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CLINICAL PHARMACOKINETIC STUDIES OF PERPHENAZINE

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1 A gas-chromatographic method was used for the study in man of the kinetics of perphenazine (PPZ) and its sulphoxide metabolite (PPZ-SO). Various forms of PPZ administration were applied in eighteen schizophrenic patients and four healthy volunteers.

2 Following an i.v. dose of 5 or 6 mg a considerable fluctuation in the plasma concentration was noted before the exponential elimination phase. The average terminal half-life of PPZ was approximately 9.5 hours. PPZ-SO showed up quickly but in low concentrations.

3 After an oral dose of 6 mg no PPZ was detected in plasma and PPZ-SO only as traces. During continuous oral medication, 12 mg three times daily, a low systemic availability and a high PPZ-SO/PPZ ratio was found suggesting a marked first pass effect.

4 PPZ-enanthate given i.m. fortnightly resulted in PPZ-levels comparable to those seen after continuous oral medication, but PPZ-SO concentration were much lower. No accumulation was observed. The systemic clearance rate (average approximately 100 l/h) was the same after PPZ-enanthate i.m. and PPZ i.v., but varied three-fold individually.

5 Side effects were mostly, but not always, registered concomitant with high plasma levels of PPZ.

Introduction

The pharmacokinetics of neuroleptic drugs in man are still not well explored, in contrast to tricyclic antidepressants for example (Sjöqvist, 1971; Gram, 1974). For neuroleptics given in low doses the main reason seems to be lack of reliable plasma assays, but the complicated metabolic pattern of these drugs may also be responsible. With sufficient clinical kinetic information on neuroleptics it should be possible to investigate if these drugs act *per se* or through psychoactive metabolites, and subsequently a correlation between clinical effects and the plasma concentrations should be in sight. Furthermore, possible interactions with common concomitant therapy may be explained together with therapeutic resistance caused by exceptional individual kinetic variations.

Information on assays and the human kinetics of neuroleptics is now emerging (Curry, 1968; Turano, March, Turner & Merlis, 1972; Jørgensen & Gottfries, 1972; Simpson, Lament, Cooper, Lee & Bruce, 1973; Mårtenson & Ross, 1973; Kelsey, Keskiner & Moscatelli, 1973; Forsman & Öhman, 1974) and also perphenazine's (PPZ, Trilafon®) kinetics in man have been touched on (Huang & Kurland, 1964; van Kempen, 1971; Larsen & Naestoft, 1973; Hansen & Kragh-Sørensen, 1973; Hansen & Larsen, 1974). Recently a new, specific and sensitive plasma assay for PPZ and its sulphoxide metabolite (PPZ-SO) was published from our laboratories (Larsen & Naestoft, 1975). The present study was subsequently undertaken to clarify some human kinetic parameters after different kinds of administration of this widely used neuroleptic. The purpose was to create the basis

for later studies of the correlation between kinetic behaviour and clinical effects of PPZ in order to establish a therapeutic plasma range, if possible.

Patients and volunteers

A total of eighteen patients and four healthy subjects volunteered for the study. Age, sex, weight are given in Tables 1, 2 and 3. All the patients were diagnosed as schizophrenics according to the WHO classification system and were hospitalized in the psychiatric ward, needing neuroleptic drug therapy. Otherwise they were completely healthy as judged from clinical and biochemical examinations; hepatic, renal and cardiovascular functions were in particular found normal. All patients had previously been treated with various neuroleptics and some other drugs, but not for the last 3-4 weeks before the study, except if specifically indicated. During the investigational period no other medication was allowed except what is stated in Table 2. If a patient needed an anti-Parkinsonian drug, this was continued to the end of the period. The investigational scheme, its purpose and its potential risks was thoroughly explained to all patients before they gave their consent. The four healthy volunteers were all male physicians at the hospital in excellent physical and psychic conditions.

Investigational design

Both single dose and multiple dose kinetics were investigated after parenteral, as well as after oral administration. Only total plasma concentrations were measured and no attempt was made to examine the protein binding. Urine was collected and stored, and the analytical results will be published elsewhere. The following side-effects were specifically recorded: akathisia, akinesia, sleepiness and Parkinsonism, the volunteers by self-rating and the patients by global evaluation.

