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Serum Concentrations of *cis*(Z)-Flupentixol and Prolactin in Chronic Schizophrenic Patients Treated with Flupentixol and *cis*(Z)-Flupentixol Decanoate

A. Jørgensen[1], J. Andersen[2], N. Bjørndal[3], S. J. Dencker[4], L. Lundin[4], and U. Malm[4]

[1] Biochemical Department, H. Lundbeck & Co. A/S, Ottiliavej 7–9, DK-2500 Copenhagen-Valby, Denmark
[2] Department E, Sct. Hans Hospital, Roskilde, Denmark
[3] Department H, Sct. Hans Hospital, Roskilde, Denmark
[4] Department II, Lillhagen Hospital, Gothenburg, Sweden

Abstract. Nine chronic schizophrenic patients selected from three hospital departments were treated with flupentixol (orally and IV) and *cis*(Z)-flupentixol decanoate in Viscoleo (IM) in a three-phase pharmacokinetic study. Oral administration (single and repeated dosage) showed a relatively slow absorption with maximum serum concentration around 4 h after administration. Intravenous injection indicated multicompartment kinetics for *cis*(Z)-flupentixol. The biological half-lives calculated after the different doses were the same, indicating that the pharmacokinetics of *cis*(Z)-flupentixol does not differ between single and repeated administration and does not change when moderately higher doses are given. The bioavailability of orally administered *cis*(Z)-flupentixol was calculated to be about 40 % with IV injection as reference. After IM administration maximum serum concentration was seen between 4 and 10 days in most patients. Calculation of a disappearance half-life gave very variable results, indicating that the release of the drug from the oil depot is not a monoexponential process. The intramuscular depot had a much lower bioavailability than IV injection, which means that steady state has not been obtained after 8 weeks of depot treatment. Serum prolactin concentrations were elevated during neuroleptic treatment, but no correlation was found between prolactin concentrations and the serum concentrations of *cis*(Z)-flupentixol. A correlation between the changes in clinical ratings and concentrations of *cis*(Z)-flupentixol or prolactin was not found.

Key words: Neuroleptic – Flupentixol – Flupentixol decanoate – Serum levels – Prolactin

The importance of establishing exact measures of the effect of treatment with neuroleptic drugs has created an increasing interest in estimation of drug levels. Previously, a serious obstacle to such studies was that reliable analytical methods were not available, but with the introduction of radioimmunoassay techniques, and not least high performance liquid chromatography, methodology is no longer a limiting factor. Although the ultimate aim of blood level studies is to establish a correlation between drug level and clinical effect in order to guide the treatment by drug monitoring, it is obviously essential to base such studies on fundamental pharmacokinetic studies of the drug in question. The present study was carried out to obtain such basic pharmacokinetic knowledge of the neuroleptic drug *cis*(Z)-flupentixol in patients with chronic schizophrenia. *Cis*(Z)-flupentixol has the advantage over most other neuroleptic drugs of representing only one active compound, the metabolites being devoid of neuroleptic activity in pharmacological studies (Christensen, unpublished data). Moreover, the drug is available in both oral and IM depot forms, and a simple and reliable radioimmunoassay for active drug is available (Jørgensen 1978). In addition to the main object of the present study – to study the pharmacokinetics of *cis*(Z)-flupentixol in patients – we have measured prolactin levels. By rating of the patient's clinical condition we have also attempted to correlate the levels of both *cis*(Z)-flupentixol and prolactin with clinical outcome.

Offprint requests to: Dr. A. Jørgensen

Materials and Methods

Patients. Thirteen chronic schizophrenic patients, who gave informed consent to participate, were entered into the trial. They were selected from three hospital departments as being well stabilized on neuroleptic therapy. They were considered suitable subjects for treatment with the several drug and placebo regimens. Four of the patients dropped out very early in the trial because they refused to allow blood samples to be taken. Only the results from the nine patients who completed the trial have been included in the present paper. They all had severe chronic schizophrenia as defined by Schneider (1959). Of the nine patients eight had been ill for more than 10 years. The length of the total mental hospital stay was more than 1 year. Five of the nine patients were treated in an outpatient setting, whereas the remaining four were chronic inpatients. Details of the patients' sex, age, duration of illness, body weight, and height are shown in Table 1.

