PLASMA LEVELS OF PERPHENAZINE AND ITS MAJOR METABOLITES DURING SIMULTANEOUS TREATMENT WITH ANTICHOLINERGIC DRUGS

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1 A gas chromatographic method was applied to study plasma levels of perphenazine (PPZ) and its major metabolites in man before and during simultaneous antiparkinson treatment. Twenty-six psychotic patients received various forms of PPZ administration as well as antiparkinson drugs.

2 Biperidine (5 mg) was administered intravenously to each of five patients, who 5 days earlier had had a single dose of PPZ-enanthate i.m. No significant alterations in plasma concentrations of PPZ were observed.

3 In fourteen patients receiving oral PPZ treatment the plasma levels of PPZ and its metabolites did not deviate significantly from controls after addition of biperidine or orphenadine given for 3 weeks in fixed oral doses.

4 The ratio between PPZ plasma concentration measured 4 and 7 h after the morning dose was not affected by concomitant antiparkinson therapy.

5 It is concluded that no clinically relevant pharmacokinetic interaction takes place between PPZ and two generally used antiparkinson drugs during steady-state conditions in psychotic patients.

Introduction

The human pharmacokinetics of a widely used neuroleptic, perphenazine (PPZ) (Trilafon®) has been extensively studied by our group (Eggert Hansen & Larsen, 1974; Eggert Hansen, Rosted Christensen, Elley, Bolvig Hansen, Kragh-Sørensen, Larsen, Naestoft & Hvidberg, 1976; Bolvig Hansen & Larsen, 1977), but never with a view to a possible interaction between neuroleptics and antiparkinsonism drugs of the anticholinergic type. Interactions between the two kinds of drugs have, however, been suspected (Loga, Curry & Lader, 1975; Singh & Kay, 1975a and b) and may be of clinical importance, as extrapyramidal side-effects frequently appear during neuroleptic therapy and necessitate additional treatment with antiparkinsonism drugs.

The aim of the present investigation has been to evaluate whether initiation of antiparkinsonism treatment with drugs such as biperidine and orphenadine to patients receiving continuous therapy with PPZ, would influence the plasma levels of this

drug and its metabolites to an extent, where *clinical* interaction may be apprehended. In order to do so, it is important to monitor the steady-state plasma concentrations of both the investigated drug and its major metabolites before and during additional anticholinergic therapy.

Methods

Patients and general design

A total of 44 patients agreed to take part in the investigation, and 26 completed the study. Age, sex and weight, as well as diagnoses and daily dose of PPZ are listed in Tables 1 and 2. All patients were hospitalized during the entire study and were on neuroleptic drug therapy according to the routine treatment of such patients in the department. In all other respects the patients were completely healthy, as judged from

clinical and biochemical examinations. In particular, hepatic, renal and cardiovascular functions were found normal. Some of the patients had previously been treated with PPZ, but not for the last 4 weeks prior to the study. No other medication was allowed during the period of investigation, except for occasional nitrazepam. The purpose of the study, its implementation and potential risks were thoroughly explained to the patients, before they gave their verbal consent to enter the study.

Plasma levels of PPZ and two metabolites were measured before and during treatment with one of two antiparkinsonism drugs. PPZ was administered either parenterally or orally. Side-effects such as akathisia and Parkinsonism were evaluated according to a

specified rating scale (Simpson & Angus, 1970) to exclude patients with side-effects.

Parenteral administration

This part of the study was aimed at measuring the possible immediate effect of parenterally administered antiparkinsonism drugs on PPZ and PPZSO plasma concentrations after a single dose of PPZ-enanthate (Trilafon® -enanthate). Five patients (Nos 1–5) received PPZ-enanthate as an intramuscular injection in the gluteal region on day 1. The doses are given in Table 1. On the fifth day, at 10.00 h, 1 ml of an injection solution taken from an ampoule identical to a normal Akineton® -ampoule, but not containing

Table 1 Clinical data and diagnoses for five patients, treated 5 days earlier with Trilafon® -enanthate i.m.