Five different investigational protocols were used:

Protocols for intravenous administration: (a) Four patients (nos. 1-4) received an i.v. injection of PPZ (5 mg) (Inject. Trilafon®) in the morning and venous blood samples were drawn at frequent intervals for the next 24 h (cf. Figures 1a & b). (b) Four volunteers (nos. 19-22) received an i.v. injection of PPZ (6 mg) (Inject. Trilafon®) and venous blood samples were drawn frequently for the next 24 h (cf. Figures 1a & b). The reason for using 6 mg in part (b) was the intention of also examining the systemic bioavailability of PPZ by comparing the results with those obtained after oral administration (see below). However, only 2 and 4 mg tablets are available. In both part (a) and (b) the subjects had fasted overnight and no meals were allowed for the first 5 hours. During the entire investigation the subjects were resting comfortably in bed.

Protocols for oral administration: (c) Six weeks after the i.v. dose the four healthy volunteers received an oral dose of PPZ (6 mg) (Tabs. Trilafon®) and blood samples were drawn frequently during the first 4 h, thereafter with longer intervals up to 30 hours. Prior to the investigation the subject had been fasting for 8 hours. (d) Four patients (nos. 5-8) were investigated after 1 week of continuous PPZ treatment on a dose of 12 mg three times daily (06.00 h, 14.00 h, 22.00 h). On the day of investigation blood samples were taken just before the 06.00 h dose and then every hour for the next two dose intervals (i.e. until 22.00 h, cf. Figure 2). Normal meals were allowed.

Protocol for continuous parenteral medication with PPZ-enanthate: (e) Ten patients (nos. 9-18) received PPZ-enanthate (Inject. Trilafon-enanthate®), deeply intramuscularly in the gluteal region, at intervals of 2 weeks. The doses are stated in Figure 3. During the initial two periods blood samples were drawn every day or every second day in the beginning, later with greater intervals (cf. Figure 3). During the following periods (up to 14 weeks of treatment) only one blood sample was taken just before the next injection. In one patient (no. 17) the dosage was changed from the first to the second period due to side-effects. In some of the patients additional medicine was given (cf. Table 2). In most patients treated with PPZ-enanthate the treatment was a continuation of oral or i.m. medication. However, only the second dose interval (i.e. the second 2-week period) was used for calculations. During the last periods several of the patients were discharged from hospital and seen in the out-patient clinic.

Analytical procedures

The assay was performed on plasma (2.5 ml), from which PPZ and PPZ-SO were extracted in alkaline solutions and the extracts washed over sulphuric acid. The compounds were then re-extracted and derivatized with N,O-bis-(trimethylsilyl)-acetamide making stable trimethylsilyl derivatives. A gas chromatograph equipped with an electron capture detector was used. Within the therapeutic range, the accuracy of the assay was found to be ±10% for both compounds. The lower limit for quantitation was found to be 0.2 μg/l $\cong$0.5 nmol/l. For further details see Larsen & Naestoft (1975).

In the majority of plasma samples the 7-hydroxy metabolite was also measured. However, the plasma concentrations of both the