Drug Preparations. Fluanxol (H. Lundbeck & Co. A/S, Copenhagen) tablets containing 1 and 5 mg flupentixol were used for oral administration of 10 mg or less. Fluanxol drops containing 100 mg/ml flupentixol were used for oral doses of more than 10 mg. Injectable flupentixol containing 1 mg/ml flupentixol was used for IV injection. Flupentixol, which is present in all these preparations, is a 1:1 mixture of *cis*(Z)-flupentixol and *trans*(E)-flupentixol. For the IM injections, Fluanxol Depot, 20 mg/ml of *cis*(Z)-flupentixol decanoate in Viscoleo (Danish Soyacake Factory Ltd., Copenhagen) was used for doses below 100 mg and Fluanxol

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Table 1. Patient data and dosage

Patient No.	Sex	Age (years)	Duration of disease (years)	Body weight (kg)	Height (cm)	Repeated oral dose (mg) Dose level			Fourth depot inj. (mg) Dose level	
						1	2	3	1	2
1	M	62	33	84	184	5	10	40	40	60
2	M	40	10	61	178	5	10	60	100	150
3	M	48	11	106	184	5	10	20	20	40
4	M	44	13	58	162	5	10	20	60[a]	60
5	M	46	18	67	171	5	10	20	80[a]	80
6	M	37	14	55	165	5	10	20	20	20
7	M	37	16	73	171	5	10	–	20	40
8	M	25	1	71	178	5	10	–	10[a]	–
9	F	37	24	55	161	5	10	–	10	20

[a] Only third injection on this dose

Table 2. Study design and dosage

Pre-treatment period	Phase 1 (Single dose)	Phase 2 (Repeated oral dose)	Phase 3 (IM depot)
No neuroleptic drug for 3 weeks, when treated orally, and for 3 months, when given IM depot	Single oral dose of 5 mg flupentixol. Single IV dose of 2 mg flupentixol	Repeated administration of 5 mg, 10 mg, and if possible higher doses of flupentixol for 7 days. Last dose is followed by a 6-day placebo period	Repeated IM injection of *cis*(Z)-flupentixol decanoate in Viscoleo with intervals of 2 weeks. Two dose levels each given four times

Depot, 100 mg/ml of *cis*(Z)-flupentixol decanoate in Viscoleo, for doses of 100 mg or more.

Study Design and Dosage. As shown in Table 2 the study consisted of a pre-treatment period and a three-phase treatment period made up of a single dose phase, a repeated oral dose phase and an IM depot phase. The pre-treatment period was a wash-out period without neuroleptic medication. The duration of this period was 3 weeks if the patient was on oral medication before entering the study, and 3 months if the patient was on depot treatment. In phase 1 of the treatment period single doses of 5 mg flupentixol orally and 2 mg flupentixol IV were given with an interval of 5 days. In phase 2 oral dose levels of 5 mg, 10 mg and in six patients a third level of 20, 40, or 60 mg of flupentixol were given repeatedly once daily for 7 days. The last dose was followed by a 6-day placebo period. In phase 3 repeated IM injection of *cis*(Z)-flupentixol decanoate in Viscoleo was given at fortnightly intervals at two individualized dose levels, 10 – 100 mg and 20 – 150 mg, each given for 8 weeks. The last injection period was followed by an 8-week placebo period. The doses administered to the individual patients are shown in Table 1.

Blood Sampling. Venous blood samples for estimation of *cis*(Z)-flupentixol were taken from the patients at various times after administration. In phase 1 samples were taken before and 2, 4, 6, 8, 12, 24, 48, and 72 h after oral administration, before and approximately 2, 10, 20 min, 1, 2, 4, and 24 h after IV injection. In phase 2 blood samples were obtained after 1 week of treatment at time 0, 4, 8, 12, and 24 h relative to the last dose on each dose level. At the highest dose level samples were also drawn at 48, 72, and 96 h after the last dose. In phase 3 blood samples were obtained in the first and the fourth dosage interval on the first dose level, but only at the fourth dosage interval on the second dose level. Blood sampling times relative to injection were at 0, 1, and 4 h, 2, 4, 7, 10, and 14 days. In the final placebo period blood samples were drawn weekly.

Venous blood samples for estimation of prolactin concentrations were obtained in the morning, after the patient had been awake for 2 – 3 h and before they had received any medication. Precautions were taken not to stress the patient before and during blood sampling and the patient was only allowed a light breakfast. The blood samples were taken at the start of the study, before and at 24 h after the last dose on each dose level with repeated oral administration (phase 2), and before injection and at day 7 and 14 in the depot dosage intervals, in which blood samples for estimation of *cis*(Z)-flupentixol were taken (phase 3).