Patient No.	Sex	Age (years)	Weight (kg)	Dose/14 days (mg)	Diagnosis
1	M	36	68	75	Schizophrenia
2	M	30	82	100	Schizophrenia
3	M	27	73	100	Schizophrenia
4	M	32	71	100	Schizophrenia
5	M	32	88	100	Schizophrenia

Table 2 Clinical data and diagnoses for twenty-one patients, on continuous PPZ treatment

Patient No.	Sex	Age (years)	Weight (kg)	Dose/day (mg)	Diagnosis
C 6	M	20	87	24	Psychosis limitare
7	F	52	54	24	Reactive confusion
15	M	29	75	48	Schizophrenia
16	F	55	66	35	Reactive psychotic paranoia
18	F	30	77	36	Schizophrenia
20	F	38	52	24	Reactive psychotic paranoia
24	F	53	53	24	Schizophrenia
O 8	F	58	58	36	Schizophrenia
9	M	25	61	36	Schizophrenia
14	F	46	54	24	Reactive confusion
17	F	26	60	24	Schizophrenia
19	F	53	62	24	Reactive psychotic paranoia
21	F	58	54	24	Reactive psychotic paranoia
26	F	24	52	24	Psychosis limitare
B 10	F	57	62	36	Schizophrenia
11	F	29	48	24	Psychosis limitare
12	F	44	57	48	Reactive psychotic paranoia
13	M	29	75	24	Psychosis limitare
22	F	37	49	24	Reactive psychotic paranoia
23	M	34	68	24	Psychosis limitare
25	F	24	52	36	Psychosis limitare

C = control group; O = orphenadine group; B = biperidine group.

Investigational design

▲ Random allocation of the patients into three groups of antiparkinson treatment

▲▲ Blood samples

C_0 : Control period sampling

C_1 : First sampling period during antiparkinson treatment

C_2 : Second sampling period during antiparkinson treatment

Figure 1 Investigational design of the oral study. ↑ Random allocation of the patients into three groups of antiparkinson treatment. ↑↑ Blood samples. C_0 control period sampling; C_1 first sampling period during antiparkinson treatment; C_2 second sampling period during antiparkinson treatment

biperidine, was given intravenously. At 12.00 h 1 ml from a regular Akineton® -ampoule (5 mg biperidine/ml) was given intravenously. Blood samples for determination of PPZ and perphenazine sulphoxide (PPZSO) were drawn frequently over the day, most intensively around 10.00 h and 12.00 h (ref. Figure 2). The patients were fasting until 16.00 h.

Oral administration

The schedule for oral PPZ administration is seen in Figure 1. This part of the study was aimed to measure the long-term influence of orally given anti-cholinergic drugs on the steady-state level of PPZ and two of its metabolites. Twenty-one patients (Nos 6–26) were treated with Trilafon® tablets from the same batch and given under close supervision of a nurse three times daily (06.00 h, 14.00 h, 22.00 h) for a period of 6 weeks. During the first 1.5 weeks the doses were individualized according to the routine of the department. Thereafter no changes of the PPZ-dose were allowed during the investigation period. Patients, who developed neurological side-effects within the first 3 weeks (before the allocation into the antiparkinson treated groups) were excluded from the study and eventually replaced by other patients until the predetermined number of totally twenty-one subjects was

reached. In week 3, three blood samples with an interval of 2 days between each sample were drawn 7 h after the morning dose, in order to characterize a base-line steady-state level (denoted as C_0) (Bolvig Hansen & Larsen, 1977). At the end of week 3 the patients were allocated at random into one of the following three groups:

(1) *A control group:*

The PPZ treatment was continued without concomitant medication (no placebo was given).

(2) *An orphenadine group:*

The PPZ treatment was supplemented with peroral orphenadine 50 mg three times daily (06.00 h, 14.00 h, 22.00 h).

(3) *A biperidine group:*

The PPZ treatment was supplemented with peroral biperidine 2 mg three times daily (06.00 h, 14.00 h, 22.00 h).

During the last 3 weeks of the study (i.e. during the period of combined treatment) a total of six blood samples were drawn from each patient 7 h after the morning dose. These samples were divided chronologically into two groups, each with three blood samples (denoted C_1 and C_2 , respectively) and the average plasma concentration level for each group was calculated according to Bolvig Hansen & Larsen (1977). In order to obtain an impression of the fluctuation in the plasma concentration between two doses, a blood sample was also drawn 4 h after the morning dose twice during the last week.

The part of the research team, who were responsible for the chemical analysis was blind concerning the medication of the patients.