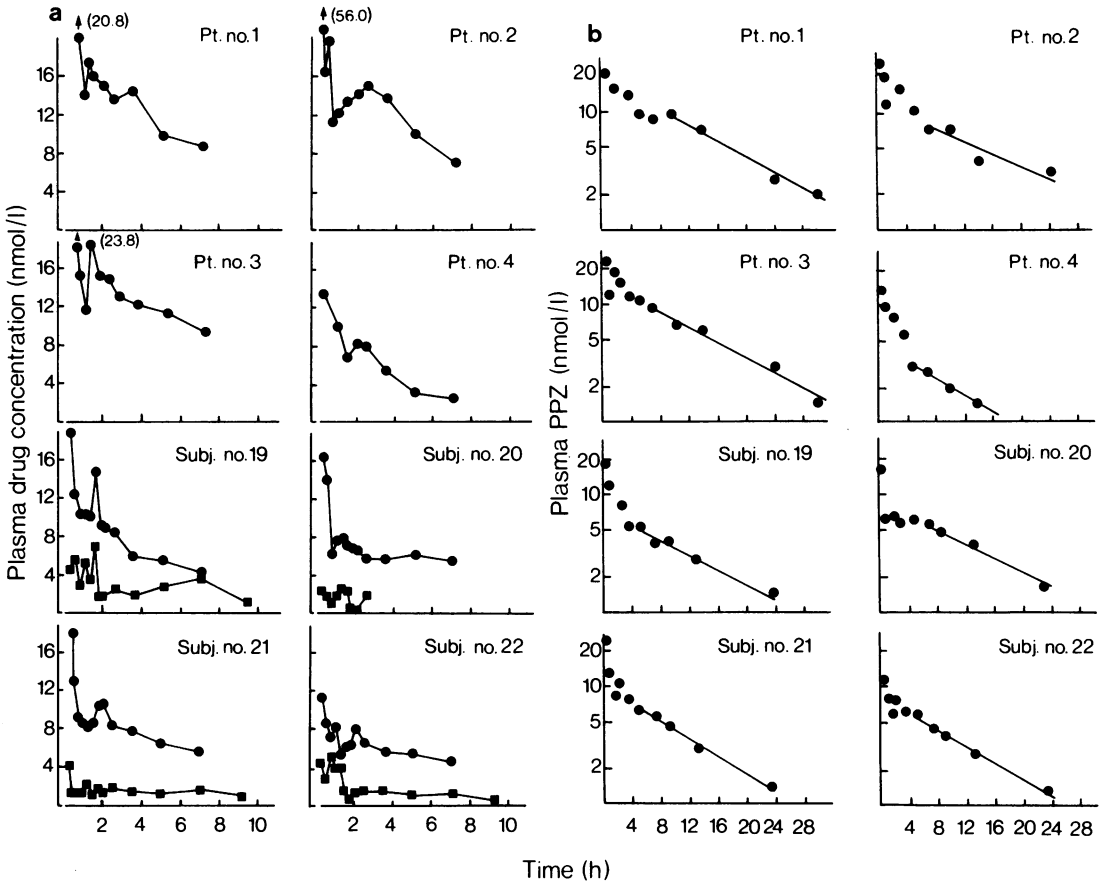

Figure 1a Plasma concentrations of PPZ (•) and PPZ-SO (▪) from the eight subjects (cf. Figure 1b) during the first 7 h after a single i.v. dose of PPZ. Measurements of plasma PPZ-SO were only carried out in patients no. 5-8. Note the ordinate is an arithmetic scale.

Figure 1b Plasma concentrations of PPZ from eight subjects after a single i.v. dose of PPZ. Note the ordinate is a logarithmic scale. The terminal elimination curve is drawn.

non-conjugated and the conjugated forms of this metabolite are negligible compared to PPZ (<5%).

In all ten patients treated with PPZ-enanthate i.m. PPZ and PPZ-SO were also analysed in whole blood. However, these results were difficult to interpret as an *in vitro* sulphoxidation sometimes seems to occur unpredictably in whole blood, but not in plasma (unpublished observations). In all cases, therefore, special precautions were taken to separate plasma from blood as quickly as possible in order to avoid a possible cause of error in the plasma determination.

Samples of the injection preparations and the tablets used were analysed in order to verify the declared content. In all cases the content of PPZ was found in accordance with the declaration.

Calculations

Terminal half-lives (β-slope) after i.v. injections were calculated by the least squares method based on the last four to five plasma concentrations in a semi-logarithmic plot (Figure 1b). Systemic clearance (Cl_s) was estimated by:

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

where AUC is the area under the total plasma concentration time curve after either i.v. or i.m. injections calculated by the trapezoidal rule and the remaining area estimated as the last concentration divided by β. The apparent volume of