The blood samples were taken from the cubital vein. Ten to 15 ml of blood were collected in a glass tube. After coagulation and centrifugation the serum was removed and frozen (– 18° C). The samples were kept frozen until analysis which was carried out within 6 months of collection of the first samples.

Analytical Procedures. The serum concentrations of *cis*(Z)-flupentixol were determined by a radioimmunoassay with a limit of sensitivity of 0.2 – 0.3 ng/ml and a good specificity with respect to *cis*(Z)-flupentixol (Jørgensen 1978). During administration of flupentixol the patients received the same amount of the *trans*(E)-isomer as of the *cis*(Z)-isomer. The *trans*(E)-isomer is co-estimated to about 7%, but as the *cis*(Z)/*trans*(E) ratio remains constant at around 1 (Muusze et al. 1977) it is possible to correct for this interference. *Cis*(Z)-flupentixol decanoate is co-estimated to about 6%, but the serum concentration of this compound is considered to be too low to influence the determination of *cis*(Z)-flupentixol after

injection of Fluanxol Depot (Jørgensen 1978). The within-assay standard deviation is 6–7% and the between-assay standard deviation is about 20%. Because of this difference samples from the same patient were analysed in only two assays, one following oral and IV administration and the other following IM depot injection. The serum concentrations of prolactin were determined by a radioimmunoassay utilizing ^{125}I and a double antibody technique (Kazuko et al. 1976). The relative standard deviation of the assay was 4–5%. The prolactin estimations were performed by BIO-DATA Lab., Kolding, Denmark.

Data Treatment. The biological half-life of *cis*(Z)-flupentixol was determined after oral and IV administration by using the terminal exponential declining part of the serum concentration curve to obtain the elimination parameter β, which is $-2.303 \times$ slope in a semilogarithmic system. The biological half-life, $t_{1/2}$, is then $0.693/\beta$. The time periods used were 12–72 h after single dose, 2–24 h after IV injection, and 12–96 h after the last dose with repeated oral administration. In the same way a disappearance half-life could be estimated after the last IM dose by using the concentration data from 2 weeks after administration and onward.

The areas under the serum concentration curves (AUC) were calculated by the trapezoidal rule for a dosage interval with repeated administration and from time 0 to the last measured point (72 h after oral administration and 24 h after IV injection) for single dose administration. The remaining part of the total area for single dose administration was calculated from the formula $AUC_{T-\infty} = C_T/\beta$, in which C_T is the serum concentration at the last sampling time (T) and β is a parameter calculated as described above. Based on dose and AUC after IV injection the systemic clearance Cl_s was calculated from the formula:

$$Cl_s = \frac{\text{dose}}{AUC}.$$

For the mutual correlations of dose, concentrations of *cis*(Z)-flupentixol, prolactin concentrations and clinical assessments we used Pearson's product moment correlation coefficient (Kendall and Stuart 1973).

Clinical Assessments. The following rating scales were used to assess the symptoms and signs as well as possible side effects of the drug: Clinical Global Impression (CGI; a slightly modified version of the scale described by Guy 1976), Brief Psychiatric Rating Scale (BPRS), 16 items, (Overall and Gorham 1962) and Extrapyramidal Side Effects Scale (EPS), 12 items, (Simpson and Angus 1970).

CGI and BPRS were completed in the morning of each blood sampling day in phase 1. Phase 2 was the same except that for the placebo period assessments were made only on days 2 and 4. In phase 3 assessment were performed on days 0, 7, and 14 of the dosage intervals, during which blood were taken, and at the end of weeks 2 and 8 in the placebo period.

The EPS scale was completed in the morning of each blood sampling day in all three phases, except that they were restricted to days 2 and 4 in the phase 2 placebo period.

Results

Serum Concentrations of cis(Z)-Flupentixol After Single Dose Administration (Phase 1). Administration of a single dose of 5 mg flupentixol gave a serum concentration curve for *cis*(Z)-flupentixol which in all nine patients reached a maximum at 4 h after administration (see e. g., Fig. 1 a). One patient (No. 2) showed the same concentration at 2 h and three patients (Nos. 5, 6, 8) the same concentration at 6 h as that measured at 4 h. The maximum serum concentrations ranged from 1.2 (No. 8) to 2.5 (No. 9) ng/ml.

