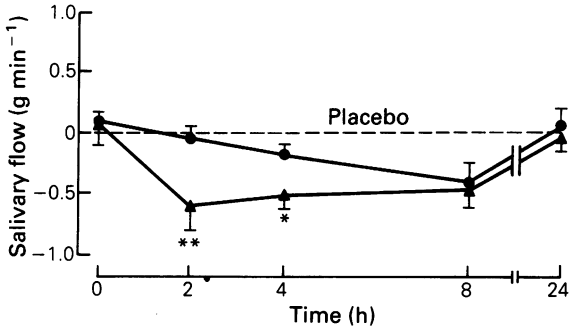

Figure 2 Salivary flow (g min^{-1}) shown as mean difference from placebo (± s.e. mean) following prochlorperazine 12.5 mg i.v. (▲) and 50 mg orally (●) in seven healthy male volunteers. (**$P < 0.025$, *$P < 0.05$).

Pharmacodynamic measures The supine heart rates were similar following all three treatments. However, a rise in standing heart rate was observed following i.v. PCZ, which was significant compared with both placebo and oral treatment ($P < 0.05$ at 4 h). An increase in the heart rate was also observed after oral treatment which was maximal at 8 h, but this change just failed to reach statistical significance compared with placebo. No difference was observed in the supine and erect mean arterial pressures.

The salivary flow decreased between 2 and 8 h after intravenous PCZ, with a minimum at 2 h ($P < 0.025$) and a return to baseline by 24 h (Figure 2). A similar trend was observed following oral treatment with a minimum at 8 h, but this change just failed to achieve statistical significance.

The flare and weal volume response to intradermal histamine was not affected acutely by any treatment.

The plasma prolactin concentration was elevated significantly at 15 min (first sampling point) following i.v. PCZ, being maximal at 0.5 h (1367 ± 199 μiu ml^{-1}) and then declining to near baseline levels by 24 h (Figure 3). Plasma prolactin concentrations rose more slowly after oral PCZ to a peak at 4 h (796 ± 173 μiu ml^{-1}) and fell gradually to near baseline values at 24 h. Placebo treatment did not affect prolactin levels.

The total choice reaction time was prolonged following intravenous PCZ with the maximum effect at 2 h ($P < 0.01$). Following oral dosing there was a gradual increase in the reaction time with a maximum effect at 6 h ($P < 0.05$). No significant changes were observed after placebo treatment. Both components of the total reaction time (recognition and movement times), contributed to the observed changes.

The critical flicker fusion frequency (c.f.f.f.) threshold

Table 2 Urinary recoveries of drug and metabolite after 12.5 mg i.v. and 50 mg oral prochlorperazine

	Route of administration					
	Intravenous (12.5 mg)			*Oral (50 mg)*		
	Time of urine collection					
Drug/Metabolite	*0–4 h*	*4–8 h*	*8–24 h*	*0–4 h*	*4–8 h*	*8–24 h*
Prochlorperazine (PCZ) (μg)	0.5 ± 0.1	0.42 ± 0.1	1.6 ± 0.4	0.2 ± 0.02	0.61 ± 0.2	1.04 ± 0.2
N-Desmethyl PCZ (μg)	ND	ND	0.3 ± 0.02	0.2 ± 0.06	0.77 ± 0.4	2.0 ± 0.5

ND – not detectable.

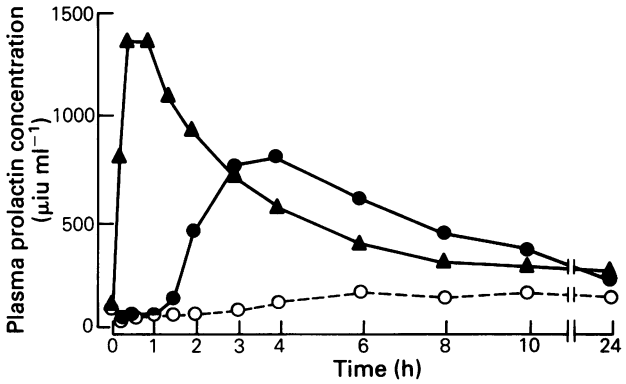

Figure 3 Mean plasma prolactin concentration (μiu ml^{-1}) following single dose placebo (○), prochlorperazine 12.5 mg i.v. (▲), and 50 mg orally (●) in seven healthy male volunteers.