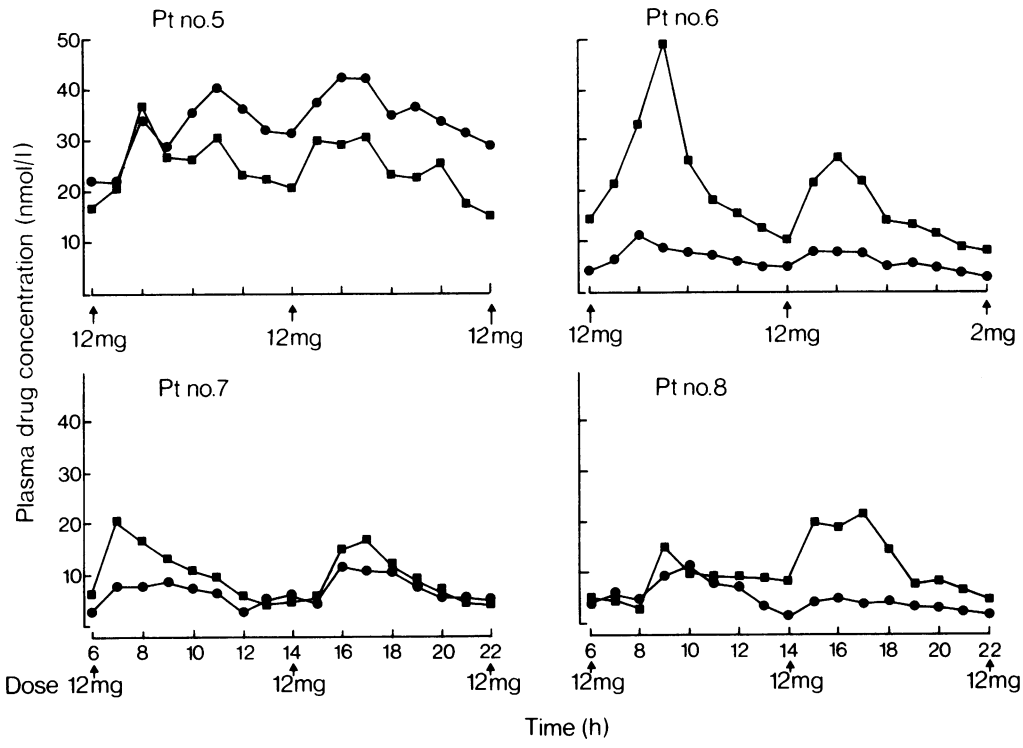

Figure 2 Plasma concentrations of PPZ (•) and PPZ-SO (▪) from four patients on continuous treatment with PPZ every 8 h (steady-state conditions), during two dose intervals.

distribution $V_{D\beta}$ was calculated from the i.v. curves by:

$$V_{D\beta} = \frac{Cl_s}{\beta} = \frac{Dose}{AUC \cdot \beta}$$

During oral treatment the AUC was measured in two consecutive 8 h periods for both PPZ and PPZ-SO. An estimation of the systemic bioavailability was made on the basis of the AUC of PPZ using the average of the AUC i.v. (patient nos. 1-4 and subject nos. 19-22) as a reference corrected for dose, cf. Table 3.

Table 1 Data and results for four patients and four volunteers receiving an intravenous injection of PPZ

Subject number	*Age (years)*	*Sex*	*Weight (kg)*	*PPZ dose (mg)*	$T_{\frac{1}{2}}$ *(h)*	β (h^{-1})	*Plasma clearance (Dose/AUC (l/h)*	V_D *(Cl/β.kg) l/kg*
1	60	F	59.0	5	9.0	0.076	49	10.8
2	36	M	54.5	5	12.3	0.056	68	22.2
3	47	M	79.9	5	9.5	0.073	57	9.8
4	20	M	61.5	5	8.1	0.086	183	34.6
19	28	M	69.0	6	9.8	0.071	131	26.7
20	36	M	78.2	6	9.6	0.072	120	21.3
21	34	M	83.5	6	8.4	0.083	106	15.3
22	38	M	85.0	6	8.5	0.082	144	20.7
					Mean 9.4		107	