From the exponentially declining serum concentration curves biological half-lives were calculated for the period 12–72 h (Table 3). Mean biological half-life was 35.9 h (SD 7.1, range 27.6–47.1). In one patient (No. 8) no half-life could be estimated as the levels at 48 and 72 h were below the limit of sensitivity of the analytical method.

Intravenous injection of 2 mg flupentixol gave very high serum concentrations when measured within a few minutes of administration. The initial high serum concentration was followed by a very rapid decline which after about 1 h passed into a slowly declining curve (Fig. 1 b). In six of the nine patients a biological half-life could be estimated from the concentrations measured at 2, 4, and 24 h after administration (Table 3), whereas in three patients (Nos. 1, 7, 8) it was clearly seen that the decline was not exponential. The mean systemic clearance, CL_s, was 0.29 (SD 0.13) l/min, (range 0.15–0.51).

Serum Concentrations of cis(Z)-Flupentixol After Repeated Oral Administration (Phase 2). The serum concentration curves after repeated oral administration resembled those seen after single oral administration (Figs. 1 c and 2 a). In all but a few cases the maximum serum concentration was seen at 4 h after administration. The data indicate that the patients have only reached steady-state conditions with the 5 mg dose, since for the 5 mg dose level the 24-h serum concentration did not differ significantly from the 0 h value (Sign test, $P = 0.50$), whereas the 24-h value was significantly higher than the 0-h value at the 10 mg dose ($P = 0.004$) and at the higher doses taken together ($P = 0.03$). For the 5 mg dose the mean ratio of maximum serum concentration to minimum serum concentration (the minimum taken as the mean of the 0- and 24-h values) was 2.2 (range 1.4–3.0). The last two serum concentrations on the highest oral dose, together with the concentrations measured in the placebo period following the highest dose, showed an exponential decline and enabled us to estimate a biological half-life in all patients (Table 3). The half-lives ranged from 22–44 h with a mean (SD) of 33.9 (7.3).

Although some variation in the biological half-life (Table 3) was seen within the individual patients the half-lives calculated after the three different treatments, single oral administration, IV injection and repeated oral administration, showed a good agreement. The total mean (SD) was 34.7 (9.5) h, a value which is close to the means found for each of the three individual treatments.

Serum Concentrations of cis(Z)-Flupentixol After Injection of cis(Z)-Flupentixol Decanoate (Phase 3). The two samples drawn at 1 and 4 h on the day of injection had concentrations of *cis*(Z)-flupentixol which were equal to the serum concentrations measured in the samples drawn immediately before the injection of *cis*(Z)-flupentixol decanoate in Viscoleo. Thus, rather than showing an immediate rise, the serum concentration rose slowly to reach a maximum value 4–10 days after injection in most patients. In a few cases the maximum was seen as early as 2 days and in one case as late as 14 days after injection. An example of a fourth injection serum concentration curve is shown in Fig. 1 d and a mean