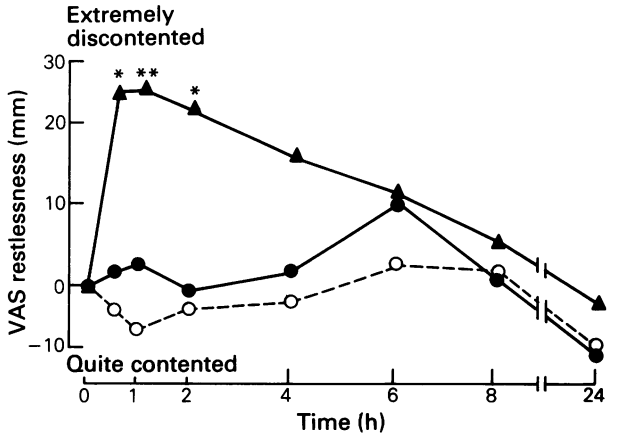

Figure 4 Visual analogue scale of restlessness expressed as change from baseline score following placebo (○) 12.5 mg i.v. (▲) and 50 mg oral (●) prochlorperazine ($n = 7$). (**$P < 0.01$, *$P < 0.05$).

frequency was impaired following i.v. treatment, with a maximum decrease of 1.5 Hz at 1 h ($P < 0.01$). A similar trend with delayed maximal effect was observed after oral dosing, but this was not statistically different from placebo.

Letter cancellation was impaired following i.v. treatment when compared with oral and placebo treatment at 2 h ($P < 0.01$) and 4 h ($P < 0.05$). The changes after oral treatment could not be differentiated from placebo.

Subjective ratings Subjects rated themselves more restless during the first 2 h following i.v. PCZ ($P < 0.01$ at 1 h) and less so thereafter, (Figure 4). After oral administration, self scored restlessness increased significantly over placebo from 6–8 h. At 24 h there was no difference for either treatment.

Self-scored sedation was also marked within the first 2 h following i.v. PCZ, declining thereafter, while sedation occurred at 4–8 h after oral dosing. The subscale on dryness of mouth did not distinguish drug from placebo.

Repeat dosing study

Of the 10 subjects recruited, two withdrew on the first day and another two were withdrawn on the third day, one because of akathisia and one because of an extrapyramidal reaction (see below). Therefore, the kinetic and pharmacodynamic data refer to the remaining six subjects who completed the study. Plasma concentrations of PCZ were below the limit of assay on day 1 in subject 5. Plasma concentrations of *N*-desmethyl PCZ were below the level of assay on day 1 in subjects 4 and 5 and on day 7 in subject 4.

Table 3 Pharmacokinetic parameters describing the fate of prochlorperazine after multiple oral doses of 25 mg twice daily for 14 days

Subject	*Age (years)*	*Weight (kg)*	*Day 7* C_{ss} *(ng ml^{-1})*	*Day 14* C_{ss} *(ng ml^{-1})*	$t_{½}$ *(h)*
1	22	70.1	4.3	2.5	29
2	23	83.2	5.0	5.0	9
3	23	73.5	2.9	4.2	17
4	23	88.2	0.8	0.9	–
5	21	75.0	1.6	ND*	–
6	22	70.0	1.5	1.3	18
Mean	22.3	76.7	2.7	2.3	18
s.e. mean	0.3	3.0	0.7	0.8	4

*ND – Not detectable.