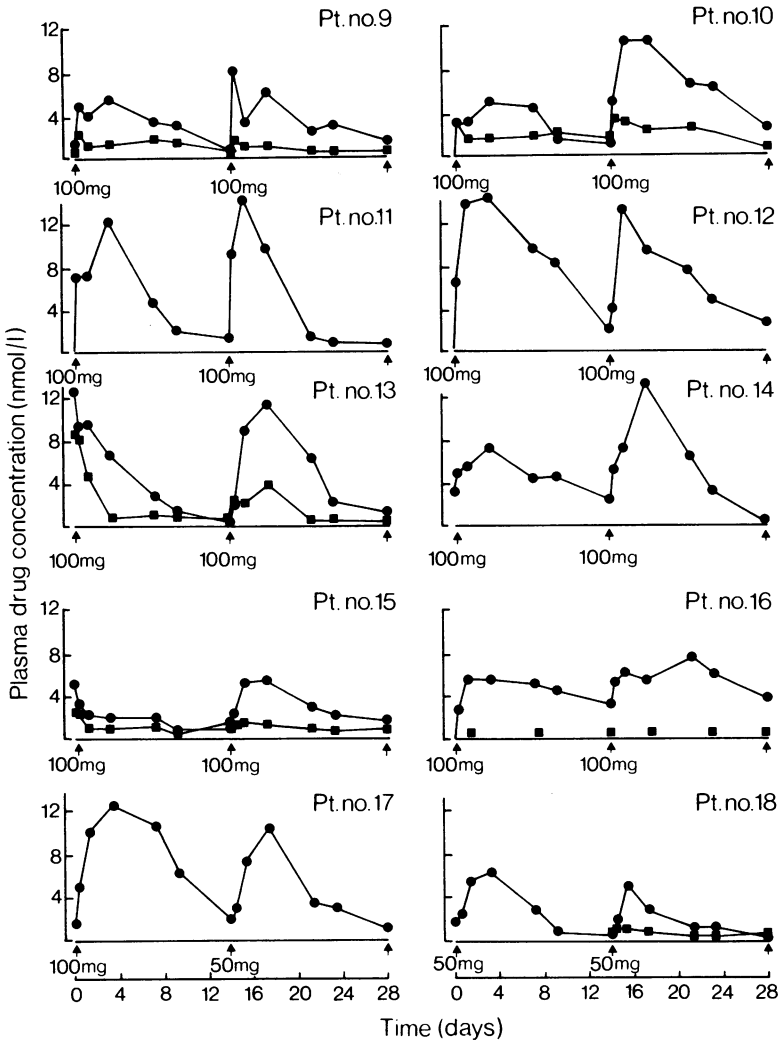

Figure 3 Plasma concentrations of PPZ (•) and PPZ-SO (▪) during two dose intervals (of 2 weeks each) in ten patients treated with PPZ-enanthate i.m. Some of the patients had been treated with PPZ tablets until PPZ-enanthate was started. Only the second period was used for calculations.

Results

From Figure 1b it is evident that the terminal PPZ elimination from plasma after i.v. injection is exponential, and that more than one compartment is involved. However, when all the actual observed concentrations during the first 6 h are plotted (Figure 1a), it is a rather uniform finding that a redistribution phenomenon takes place. Consequently, to define a clear α-phase is not possible and further attempts to calculate different distribution volumes and the true elimination constant were avoided. Table 1 gives the terminal half-life ($T\frac{1}{2}$), β, V_{d_β} and the plasma clearance for eight subjects. The half-life of PPZ in plasma was found to be 9.4 h varying from 8.4 to 12.3 h. The clearance, however, varied more than three-fold in this limited sample. PPZ-SO appears rapidly, but in relatively low concentrations (Figure 1a).

By analysing plasma from four volunteers after a single oral dose of PPZ (6 mg), no PPZ at all could be detected, even after an extended period of time. Only in few instances were low concentrations of PPZ-SO demonstrated.

The plasma concentration time curves for both PPZ and PPZ-SO from four patients on continuous oral medication during two dose intervals under steady-state conditions are given in Figure 2. It is evident that the metabolite level is much higher than seen after parenteral administration.

Figure 3 presents the plasma concentration curves during two fortnightly dose intervals in ten patients receiving intramuscular injections of PPZ-enanthate. Table 2 gives the clearance values for PPZ after the enanthate injections. The results are in excellent agreement with the results obtained after i.v. application. A substitute for the AUC during a dose interval was sought, but no single day value could be used. Figure 4 shows that the mean of the results from day 3 and day 9 is highly correlated to the AUC. Table 4 gives the minimum concentrations obtained at the end of further dose intervals during continued PPZ-enanthate treatment. No accumulation of PPZ or PPZ-SO could be demonstrated.

The systemic availability of PPZ during continuous oral medication seems to be variable and often poor (Table 3). Concomitantly the PPZ-SO/PPZ ratio was found high.

The results of the side-effect registration were not suitable for a detailed evaluation, in particular not for the purpose of describing a relationship

Table 2 Data and plasma clearance values for ten patients receiving intramuscular PPZ-enanthate every 2 weeks For the doses given see Figure 3. The clearance is calculated on the basis of the second treatment period

Subject number	*Age (years)*	*Sex*	*Weight (kg)*	*Plasma clearance (Dose/AUC l/h)*	*Other medication*
9	37	F	63.0	160	Nortriptyline (25 mg x 2)
10	38	M	82.0	81	Benztropine
11	32	M	75.0	118	Biperidine
12	61	F	61.0	83	0
13	20	M	62.0	100	Biperidine
14	30	M	100.0	102	Lithium carbonate from day 15
15	26	F	60.0	162	0
16	30	M	85.0	93	0
17	37	M	54.0	58	Biperidine
18	27	F	49.0	140	Biperidine
1-4 (cf. Table 1)				89	
19-22 (cf. Table 1)				125	
Mean plasma clearance:				110 107	

Table 3 Data and results from two 8 h period (a dose interval) from four patients in steady state, treated with PPZ orally (12 mg) every 8 h

Subject number	*Age (years)*	*Sex*	*Weight (kg)*	*8 h period*	*'f'*	*Ratio: $\frac{PPZ\text{-}SO_{AUC}}{PPZ_{AUC}}$*
i.v. (19-22)					(1.00)	0.22
i.m. (9, 10, 13, 15, 18)					(1.00)	0.24
5	42	F	58.1	1	0.92	0.80
				2	1.05 → 0.99	0.68 → 0.74
6	25	M	63.0	1	0.21	3.25
				2	0.18 → 0.20	2.63 → 2.94
7	21	M	60.0	1	0.18	1.72
				2	0.22 → 0.20	1.17 → 1.45
8	25	M	67.7	1	0.19	1.23
				2	0.10 → 0.15	3.59 → 2.10

'f' is the estimated relative systemic bioavailability factor after oral administration calculated by dividing the actual oral AUC (corrected for dose) by the average i.v. AUC (corrected for dose).