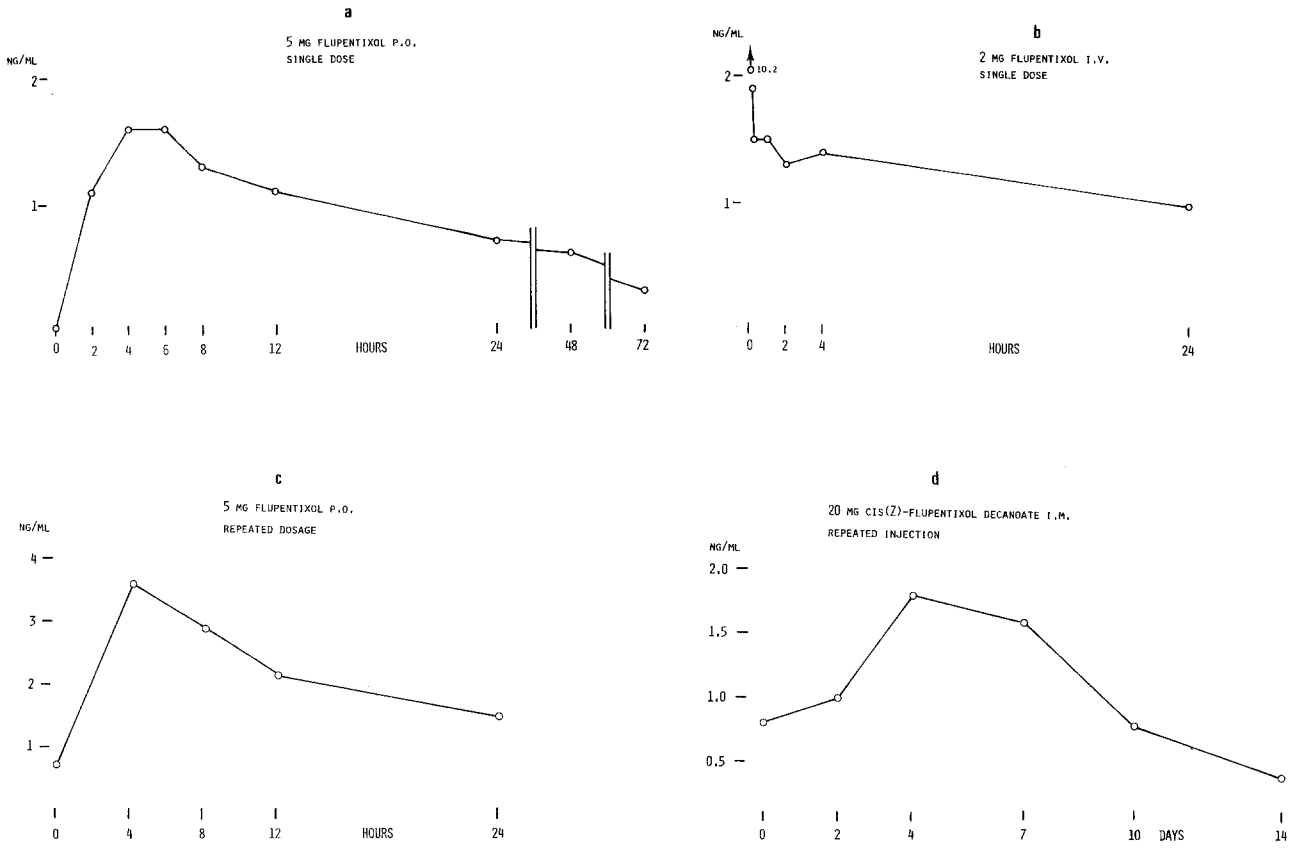

Fig. 1a–d. Serum concentrations of *cis*(Z)-flupentixol (ng/ml) in samples from patient No. 6. **a** Single oral dose; **b** single IV dose; **c** repeated oral dose; **d** repeated IM depot injection

Table 3. Biological half-lives of *cis*(Z)-flupentixol

Patient No.	Single oral dose	Repeated oral dose	IV inj.	Repeated oral dose as % of single oral dose	IV inj. as % of single dose
1	27.6	31.4	–	114	–
2	37.2	40.1	47.0	108	126
3	45.6	36.3	47.0	80	103
4	32.4	44.3	20.9	137	65
5	47.1	34.6	24.9	74	53
6	35.4	35.0	50.2	99	142
7	31.0	38.2	–	123	–
8	–	23.6	–	–	–
9	31.2	22.0	15.4	71	49
mean (SD)	35.9 (7.1)	33.9 (7.3)	34.2 (15.5)	101 (24)	90 (40)

Total mean (SD): 34.7 (9.5)

concentration curve normalized to a 40 mg dose is shown in Fig. 2b. As expected the 14-day serum concentration was significantly higher than the pre-injection concentration (sign test, $P = 0.035$) at the first injection, whereas the corresponding values were similar at the fourth injection on each dose level. Two patients (Nos. 4, 5) who had had their dose changed between the first and the fourth injection, were excluded from the latter comparison. The maximum/minimum (mean of pre-injection and 14-day value) concentration ratio in the fourth dosage interval ranged from 1.2 to 5.3 with an overall mean (SD) of 2.4 (1.2). For the fourth dosage interval significant correlations were found for dose against minimum serum concentration ($r = 0.93$, $P = 1.00$), maximum serum concentration ($r = 0.88$, $P = 1.00$), and AUC ($r = 0.92$, $P = 1.00$). The two former correlations are shown in Fig. 3. No correlation was found for dose against maximum/minimum ratio. On the assumption that the serum concentration curve had a monoexponential decline from 14 days after the last injection and onwards, a disappearance half-life could be estimated in six patients. In three patients (Nos. 2, 4, 7) the curves were clearly non-exponential and no half-life was estimated. The calculated disappearance half-lives showed a very large variation, from 5–113 days with a mean (SD) of 46 (40).