Steady state kinetic data The kinetic parameters are shown in Table 3. The mean peak plasma concentrations of PCZ and *N*-desmethyl PCZ in four subjects following the first dose on day 1 were 1.21 ± 0.04 and 1.15 ± 0.23 ng ml^{-1}, with AUC values of 8.0 ± 1.8 ng ml^{-1} h and 8.7 ± 1.7 ng ml^{-1} h, respectively (Figure 5). Accumulation

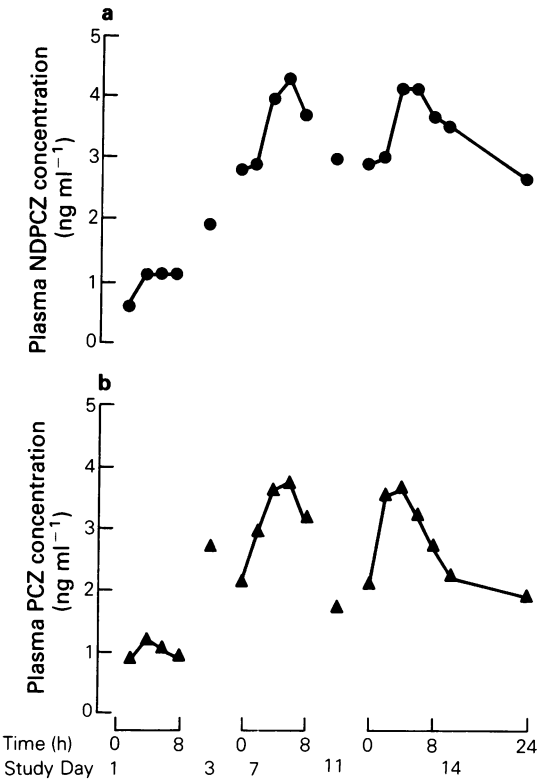

Figure 5 Plasma prochlorperazine concentration (ng ml^{-1}) (a) and *N*-desmethyl prochlorperazine concentration (ng ml^{-1}); (b) following dosing with prochlorperazine 25 mg twice daily. Concentrations are shown at 2, 4, 6 and 8 h after dosing on days 1 and 7 and for a further 10 and 24 h on day 14. Trough concentrations (pre morning dose) are shown for days 3, 7, 11 and 14.

was observed for both parent drug and metabolite. Steady state was reached by day 7 with a mean AUC(0,12) of 32.3 ± 8.3 ng ml^{-1} h for PCZ and of 35.0 ± 11.7 ng ml^{-1} h for *N*-desmethyl PCZ. These values were similar to those on day 14 (29.8 ± 8.5 and 37.8 ± 11.8 ng ml^{-1} h, respectively). The terminal half-life of PCZ after the last dose on day 14 was 18.1 ± 4.0 h.

Increasing amounts of PCZ were excreted during the dosing period but the total urinary recovery was low, being 0.55 ± 0.3 mg on day 1, 2.8 ± 1.1 mg on day 7 and 7.3 ± 1.4 mg on day 14.

Adverse effects Two subjects had extrapyramidal reactions. The first was on a 25 mg three times daily regimen and developed akathisia from day 1 after the third dose and had to withdraw by the third study day. The second subject was on a 25 mg twice daily regimen and developed a dystonic reaction, mainly facio-lingual, on day 3 at about 4 h after the morning dose. This responded to treatment with procyclidine (10 mg intravenously). The plasma PCZ and *N*-desmethyl PCZ and prolactin concentration-time profiles for these two subjects were similar to those of the other subjects.

