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# Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers

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**1** The pharmacokinetics and pharmacodynamics of prochlorperazine were studied in healthy volunteers using a recently developed h.p.l.c. assay.
**2** Eight subjects received 12.5 mg and 6.25 mg i.v. doses of prochlorperazine, a 25 mg oral dose and placebo in random order.
**3** Plasma half-life ($t_{½}$) of prochlorperazine was 6.8 ± 0.7 h and 6.9 ± 0.8 h for the 12.5 mg and 6.25 mg i.v. doses respectively. Apparent volume of distribution and plasma clearance were high and the kinetics did not appear to be dose-related.
**4** Absorption of oral prochlorperazine appeared to be slow and bioavailability was very low. A metabolite, possibly prochlorperazine sulphoxide, was noted after oral dosing.
**5** Mild sedation was common after i.v. prochlorperazine, but cardiovascular effects were minimal. The main adverse effect was akathisia which was reported by five out of eight subjects after the higher i.v. dose.
**6** These results provide preliminary information on the pharmacokinetics of i.v. prochlorperazine which were previously unknown.

**Keywords** pharmacokinetics prochlorperazine

## Introduction

Although prochlorperazine has been in clinical use for over 30 years, little is known of the pharmacokinetics of this drug. Present recommended dosage schedules are based on early studies in patients receiving prochlorperazine by different routes and for a variety of indications (Friend & McLemore, 1957; Bardfield, 1966). Oral prochlorperazine is widely prescribed, but it is not known if the drug is well absorbed from the gut. We have developed an h.p.l.c. method using electro-chemical detection to measure prochlorperazine in plasma (Fowler *et al.*, 1986) and have investigated the pharmacokinetics of prochlorperazine in normal volunteers given single intravenous (i.v.) and oral doses.

## Methods

The study was approved by the ethics committee of the University of Newcastle upon Tyne. Informed consent was obtained from the volunteers, who attended the clinical laboratory on four separate occasions at least 1 week apart and on each occasion received one of the following schedules in random order.

1. Oral placebo and normal saline i.v.
2. 25 mg oral prochlorperazine and normal saline i.v.
3. Oral placebo and 6.25 mg prochlorperazine i.v.
4. Oral placebo and 12.5 mg prochlorperazine i.v.

Subjects fasted overnight and the study was started at 09.00 h the following day. Initial assessments were made after a 10 min rest period and the subjects remained recumbent for the first hour of the study. They were then allowed to eat and drink and resume normal activities within

the laboratories. Subjects rested again for 5 min before each of the subsequent set of measurements.

Blood samples (10 ml) were obtained through an indwelling cannula placed in a forearm vein for the first 8 h of the study. The cannula was kept patent with heparinised saline. Samples taken after 8 h were obtained by venepuncture from an antecubital vein. The i.v. injection of prochlorperazine or saline was given into an antecubital vein in the opposite arm from that used for blood sampling. Samples for estimation of plasma prochlorperazine were taken pre-treatment and at 0.08, 0.16, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after treatment and were assayed by h.p.l.c. with electrochemical detection as previously described (Fowler *et al.*, 1986). The coefficient of variation between assays was 6% and the minimum quantifiable level of prochlorperazine was 1 ng $ml^{-1}$. Samples for estimation of serum prolactin were taken pre-treatment and at 1, 2 and 4 h after dosing and were assayed by the Regional Radio-immunoassay Laboratory.

Pharmacokinetic analyses were performed using an exponential stripping programme, ESTRIP, as previously described (Bateman *et al.*, 1981) and the area under the plasma concentration time curves (AUC) was obtained by integration of the best fitting polyexponential equation. Clearance was calculated from:

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC}}$$

and the apparent volume of distribution ($V$) from:

$$V = \frac{\text{Clearance}}{\beta}$$

where $\beta$ is the terminal elimination rate constant.

Several parameters were measured to assess the effects of prochlorperazine. Heart rate was measured using ECG and an instantaneous rate meter (Ormed 4522) and was recorded on a four channel pen recorder (Ormed MX412). Blood pressure was measured using a Hawkesley random zero sphygnomanometer and the phase IV diastolic pressure was used. The mean of two recordings was used on each occasion. Mean blood pressure was calculated by adding one third of the pulse pressure to the diastolic pressure.