Table 4. Areas under the serum concentration curves (AUC) from periods with single dose administration and periods with the patient in steady state. AUC values are given ng/ml × h per mg dose of *cis*(Z)-flupentixol

Patient No.	Single oral dose 5 mg	Repeated oral dose 5 mg	IV dose 2 mg	IM depot dose level 1 fourth injection	IM depot dose level 2 fourth injection	Mean oral AUC as % of IV AUC
1	20.2	20.2	83.7	9.9	21.0	24.1
2	17.8	22.2	68.2	35.0	31.4	29.3
3	51.5	28.3	109.0	17.7	28.9	36.6
4	26.4	27.6	39.8	–	27.6	67.8
5	16.4	20.2	53.9	–	53.2	34.0
6	26.8	21.8	102.8	25.5	38.4	23.6
7	26.1	27.4	66.5	29.9	37.7	40.2
8	10.5	13.9	32.9	–	–	37.1
9	27.5	30.8	41.1	–	17.6	70.9
Mean (SD)	24.8 (11.6)	23.6 (5.3)	66.4 (27.5)	28.8 (11.2)		40.4 (17.4)

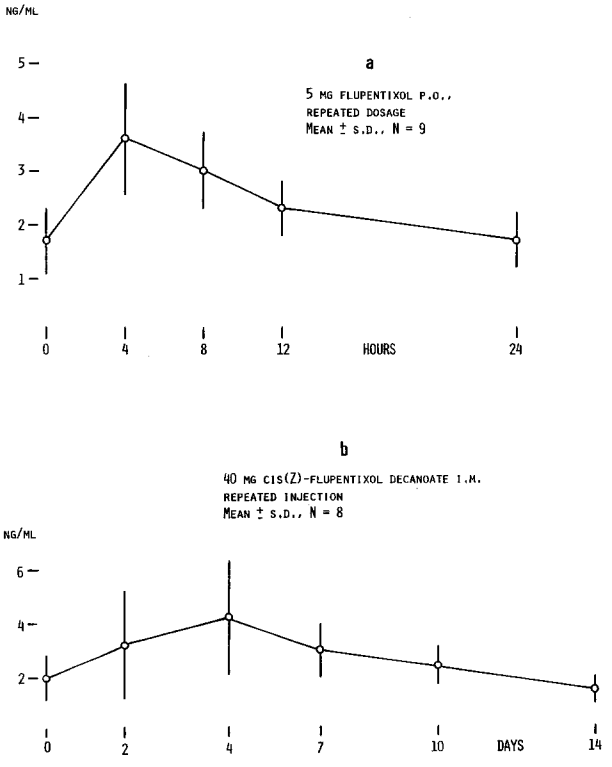

Fig. 2a and b. Mean serum concentrations of *cis*(Z)-flupentixol (vertical bars give ± SD). **a** 5 mg flupentixol orally for 7 days; **b** *cis*(Z)-flupentixol decanoate in Viscoleo given with fortnightly intervals for 8 weeks. The concentrations are normalized to a 40 mg dose

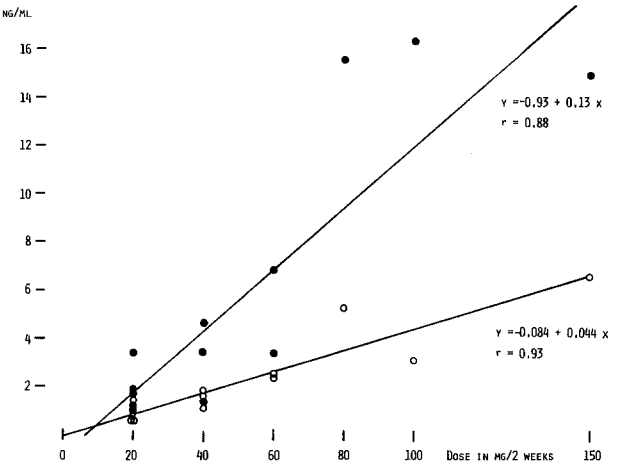

Fig. 3. Correlations between the serum concentrations of *cis*(Z)-flupentixol given as the maximum values (closed circles) and the minimum values (open circles) after treatment with 2-week intervals for 8 weeks

Estimation of Areas Under the Serum Concentration Curves (AUC). The AUC values in ng/ml × h per mg dose of *cis*(Z)-flupentixol have been calculated for the two periods with single dose administration and for the repeated dose period during which the patients are considered to be in steady-state i.e. single oral dose (5 mg), IV injection (2 mg), repeated oral dose with 5 mg and the fourth injection of depot on each dose level (Table 4). Apart from patient No. 3 who had a very high single dose AUC, the AUC values of the two oral doses were in good agreement with each other, with a mean AUC (SD) for all patients of 24.2 ng/ml × h per mg (8.8). When body weights were taken into account the relative SD became higher and the mean (SD) was 1744 ng/ml × h × mg/kg (1048).