Pharmacodynamic parameters There were no significant changes in the supine pulse rate during and after the 14 day dosing period. However, the standing pulse rate rose steadily during the dosing period (Figure 6); this rise being most marked at 4 h after the morning dose and maximal on day 7 (13 beats min^{-1}; $P < 0.01$ compared with pre-treatment). In the post-dosing period the pulse rate gradually returned to pre-treatment values. There was also a fall in standing mean arterial pressure during

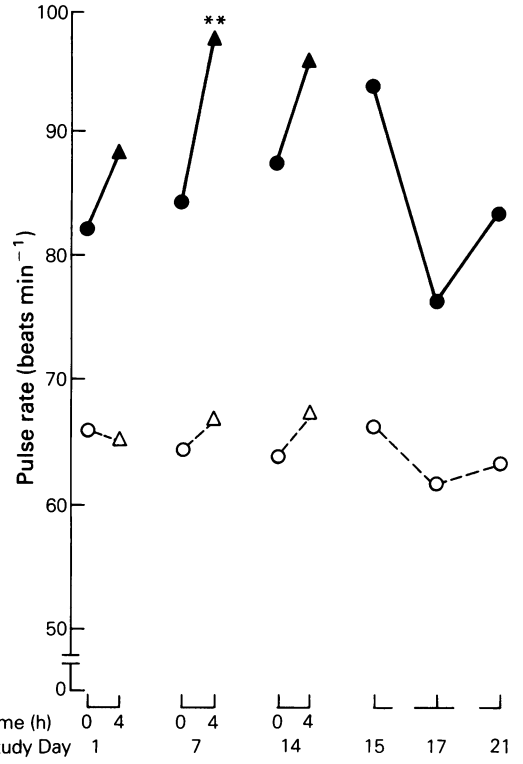

Figure 6 Mean pulse rates lying (○–△) and standing (●–▲) premorning dose and 4 h later on days 1, 7 and 14, on the morning of days 15, 17 and 21 after prochlorperazine 25 mg twice daily from days 1 to 14 ($n = 6$). (** = $P < 0.01$).

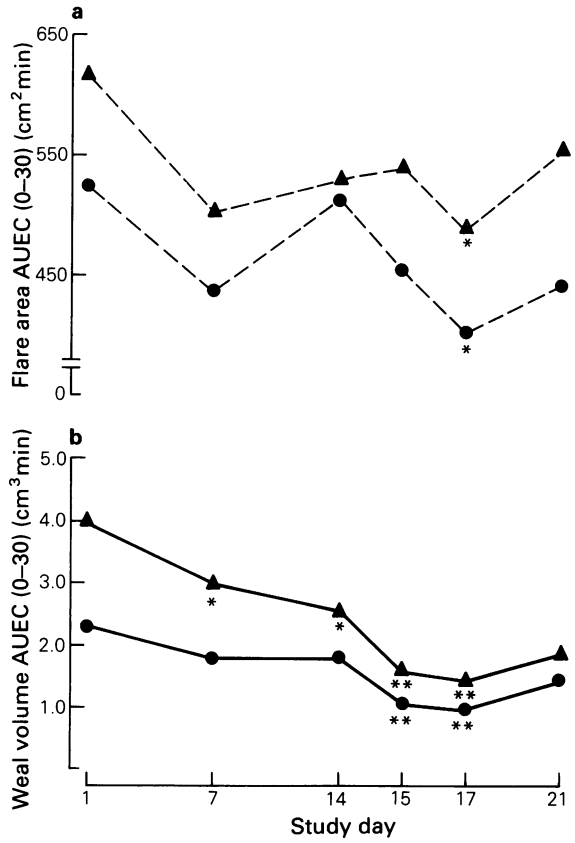

Figure 7 Mean histamine weal (b) and flare (a) response measured as the area under effect-time curve (AUEC) (0–30 min) following intradermal histamine 10 μg (▲) or 20 μg (●) during dosing with prochlorperazine 25 mg twice daily from days 1 to 14 ($n = 6$). (*$P < 0.05$; **$P < 0.01$ compared with placebo).

treatment which was maximal 4 h post dosing on day 14 (−6.3 mm Hg, $P < 0.01$ compared with pre-treatment).