Heart rate (over 1 min) and blood pressure were recorded pre-treatment and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after treatment.

The ability to concentrate was assessed by the subjects attempting to repeat 10 random numbers between 0 and 9. Two sets of numbers were read to the subject at each time point and the mean number of digits recalled was recorded. Sedation was assessed using a visual analogue scale. Sedation and random number recall were recorded pre-treatment and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 h after treatment.

The subjects were also asked to report any adverse effects and the interval between drug administration and their onset, and their character, severity and duration was noted.

## Results

Nine volunteers participated in these experiments and five men and three women completed the study. Mean age was 33.8 years (range 22–48). The remaining subject withdrew from the study after the first experimental day because of severe akathisia. Data from this subject have been included in the assessment of adverse effects, but not in the pharmacokinetic analysis.

### *Pharmacokinetics of prochlorperazine*

On two occasions a machine fault led to loss of plasma samples and insufficient plasma remained for the assay to be repeated. Prochlorperazine plasma concentrations were therefore measured in only six out of the eight subjects for the lower i.v. dose.

Following i.v. administration, the plasma concentration-time profile of prochlorperazine was adequately described by a biexponential equation. Figures 1 and 2 show mean plasma concentrations for the 12.5 mg and 6.25 mg i.v. doses respectively. The calculated pharmacokinetic parameters for the 12.5 mg and 6.25 mg i.v. doses are shown in Tables 1 and 2. There was marked interindividual variation in pharmacokinetics, but mean terminal half-life (± s.e. mean) was very similar for the two doses (6.8 ± 0.7 h for the higher dose and 6.9 ± 0.8 h for the lower dose). Plasma clearance and volume of distribution ($V$) of prochlorperazine were both high, but no significant differences were found between the two i.v. doses. These results suggest that prochlorperazine does not have dose-dependent kinetics over the dose range studied.

Following oral administration, prochlorperazine was identified in plasma in only four out of eight subjects. In these subjects the time to achieve peak plasma concentrations varied between 1.5 and 5 h and the median peak concentration was 3.4 ng $ml^{-1}$ (range 1.6–7.6). Prochlorperazine was present in a maximum of six of the plasma samples for any subject and it was

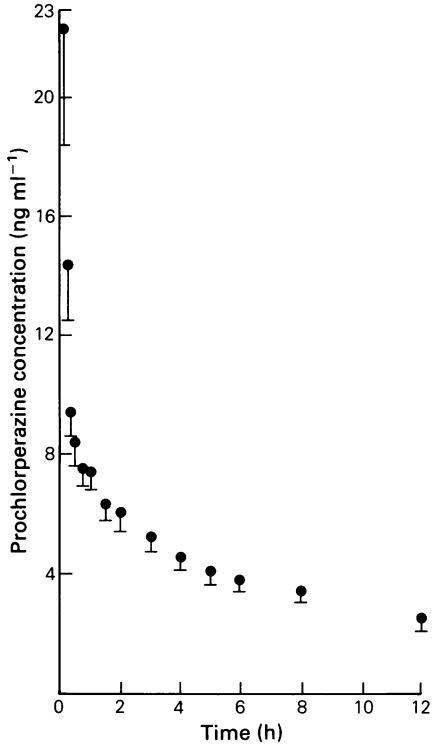


**Figure 1** Plasma prochlorperazine concentrations (mean ± s.e. mean) in eight normal subjects after 12.5 mg i.v. prochlorperazine.

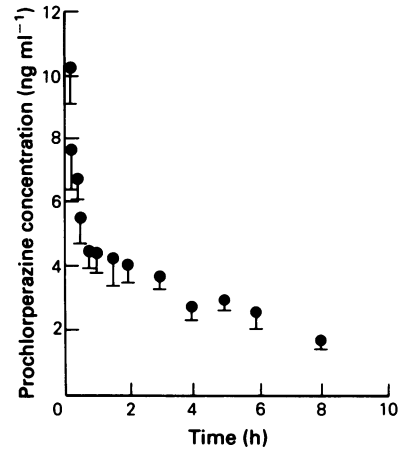


**Figure 2** Plasma prochlorperazine concentrations (mean ± s.e. mean) in six normal subjects after 6.25 mg i.v. prochlorperazine.