The AUC after IV injection was higher than that found after oral administration with all patients. When expressed in relative terms the mean oral AUC of each patient was 24–71 % of the IV AUC (mean 40.4, SD 17.4). The AUC values after IM injection in general show poorer agreement between the two periods and a somewhat higher standard deviation than seen with the two oral treatments. Mean (SD) for AUC after IM injection was found to be 28.8 (11.2) ng/ml × h per mg and 2013 (776) ng/ml × h per mg/kg. The oral mean AUC relative to IM mean AUC was found to be 34–171 % with mean (SD) 101.9 (49.6).

Serum Prolactin Concentrations. The serum prolactin concentrations are shown in Table 5. The prolactin levels are in general elevated compared to the starting value, but only the highest oral dose and day 7 in the first depot interval give a significant difference. A significant correlation between rise in serum prolactin concentration relative to the starting value and serum *cis*(Z)-flupentixol concentration could not be demonstrated. Neither could changes in prolactin between different administrations or within the same administration interval be found to correlate to changes in *cis*(Z)-flupentixol concentration.

Table 5. Prolactin serum concentrations (μg/l)

Phase	Day	1	2	3	4	5	6	7	8	9
1	0	8.0	8.0	12.9	19.6	3.7	12.6	5.9	12.6	31.9
2	7	16.8	11.2	14.1	13.7	4.0	20.3	11.7	25.8	96.3
2	8	10.2	14.8	13.7	13.9	4.8	11.5	10.9	22.3	69.9
2	14	23.2	11.8	21.3	13.4	6.8	22.8	20.9	–	143.2
2	15	16.1	8.9	19.4	12.9	7.3	22.1	15.7	–	122.7
2	21	35.4	33.8	35.4	22.5	22.1	15.7	–	21.8	–
2	22	37.4	23.8	31.4	23.2	18.3	33.2	–	26.7	–
3	0	14.2	5.2	7.1	4.0	3.0	12.6	11.9	22.0	27.1
3	7	23.5	30.2	16.6	26.8	31.9	25.1	12.4	26.4	35.4[a]
3	14	18.3	10.0	17.5	4.3	3.9	15.4	11.9	14.5	41.3
3	42	39.8	12.6	11.2	6.3	4.4	17.1	11.5	–	32.4
3	49	31.0	19.8	13.6	7.3	38.0	18.0	10.9	–	–
3	56	20.3	7.7	10.1	6.5	5.2	16.2	12.3	–	27.5
3	98	24.0	14.4	14.4	26.4	34.0	17.8	14.8	–	39.9
3	105	17.7	21.8	13.6	32.8	23.4	17.4	17.8	–	36.3[a]
3	112	10.8	8.6	10.0	12.3	7.7	14.7	9.2	–	37.1

[a] Sample from day 3 of the dosage interval instead of day 7 as planned

Clinical Assessments. A correlation analysis was performed for the *cis*(Z)-flupentixol serum values and prolactin serum concentrations against the data obtained from the three rating scales for each patient. No correlation was found between the serum concentrations of the active drug or prolactin and the results from the scales. Therefore, we do not consider that the individual patient data merit discussion in this paper.

The CGI was between 2 and 4 in seven patients. Two patients reached degree 6–7 for short periods during the trial. The scores on the 16-item BRPS scale decreased slightly during the trial. The mean total score on entry was 14.4, at the end of the second depot period 12.2 and at the end of the last placebo period 11.3. Two of the patients showed deterioration during the 8-week placebo period. The total EPS score ranged between 1 and 5 and no significant changes were found. The patients did not report extrapyramidal symptoms. No antiparkinsonian drugs were used during the study.