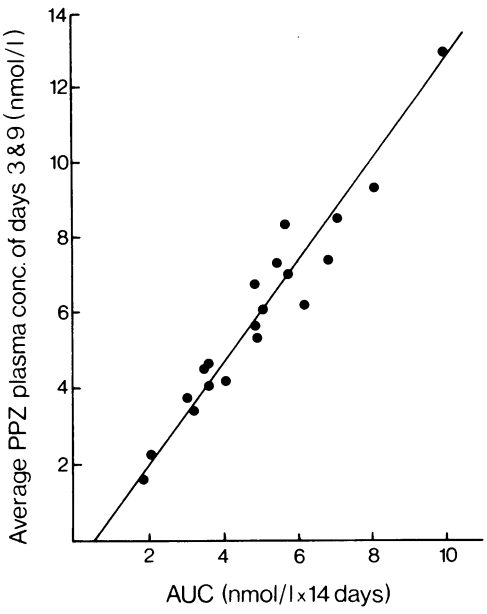

Figure 4 The correlation ($r = 0.97$) between the AUC of the PPZ plasma concentration-time curves of Figure 3 and the average of the plasma concentrations of days 3 and 9.

between plasma level and acute side-effects. However, after i.v. administration the listed side-effects appeared rapidly in almost all cases, although to a varying degree, but they outlasted the fall in the plasma concentration by several hours. Among the patients on continuous treatment, akathisia and Parkinsonism were associated with high PPZ concentrations (patient nos. 5, 10, 11, 13 and 17). On the other hand patients nos. 12 and 14 had high levels without serious side-effects and patient no. 18 had side-effects with a low plasma level.

Discussion

The clinical pharmacokinetics of PPZ have not been studied in detail before. The present results reveal some rather peculiar features, that might have clinical implications. Thus in the first 3-5 h after an i.v. injection considerable fluctuations in plasma concentrations seem to be a constant phenomenon. This initial phase of redistribution could reflect a significant entero-hepatic circulation, but it is not related to intake of food. The last part of the i.v. curves is clearly exponential, giving an average half-life of PPZ of approximately 9.5 hours.

The average systemic clearance after i.v. administration was calculated to approximately 100 l/h (= 1.6 l/min), which is close to the expected hepatic flow rate. Assuming complete availability for PPZ-enanthate i.m., the clearance for this administration form is of the same order of magnitude. This rather high systemic clearance may suggest that PPZ is not only extracted from

Table 4 Plasma concentrations (nmol/l) of PPZ and PPZ-SO in ten patients treated with PPZ-enanthate i.m. Blood samples taken just before the next injection, i.e. at the end of each 2 week period. For the doses given see Figure 3

Patient number		*End of week number* 2	4	6	8	10	12	14
9	PPZ	0.7	1.7	3.0	<0.5	2.5	2.5	1.0
	PPZ-SO	0.7	0.7	1.4	0.7	1.0	0.7	1.0
10	PPZ	1.2	2.7	4.2	3.5	5.0	2.2	–
	PPZ-SO	1.7	0.7	1.7	0.7	1.0	<0.5	–
11	PPZ	1.5	1.0	1.2	1.2	1.0	1.0	<0.5
	PPZ-SO	–	–	0.7	0.7	0.5	0.5	<0.5
12	PPZ	2.2	3.0	3.7	1.7	1.2	<0.5	–
	PPZ-SO	–	–	2.4	1.2	0.7	<0.5	–
13	PPZ	<0.5	1.5	<0.5	0.5	1.2	–	–
	PPZ-SO	0.7	0.5	0.7	<0.5	<0.5	–	–
14	PPZ	2.7	<0.5	–	–	–	–	–
	PPZ-SO	–	–	–	–	–	–	–
15	PPZ	1.2	2.0	–	–	–	–	–
	PPZ-SO	1.7	1.2	–	–	–	–	–
16	PPZ	3.5	4.2	–	–	–	–	–
	PPZ-SO	<0.5	<0.5	–	–	–	–	–
17	PPZ	2.0	1.2	1.0	<0.5	<0.5	0.7	<0.5
	PPZ-SO	–	–	0.7	<0.5	<0.5	1.2	<0.5
18	PPZ	0.7	0.5	<0.5	<0.5			
	PPZ-SO	–	0.7	0.7	0.7			

plasma in the liver (Wilkinson, 1975). Therefore it would be of interest to examine the whole blood/plasma ratio for PPZ, but this must wait until the methodological problems mentioned previously have been settled. By comparing the clearance values with the age of the patients a decrease in the clearance with increasing age cannot be ruled out (Tables 1 & 2), but more extensive studies are needed.