A statistically significant, and progressive, decrease over time was observed in the weal volume response to intradermal histamine (Figure 7), and this had not returned to placebo values by day 21 i.e. 7 days after the last dose of PCZ. The effect on flare was less marked, the nadir being reached on day 17 when it was significantly less than the pre-study value ($P < 0.02$). Salivary secretion was not significantly affected.

Plasma prolactin concentrations rose on the first day following oral administration of PCZ, peaked at 4 h (510 ± 102 miu l^{-1}) and declined thereafter. A similar pattern was observed on days 7 (peak = 472 ± 98.3 miu l^{-1}) and 14 (peak = 448 ± 68 miu l^{-1}).

Despite the accumulation in plasma PCZ, the highest peak plasma prolactin was attained on day 1. This pattern was observed in all subjects. After the last dose on day 14, prolactin levels reached a peak at 4 h and declined to baseline at 24 h (117 ± 34 miu l^{-1}). Plasma prolactin levels in the 14 days after the dosing period fluctuated within the normal range.

No statistically significant changes in psychometric tests were observed during chronic administration.

Self-rating Self rating on the restlessness measure did not show any significant changes either during or after dosing in the subjects who completed this study, although two of these six complained of mild restlessness during the first 3 days of the study. Subjective scores for

sedation showed no significant changes during the 14 day dosing period. However, following discontinuation of the drug, the subjects rated themselves as being more wakeful and alert ($P < 0.05$) on day 17. Self-rated scores for dryness of mouth did not show any significant changes.

Discussion

Very low plasma concentrations of PCZ were observed after the single oral dose compared with a 4-fold lower i.v. dose. The concentrations of the *N*-desmethyl metabolite after oral administration were similar to those of the parent drug in the four subjects in whom it was measurable, but were below the assay limit after i.v. administration.

The pharmacokinetic parameters of i.v. PCZ in the present study are similar to those reported by Taylor & Bateman (1987), indicating a high clearance and volume of distribution.

The urinary recovery of parent drug was low. The piperazine phenothiazines fluphenazine (Curry *et al.*, 1979), and perphenazine (Huang & Kurland 1964; Symchowicz *et al.*, 1962), undergo negligible urinary excretion but are eliminated via the bile and faeces. A similar observation has been made for PCZ in the rat (Phillips & Biya, 1962).

Following multiple twice daily dosing, steady state appeared to be reached by 7 days. Accumulation of PCZ and its *N*-desmethyl metabolite were observed. The half-life of PCZ observed following cessation of therapy was considerably longer than that observed following single intravenous doses in this study, or reported previously (Taylor & Bateman, 1987). This may be due to a third phase of elimination not observed in single dose studies.

The pharmacological tests used in these studies were included to assess anticholinergic (pulse rate, salivary flow), α-adrenoceptor antagonist (erect pulse and blood pressure), antihistaminic (flare and weal volume response) and dopamine antagonist (prolactin) activity.

The postural tachycardia observed was considered to be a compensatory response to α-adrenoceptor blockade. Lanzoni (1958) observed a 10–20% increase in pulse and a drop in blood pressure for 10–20 min following i.v. PCZ (0.15–0.35 mg kg^{-1}) and Pevaroff *et al.* (1963) noted a compensatory rise in pulse rate at a lower dose of 0.03 mg kg^{-1} with no drop in blood pressure. The delayed rise in pulse rate observed after single dosing (2 h for the i.v. and 4 h for oral) has not been reported previously. The delay and the fact that this effect was maximal after 7 days oral therapy suggest that it might be due to the effect of a metabolite rather than the parent drug.

Salivary flow is usually regarded as a sensitive measure of anticholinergic action (Dollery *et al.*, 1976). A delayed decrease in salivary secretion was observed after i.v. PCZ but not after acute and chronic oral administration.

We observed statistically significant reductions in the flare and weal response to intradermal histamine after chronic administration but not after single doses. This suggests the possible involvement of a metabolite with antihistamine activity.