only possible to calculate an elimination half-life in two cases (GM $t_{½}$ 4.9 h; AR $t_{½}$ 3.1 h). In seven of the volunteers an unidentified peak was observed on the h.p.l.c. recording, eluting just before prochlorperazine. This peak was first seen 30 min–3 h after oral prochlorperazine administration and was assumed to be due to a metabolite. The maximum peak height occurred 1.5–4 h after dosing. The subject in whom this presumed metabolite could not be identified had the highest plasma concentrations of prochlorperazine after oral dosing and therefore did not appear to metabolise oral prochlorperazine as effectively as other subjects.

*Prolactin concentrations*

Median prolactin levels were significantly raised 1, 2 and 4 h after both 6.25 mg and 12.5 mg i.v. prochlorperazine compared to placebo ($P < 0.001$, Median test), and at each time point were

**Table 1** Pharmacokinetic parameters in healthy volunteers given prochlorperazine 12.5 mg i.v.

| *Subject* | *Age (years)* | *Weight (kg)* | $t_{½,\lambda_1}$ *(h)* | $t_{½,z}$ *(h)* | *Volume of distribution (l)* | *Plasma clearance (l h⁻¹)* |
|---|---|---|---|---|---|---|
| LN | 30 | 53.5 | 0.11 | 7.3 | 1279 | 121 |
| JL | 29 | 75.7 | 0.61 | 9.8 | 2402 | 170 |
| EM | 30 | 44.5 | 0.06 | 9.8 | 1260 | 89 |
| JD | 46 | 76.2 | 0.07 | 4.5 | 1859 | 284 |
| GM | 39 | 66.1 | 0.06 | 5.6 | 1486 | 186 |
| MG | 22 | 81.5 | 0.08 | 4.5 | 1064 | 163 |
| TB | 48 | 69.5 | 0.07 | 6.0 | 1261 | 145 |
| AR | 26 | 74.6 | 0.05 | 7.1 | 1773 | 173 |
| Mean | 33.8 | 67.7 | 0.14 | 6.8 | 1548 | 166 |
| ± s.e. mean | 3.4 | 4.5 | 0.07 | 0.7 | 155 | 20 |

**Table 2** Pharmacokinetic parameters in healthy volunteers given prochlorperazine 6.25 mg i.v.

| *Subject* | $t_{1/2,\lambda_1}$ *(h)* | $t_{1/2,z}$ *(h)* | *Volume of distribution (l)* | *Clearance ($l\,h^{-1}$)* |
|---|---|---|---|---|
| LM | 0.15 | 5.6 | 1526 | 190 |
| JL | 1.54 | 6.8 | 1518 | 155 |
| EM | 0.22 | 9.1 | 1193 | 91 |
| JD | 0.26 | 4.6 | 791 | 119 |
| MG | 0.05 | 5.9 | 1786 | 211 |
| AR | 0.12 | 9.3 | 1592 | 119 |
| Mean | 0.39 | 6.9 | 1401 | 148 |
| ± s.e. mean | 0.23 | 0.8 | 145 | 19 |

higher after the larger dose ($P < 0.05$, Sign test). The maximal concentrations were observed 1 h after i.v. prochlorperazine and, as expected, were significantly higher in women than men ($P < 0.02$, Mann Whitney U test).

Following oral prochlorperazine, prolactin concentrations did not start to rise until 2 h after administration and the highest concentrations observed were reached at 4 h. The median 4 h concentration was significantly higher than after placebo ($P < 0.001$, Median test), but was still considerably less than the maximum concentration after the i.v. doses (see Figure 3). There was no obvious relationship between serum prolactin concentrations and the concentrations of the presumed metabolite, but this needs further investigation.