Calculations of the systemic availability after oral administration were not possible after a single, low oral dose as nothing could be detected in plasma. However, after continuous oral medication with larger doses estimations reveal a poor systemic availability in three out of four cases. This could be due to a low absorption from the gut, but a pronounced first pass effect must also be considered. PPZ is rapidly metabolized to its sulphoxide product, presumably its main metabolite. Maximum levels of PPZ-SO in plasma occur 10-15 min after an i.v. injection, but in low concentrations. By oral administration PPZ-SO concentration is very high in plasma suggesting a considerable 'first pass' metabolism, either in the intestine as seen for chlorpromazine in rats (Curry, D'Mello & Mould, 1970; Minder, Schnetzer & Bichel, 1971), or in the liver, which would be in accordance with the high values for the systemic clearance of PPZ. A possible entero-hepatic circulation may enhance the result of the latter mechanism further.

The plasma half-lives of PPZ and the plasma concentration/time curves (Figure 2) suggest oral treatment should be administered on an 8 h dose schedule. Longer intervals with higher doses would probably cause too much fluctuation. PPZ-enanthate given i.m. every second week demonstrated 'therapeutic' plasma levels for most of the period without accumulation of either PPZ or PPZ-SO in plasma. In that respect the dose interval is probably well chosen. The PPZ concentration rises in plasma within a few hours after PPZ-enanthate injection and reaches a maximum within 2-3 days. This initial high absorption peak after PPZ-enanthate may not have been intended, and its significance for the anti-psychotic effects is dubious, although the optimal therapeutic PPZ-level in plasma is still not known. Since the most serious neurological and sedative effects occurred during the first days after the injection (see below), the initial high absorption must be considered undesirable. The difference in dose/day ratio between conventional oral and i.m. enanthate administration of PPZ is very marked. However, the average plasma concentrations, e.g. expressed by the AUC in a dose interval, do not differ very much from each other, as the systemic availability is poor by the oral route. Thus, it seems hardly relevant to argue that PPZ-enanthate treatment is advantageous to oral treatment because of the low dosage, erroneously implying lower levels in the body with the same effect.

For the quick estimation of plasma kinetics of PPZ during enanthate treatment it was demonstrated that two blood samples during a 2-week period can give a representative impression of the average (but not necessarily the peak concentration (Figure 4). This observation will probably ease further studies of this administration form. The mechanism behind the low and variable systemic bioavailability after oral administration should be explored in detail, as a dose-dependent extraction cannot be excluded, although no clinical observation so far seems to support this.

Neurological and sedative side-effects were not rated precisely and frequently enough for a real evaluation. Furthermore, a bias may be introduced by the non-blind ratings, but the general impression was an excess of side-effects during the first 2-3 days after the enanthate injection, a time which later was found to coincide with the highest PPZ-concentrations. Especially one severe Parkinsonian crisis was observed (patient no. 17) at the maximal concentration. The present study has, however, not revealed a relation between the height of the plasma concentration of PPZ and the usual neuroleptic side-effects. It was not possible to investigate a relationship between the PPZ-SO concentration and side-effects on the basis of our data.

The antipsychotic effect of PPZ and its relation to plasma levels was not the aim in the present study, but such information is of paramount importance in order to evaluate if some of the clinical problems in the use of chlorpromazine also apply to PPZ, e.g. if varying sulphoxidation influences the therapeutic effect (Sakalis, Chan, Gershon & Park, 1973; Mackay, Healy & Baker, 1974), and whether or not a self-induction of the biotransformation takes place (Curry, Lader, Mould & Sakalis, 1972). Other problems are concerned with the interaction with other drugs, e.g. concomitant anti-Parkinson therapy (Rivera-Calimlim, Castaneda & Lasagna, 1973) or the demonstrated interaction between PPZ and nortriptyline (Gram, Overö & Kirk, 1974). Thus, the results of the present study do form a basis for further investigations into the relation between kinetic parameters (e.g. plasma concentrations) and the effects of PPZ.

References

CURRY, S.H. (1968). Determination of nanogram quantities of chlorpromazine and some of its metabolites in plasma using gas liquid chromatography with an electron capture detector. *Analyt. Chem.*, **40**, 1251-1257.

CURRY, S.H., D'MELLO, A. & MOULD, G.P. (1970). Destruction of chlorpromazine during absorption by rat intestine *in vitro*. *Br. J. Pharmac.*, **40**, 538-539P.