The plasma prolactin response reflects the interruption of tuberoinfundibular dopaminergic transmission (Langer *et al.*, 1977). The abrupt rise and subsequent decline after single i.v. doses is indicative of a direct dopamine receptor blockade by PCZ. Plasma prolactin levels were also increased during chronic dosing. The absence of any further increase after the first day, despite accumulation of drug and metabolite indicates a flat dose-response curve, or adaptation to further neuroleptic blockade of dopamine receptors (Rivera *et al.*, 1976).

Plasma prolactin levels declined rapidly on discontinuation of the drug, as observed after other phenothiazines (Meltzer & Fang, 1976), and were not maintained for 1 to 3 weeks as reported by Turkington (1972).

Intravenous PCZ produced significant changes in psychological measures, with impairment of performance and level of arousal. Earlier reports on the psychomotor changes following oral dosing of various piperazines are contradictory. Thus, while no changes or a stimulant effect were observed by Lehmen & Csark (1957) and DiMascio *et al.* (1963), others, including Idestrom (1960) and Nakra *et al.* (1975) observed a depressive effect. In most of these studies only one or two recordings were made after drug administration. We have assessed the subjects more frequently after drug administration and, therefore, are unlikely to have missed any possible variation in times of peak drug effect.

Use of the self-rating scales revealed a profile of restlessness which was observed during the first 2 h after i.v. dosing. This drug-induced restlessness is similar to that described for metoclopramide (Isah *et al.*, 1988). Subjective sedation was also marked during the first 2 h of i.v. PCZ and 4 h after oral PCZ. This sedative effect was mild and could, perhaps, be attributed to α-adrenoceptor or histamine H_1-receptor blockade (Peroutka *et al.*, 1977; Uzan *et al.*, 1979).

A feature of the dynamic aspect of the single dose study was that many of the pharmacological effects lagged 2–4 h behind the peak concentration of parent drug in plasma. This has been observed for chlorpromazine (Sakalis *et al.*, 1972; Smolen *et al.*, 1975).

It is difficult to determine from these studies the exact contribution of metabolites to the dynamic response. The various metabolites of phenothiazines have been shown to possess, lower affinity for D_2 dopaminergic, α_1- and α_2-adrenoceptors (Hals *et al.*, 1973). The mean oral bioavailability of the parent drug was 12.5% and since the oral dose was four times higher than the i.v. dose, the oral response should have been about one-half that detected after i.v. administration. However, we observed effects which in most instances were more than 50% of the maximal i.v. effects. This may, therefore, reflect the additional effects of metabolites at the time of the peak oral action, at which time the parent drug concentrations in plasma were similar to those after i.v. dosing.

The pharmacokinetic parameters of the subjects suffering dystonia were not different from those of the others and a pharmacodynamic explanation appears most appropriate. Garver *et al.* (1976) observed a delayed dystonic reaction following intravenous butaperazine and attributed it to dopaminergic-cholinergic imbalance during the decline of plasma drug concentration when there was transient, relatively excessive dopaminergic activity. While an imbalance between dopaminergic and

cholinergic neuronal pathways seems the most likely explanation, other neuronal pathways may be involved. In contrast, the time course of akathisia suggests a direct antidopaminergic action.

In conclusion, we have evaluated the pharmacokinetics of PCZ and confirmed its low oral bioavailability, with some accumulation during regular dosing. The pharmacological and psychologic responses observed were suggestive of antagonist actions at a number of receptors including dopamine D_2, α-adrenoceptor and muscarinic-cholinergic sites. The pattern of the dynamic responses after acute oral dosing was similar to that after i.v. adminsitration but it was delayed in onset and of lesser magnitude, suggesting that the parent drug is responsible for most of the observed effects after single doses of prochlorperazine. During chronic dosing an antihistaminic effect was observed, which was not demonstrated after single doses, and may therefore indicate the involvement of an active metabolite.

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