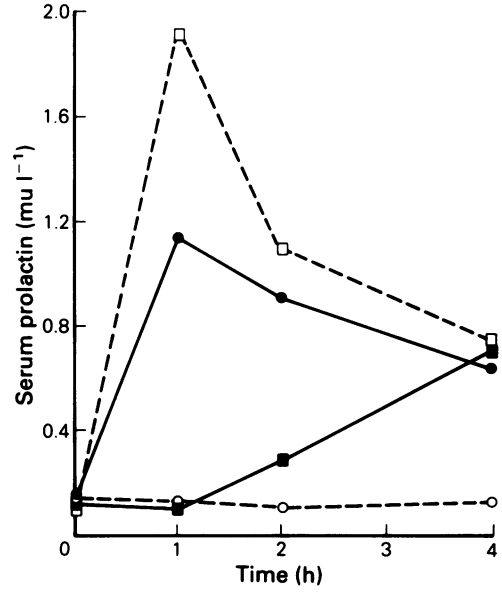


**Figure 3** Median serum prolactin levels in eight normal volunteers after oral and i.v. prochlorperazine (□ 12.5 mg i.v.; ● 6.25 mg i.v.; ■ 25 mg oral; ○ placebo).

*Sedation*

There was great variability in the degree of sedation noted by different subjects. With i.v. prochlorperazine, drowsiness began soon after drug administration and persisted for up to 2 h. Significant sedation was also noted 5 h after administration of oral ($P < 0.02$) and 6.25 mg i.v. prochlorperazine ($P < 0.05$) compared to placebo (Wilcoxon signed rank test). In all cases drowsiness was mild, could easily be overcome and was not usually felt to be unpleasant. There was no correlation between sedation (measured by the area under the sedation-time curve from 0–12 h) and the plasma concentration AUC for either of the i.v. doses.

*Random number recall*

The accuracy of random number recall varied greatly between subjects and was not significantly affected by either i.v. or oral prochlorperazine. The ability to recall random numbers was not affected by the degree of sedation.

*Blood pressure*

There were no significant changes in mean blood pressure following either i.v. or oral prochlorperazine. Two subjects who experienced severe akathisia after i.v. prochlorperazine did, however, have a rise in blood pressure 15 min after drug administration (115/71 → 129/84 mm Hg and 131/68 → 140/83 mm Hg). The blood pressure of one of these subjects had returned to the pretreatment value by 1.5 h, but the other subject's blood pressure was still raised 3 h after dosing. Increases in BP were not seen in the other volunteers.

*Heart rate*

There were no significant differences in heart rate between the four treatments at any time point, but the pattern of heart rate response did differ significantly following i.v. prochlorperazine (12.5 mg $P < 0.01$, 6.25 mg $P < 0.05$). Following placebo the resting heart rate fell initially and was significantly lower than pre-treatment values between 15 min and 3 h after dosing ($P < 0.01$ paired $t$-test). Heart rate had returned to pre-dose levels by 4 h. No such fall in heart rate was see after i.v. prochlorperazine and in four of the subjects who complained of akathisia after 12.5 mg i.v. prochlorperazine heart rate rose 15 min after dosing. This rise in heart rate was also seen in these subjects 15 min after the lower i.v. dose, although only one of them experienced adverse effects at this dosage. Heart rate had returned to pre-treatment levels by 30 min after i.v. dosing.

*Adverse effects*

The incidence of various adverse effects experienced by the subjects is shown in Table 3. Apart from sedation the main adverse effect was akathisia which was noted by six of the nine subjects who initially entered the study. The subject who withdrew after the first test day had received 6.25 mg i.v. prochlorperazine and experienced severe akathisia associated with a rise in heart rate (56 → 78 beats $min^{-1}$) and blood pressure. A further subject refused to complete all the physiological assessments on the final test day, withdrawing 3.5 h after 12.5 mg i.v. prochlorperazine, again because of akathisia, but sufficient data were obtained for this subject to be included in the results.

Symptoms mentioned by subjects with akathisia included tension, apprehension, motor restlessness, claustrophobia, inability to concentrate and feeling hot. The symptoms started within 15 min of drug administration and had usually resolved after 1–2 h. Three subjects also complained of feeling depressed and 'fed-up' or resentful about the trial and said they would not be willing to take part in a similar study again, as the adverse effects were so unpleasant. At the highest i.v. dose akathisia was not clearly related to the plasma prochlorperazine concentration as there was no difference in the area under the plasma concentration-time curve over the first 30 min between subjects with akathisia (3.2–8.8 ng $ml^{-1}$ h) and those unaffected (4.5–8.5 ng $ml^{-1}$ h). There was no correlation between the occurrence of akathisia and serum prolactin concentration.