Analytical procedure

All plasma samples were analyzed for their content of total (i.e. bound and unbound) PPZ and PPZSO (perphenazine sulphoxide). The assay was performed on plasma (2.5 ml), from which PPZ and PPZSO 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 normally obtained plasma range the accuracy of the assay was found to be $\pm 10\%$ for both compounds. The lower limit for quantitation was found to be 0.2 $\mu\text{g/l} = 0.5 \text{ nmol/l}$. The method has been described in detail previously (Larsen & Naestoft, 1975).

The plasma samples from the twenty-one patients participating in the protocol for oral administration were also analyzed for their content of dealkylated perphenazine (DAPPZ). The assay was performed on 2.5 ml plasma with an extraction procedure identical

Figure 2 The concentrations of PPZ (●) and PPZSO (○) the 5th day after an injection of Trilfon®-enantate (Doses: see table 1.) in five patients. Solvent and biperidine, respectively, injected at 10.00 h and 12.00 h.

to the above mentioned. Only the derivatization procedure differed as acetic anhydride was used instead. The lower limit for quantitation was found to be $0.2 \mu\text{g/l} \approx 0.6 \text{ nmol/l}$. This assay has been described in detail by Eggert Hansen and Larsen (1974).

Results

The plasma concentration profiles of five patients during a 12 h period 5 days after an intramuscular injection of PPZ-enanthate are presented in Figure 2. The individual variation of the plasma levels is obvious. In particular, patient No. 1 has a much higher PPZ-level than the rest of the patients in spite of a lesser dose. In patient No. 5 PPZSO was undetectable ($< 0.5 \text{ nmol/l}$). For most of these patients fluctuations are seen in the plasma concentrations of

PPZ both after the placebo injection and after an injection of biperidine. There seems to be no consequent trend in these fluctuations.

The outcome of the oral interaction study is presented in Table 3. It appears, that additional treatment with orphenadine or biperidine had no statistically significant influence on the previously obtained levels of PPZ and its metabolites. Furthermore, there was no statistically significant difference in plasma concentrations between the three groups. The actual results of the average plasma levels are given in Table 4.

Lastly, the average ratio between two plasma concentrations within the same 3 h interval was not influenced by additional antiparkinsonism drug. This ratio was for the control group 1.38 (s.d. 0.25) and for the orphenadine and biperidine group 1.39 (s.d. 0.09) and 1.41 (s.d. 0.24), respectively.

Table 3 Plasma levels of perphenazine and two of its metabolites in twenty-one psychotic patients before and after treatment with orphenadine or biperidine

		Before treatment C_0 (nmol/l)		After treatment C_2 (nmol/l)		Difference ($C_2 - C_0$) (nmol/l)	
		Mean	s.d.	Mean	s.d.	Mean	s.d.
Control group ($n=7$)	PPZ	10.7	6.9	11.5	8.2	0.8	3.8
	PPZSO	10.3	5.1	9.6	3.5	-0.7	2.7
	DAPPZ	28.5	35.6	24.1	23.8	-4.4	16.3
Orphenadine group ($n=7$)	PPZ	5.7	3.9	6.6	4.2	0.8*	1.8
	PPZSO	6.3	4.2	8.0	4.8	1.7*	2.0
	DAPPZ	9.0	4.0	9.9	5.3	0.9*	2.6
Biperidine group ($n=7$)	PPZ	7.4	9.8	9.1	11.0	1.6*	2.5
	PPZSO	7.4	5.6	8.4	7.2	1.0*	2.6
	DAPPZ	19.0	33.3	19.8	32.0	0.9*	3.0

*None of the differences in the treated groups are statistically significant (5% level) different from the corresponding differences in control group (paired t -test).