CURRY, S.H., LADER, M.H., MOULD, G.P. & SAKALIS, G. (1972). Clinical pharmacology of chlorpromazine. *Br. J. Pharmac.*, **44**, 370-371P.

FORSMAN, A. & ÖHMANN, R. (1974). On the pharmacokinetics of haloperidol. *Nord. Psychiat. Tidsskr.*, **28**, 441-448.

GRAM, L.F. (1974). Metabolism of tricyclic antidepressants–a review. *Dan. Med. Bull.*, **21**, 218-228.

GRAM, L.F., OVERÖ, K.F. & KIRK, L. (1974). Influence of neuroleptics and benzodiazepines of metabolism on tricyclic antidepressants in man. *Am. J. Psychiat.*, **131**, 863-866.

HANSEN, C.E. & KRAGH-SØRENSEN, P. (1973). Clinical-pharmacological aspects of measuring perphenazine in human blood. *Acta Psychiat. Scand. Suppl.*, **246**, 18-21.

HANSEN, C.E. & LARSEN, N.-E. (1974). Perphenazine concentrations in human whole blood. *Psychopharmacologia (Berl.)*, **37**, 31-36.

HUANG, C.L. & KURLAND, A.A. (1964). Perphenazine (Trilafon) metabolism in psychotic patients. *Arch. Gen. Psychiat.*, **10**, 639-646.

JØRGENSEN, A. & GOTTFRIES, C.G. (1972). Pharmacokinetic studies on flupenthixol and flupenthixol decanoate in man using tritium labelled compounds. *Psychopharmacologia (Berl.)*, **27**, 1-10.

KELSEY, M.I., KESKINER, A. & MOSCATELLI, E.A. (1973). Gas-liquid chromatographic analysis of fluphenazine and fluphenazone sulfoxide in the urine of chronic schizophrenic patients. *J. Chromatogr.*, **75**, 294-297.

LARSEN, N.-E. & NAESTOFT, J. (1973). Determination of perphenazine and fluphenazine in whole blood by gas chromatography. *Med. Lab. Techn.*, **30**, 129-132.

LARSEN, N.-E. & NAESTOFT, J. (1975). Determination of perphenazine and its sulphoxide metabolite in human plasma after therapeutic doses by gas chromatography. *J. Chromatograph.*, **109**, 259-264.

MACKAY, A.V.P., HEALEY, A.F. & BAKER, J.V. (1974). The relationship of plasma chlorpromazine to its 7-hydroxy- and sulphoxide metabolites in a large population of chronic schizofrenics. *Br. J. clin. Pharmac.*, **1**, 425-430.

MÅRTENSSON, E. & ROSS, B.-E. (1973). Serum levels of thioridazine in patients and healthy volunteers. *Eur. J. Clin. Pharmac.*, **6**, 181-186.

MINDER, R., SCHNETZER, F. & BICHEL, M.H. (1971). Hepatic and extrahepatic metabolism of the psychotropic drugs, chlorpromazine, imipramine and imipramine N oxide. *Naunyn-Schmiedebergs Arch. Pharmak.*, **268**, 334-347.

RIVERA-CALIMLIM, L., CASTANEDA, L. & LASAGNA, L. (1973). Effects of mode of management on plasma chlorpromazine in psychotic patients. *Clin. Pharmac. Ther.*, **14**, 978-986.

SAKALIS, G., CHAN, T.L., GERSHON, S. & PARK, S. (1973). The possible role of metabolites in therapeutic response to chlorpromazine treatment. *Psychopharmacologia (Berl.)*, **32**, 279-284.

SIMPSON, G.M., LAMENT, R., COOPER, T.B., LEE, J.H. & BRUCE, R.B. (1973). The relationship between blood levels of different forms of butaperazone and clinical response. *J. clin. Pharmac.*, **8**, 288-297.

SJÖQVIST, F. (1971). A pharmacokinetic approach to the treatment of depression. *Int. Pharmacopsychiat.*, **6**, 147-169.

TURANO, P. MARCH, J.E., TURNER, W.J. & MERLIS, S. (1972). Qualitative and quantitative report in chlorpromazine and metabolites in plasma, erythrocytes and erythrocyte-washings from chronically medicated schizophrenic patients. *J. Med.*, **3**, 109-120.

VAN KEMPEN, G.M.J. (1971). Urinary excretion of perphenazine and its sulfoxide during administration of oral and long-acting injectable form. *Psychopharmacologia (Berl.)*, **21**, 283-286.

WILKINSON, G.R. (1975). Pharmacokinetics of drug disposition. Hemodynamic considerations. *Ann. Rev. Pharmac.*, **15**, 11-27.

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