One subject also complained of a dry mouth after treatment with oral prochlorperazine, possibly due to anticholinergic effects.

## Discussion

In this study the pharmacokinetics of prochlorperazine given i.v. were adequately described by a two-compartment model and did not appear to be dose-related. Very high values were obtained for the apparent volume of distribution. The plasma clearance values were apparently greater than liver plasma flow which suggests that the liver may not be the only site of metabolism.

Following oral administration of 25 mg prochlorperazine, the drug could only be detected in four out of eight healthy volunteers, due to a combination of lack of sensitivity of the assay and low bioavailability of prochlorperazine. Sankey *et al.* (1982) measured plasma prochlorperazine in one subject after a 12.5 mg oral dose and found a peak concentration of only 0.8 ng $ml^{-1}$ at 6 h after dosing. As the limit of sensitivity of our assay was 1 ng $ml^{-1}$, it is not surprising that prochlorperazine was often not detected, despite the higher dose given.

The unidentified peak noted on most of the chromatograms following oral prochlorperazine has also been observed by the manufacturers of

**Table 3** Number of subjects experiencing adverse effects of prochlorperazine

| | *Placebo* | *Oral* | *Prochlorperazine* 6.25 mg i.v. | 12.5 mg i.v. |
|---|---|---|---|---|
| Sedation | | | | |
| Early (< 2 h) | 2 | 0 | 5 | 3 |
| Late (4–6 h) | 0 | 6 | 4 | 4 |
| Akathisia | 0 | 0 | 1 | 5 |
| Depression | 0 | 0 | 1 | 3 |
| Dry mouth | 0 | 1 | 0 | 0 |

prochlorperazine (May and Baker, personal communication) and is thought to be a sulphoxide metabolite as it elutes on the chromatograph at the same point as prochlorperazine sulphoxide. However full identification using GC-MS has so far not been carried out.

Due to the low plasma concentrations after oral prochlorperazine the AUC oral could not be measured accurately but an estimate of bioavailability was obtained using the formula:

$$\text{Bioavailability} = \frac{\text{AUCoral}}{\text{AUCiv}} \times \frac{\text{Dose iv}}{\text{Dose oral}}$$

This gave a range of bioavailablity from 0–16%. A low bioavailability due to high first-pass metabolism would be expected for prochlorperazine because of its high plasma clearance.

This study has provided useful preliminary information of the i.v. pharmacokinetics of prochlorperazine which were previously unknown. The kinetics are in many ways similar to those of chlorpromazine, the most frequently studied phenothiazine. Dahl & Strandjord (1977) reported marked interindividual variation in pharmacokinetics after a single i.m. injection of chlorpromazine and after oral administration chlorpromazine sulphoxide was identified in plasma in all patients. No patient had sulphoxide present after i.m. dosing. The authors suggested that chlorpromazine may form sulphoxide in the intestinal wall and this could also be true for prochlorperazine.

The principal adverse effect of prochlorperazine in these studies was akathisia and most of the subjects experienced this after 12.5 mg i.v. prochlorperazine. Akathisia commonly occurs in patients receiving long-term neuroleptic drugs and has been reported in 20% patients taking prochlorperazine for 3 months or longer (Ayd, 1961). In studies of metoclopramide kinetics in normal volunteers, akathisia was common after i.v. dosing and was occasionally severe (Bateman *et al.*, 1978; Graffner *et al.*, 1979). In patients receiving metoclopramide akathisia is less often reported, even after high doses (Gralla, 1983), though this may be because investigators often do not specifically question patients about such symptoms.

In this study no acute dystonic reactions occurred. Other adverse effects observed were mild and transient, although most subjects experienced some sedation.

In conclusion this study suggests that the pharmacokinetics of prochlorperazine are not dose-dependent, but after oral dosing absorption seems slow and the bioavailability of prochlorperazine may be extremely low. A metabolite is formed after oral administration and further work is required to clarify its structure, biological activities and relation to serum prolactin levels. In the meantime, however, the mechanism of action of oral prochlorperazine would appear to require further study.

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