Table 4 Plasma levels for all the patients in the peroral study

Patient No.	Group	C_0 (nmol/l)			C_1 (nmol/l)			C_2 (nmol/l)		
		PPZ	PPZSO	DAPPZ	PPZ	PPZSO	DAPPZ	PPZ	PPZSO	DAPPZ
6	C	4.9	9.2	14.0	4.7	8.1	12.2	5.7	10.4	10.6
7	C	21.3	13.4	29.2	23.2	13.7	30.7	22.7	10.3	30.5
15	C	7.9	8.0	10.8	6.4	8.0	7.3	7.7	11.2	7.8
16	C	15.5	9.5	13.8	23.3	8.8	26.3	22.9	9.1	32.9
18	C	14.5	19.5	24.6	8.9	15.6	21.0	8.9	14.7	15.3
20	C	1.0	3.1	<0.6	1.2	3.2	<0.6	1.6	3.3	<0.6
24	C	9.9	9.1	106.4	12.0	7.7	95.6	10.7	7.9	70.9
8	O	5.4	3.8	13.3	8.4	6.4	17.5	9.4	6.9	19.2
9	O	5.3	14.7	10.8	4.7	12.5	8.6	5.3	15.4	10.3
14	O	9.8	7.5	8.0	13.0	8.6	10.3	12.2	7.6	10.8
17	O	12.0	7.7	13.4	10.7	13.6	12.5	10.7	13.2	11.7
19	O	3.0	4.4	6.6	2.6	7.4	8.0	3.6	6.0	5.6
21	O	3.6	4.5	8.7	4.1	6.2	10.6	3.6	5.5	9.4
26	O	1.0	1.7	2.2	0.5	1.8	2.8	1.2	1.3	2.1
10	B	29.0	14.1	93.9	28.9	10.0	84.5	31.5	12.3	90.9
11	B	4.7	5.2	8.3	5.9	4.4	8.3	4.9	5.3	8.3
12	B	8.6	16.5	15.4	10.6	17.6	15.4	15.8	22.8	22.2
13	B	4.0	2.5	4.0	5.2	2.4	4.3	3.9	1.8	4.1
22	B	1.1	2.6	4.5	1.4	4.9	4.0	1.9	4.1	4.3
23	B	2.0	4.5	4.1	2.2	4.1	4.9	2.3	4.6	6.5
25	B	2.7	6.4	2.8	2.9	8.0	3.1	3.2	8.0	2.8

C = Control group; O = orphenadine group; B = biperidine group

Discussion

Loga *et al.* (1975) found that the plasma half life of antipyrine was significantly reduced in patients in continuous oral treatment with chlorpromazine when orphenadine was added, suggesting that the latter drug might increase the rate of metabolism of

chlorpromazine. In two studies dealing with schizophrénics (Singh & Kay, 1975a and b) it was demonstrated that benztropine and trihexyphenidyl diminished the therapeutic response to both haloperidol and chlorpromazine. Interaction studies with PPZ therefore seem clinically justified, but several possibilities of errors do exist. For example, the

procedure used for selection of patients for the study of orally administered PPZ might influence the outcome. It has been suggested that patients developing neurological side-effects on PPZ may have higher plasma levels of the drug than unaffected patients (Bolvig Hansen & Larsen, 1977). Patients, actually did have side-effects during initial PPZ-treatment, were therefore excluded from further study in an attempt to obviate possible variations in plasma levels of PPZ between patients, thereby trying to make the three groups more comparable. For ethical reasons also, patients should not suffer from side-effects without the prospect of treatment (*ref.* the control group) and the described selection procedure became therefore unavoidable.

However, doubts imposed by this procedure may not be relevant, as judged from the data of two patients with high PPZ-levels (Table 4, patients No. 10 and 17). Both received anti-cholinergic therapy, but in neither could a change in PPZ-levels be demonstrated in the treatment period.

The average plasma levels for the three groups before the antiparkinsonism treatment (Table 3) are actually not very different, although they tend to be somewhat higher in the control group.

The overall result of the oral study is that no

detectable kinetic interaction takes place between PPZ and the two anticholinergic drugs, orphenadrine and biperidine. Figure 2 illustrates, that this is true also, when biperidine is administered i.v.

A characteristic feature, also seen in previous studies is the individual variation in plasma levels, which may tend to invalidate the results, particular, when the investigated patient-groups are small. It is however impossible, for practical reasons, to apply the protocol to a larger number of patients, and although the danger of a false-negative result must be considerable from a statistical point of view, the results nevertheless indicate that there is no reason to believe that an eventual clinical interaction between the two kinds of drugs is due to pharmacokinetical interaction.

The relation between the two concentrations of PPZ within a dose interval does not reveal any significant difference in the average relation calculated for each of the treated groups. This result might indicate that the rate of absorption of PPZ from the gastrointestinal tract is unaffected by the two antiparkinson drugs.

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