Discussion

The preparations used for oral and IV administration contain flupentixol, which is a 1:1 mixture of the two geometrical isomers, *cis*(Z)- and *trans*(E)-flupentixol. Pharmacological (Møller Nielsen et al. 1973) and clinical (Johnstone et al. 1978) studies have shown that only the *cis*(Z)-isomer possesses neuroleptic activity whereas the *trans*(E)-isomer is devoid of this activity. It seems therefore relevant only to measure serum concentrations of *cis*(Z)-flupentixol as we have done in this investigation. We have no direct comparison of the kinetics of *cis*(Z)-flupentixol given alone and together with *trans*(E)-flupentixol, but for the closely related drug clopenthixol it has been shown in volunteers that administration of double the amount of the *trans*(E)-isomer does not influence the kinetics of the *cis*(Z)-isomer (Aaes-Jørgensen, unpublished data). The dose of clopenthixol, *cis*(Z)/*trans*(E)-mixture, was 30 mg in this investigation. The depot preparation *cis*(Z)-flupentixol decanoate in Viscoleo, contains the pure *cis*(Z)-isomer although in an ester form. However, the ester form is hydrolysed rapidly in the body to liberate *cis*(Z)-flupentixol which must be considered the active drug (Jørgensen et al. 1971). The major metabolites of flupentixol are flupentixol sulphoxide and N-dealkyl flupentixol (Jørgensen et al. 1969). These metabolites have no neuroleptic activity in pharmacological studies (Christensen, unpublished data) and they do not interfere with the assay of *cis*(Z)-flupentixol to any significant degree (Jørgensen 1978). The available data thus make it reasonable only to measure *cis*(Z)-flupentixol in schizophrenic patients treated with flupentixol or *cis*(Z)-flupentixol decanoate.

The biological half-life of *cis*(Z)-flupentixol as estimated after oral and IV single dose and oral repeated dosage is about 35 h. This is somewhat more than found for some other neuroleptic drugs, e.g. haloperidol, $t_{1/2} = 19.5$ h (Forsman and Øhman 1977), perphenazine, $t_{1/2} = 9.4$ h (Eggert Hansen et al. 1976), fluphenazine, $t_{1/2} = 16.4$ h (Dysken et al. 1981) and most antidepressant drugs (Molnar and Gupta 1980). The fact that the half-lives estimated after low doses given as single dose and higher doses given repeatedly are identical indicates that neither repeated administration nor moderately higher dosage influence the elimination of *cis*(Z)-flupentixol. The half-lives found in the patients are in good agreement with earlier reported half-lives of 19–38 h estimated in male human volunteers (Jørgensen 1980).

The time of maximum serum concentration (4 h) after single oral administration indicates that the absorption of *cis*(Z)-flupentixol is relatively slow. This, together with a half-life of more than 24 h, shows that once daily administration of flupentixol tablets is reasonable from a pharmacokinetic point of view, an impression which is further supported by a limited fluctuation of the serum concentration with 5 mg flupentixol tablets given once daily. With repeated oral administration, comparison of time 0 and 24 h serum concentrations shows that the patients have only reached steady-state conditions with the lower dose whereas with the higher doses steady-state has not yet been reached. The reason for this phenomenon is obscure, but it seems very unlikely that doses of the magnitude given in the present study can cause saturation of any transport/biotransformation process. With

a biological half-life as long as 35 h a treatment time of 7 days is about the limit time needed to reach steady-state.

The multiphased decline in the serum concentration after IV injection clearly demonstrates that pharmacokinetically *cis*(Z)-flupentixol follows a multicompartment model. The small number of data points, however, does not allow a computer analysis to elucidate this aspect further. Jørgensen (1980) has done computer analysis with data obtained after IV infusion of *cis*(Z)-flupentixol to human volunteers, but did not come closer to a solution than to suggest that three or more compartments are needed to describe the kinetics of *cis*(Z)-flupentixol.

As we have found in animal studies that the presence of free *cis*(Z)-flupentixol base in the *cis*(Z)-flupentixol decanoate preparation can cause high concentrations of *cis*(Z)-flupentixol a few hours after injection, we have drawn blood samples at 1 and 4 h after IM injection and compared the concentrations with those of the pre-injection samples. The fact that we did not find an increase in the concentrations on the day of injection shows that free *cis*(Z)-flupentixol base is not present in the *cis*(Z)-flupentixol decanoate preparation to any significant degree. This phenomenon has also been investigated for fluphenazine decanoate in sesame oil (Modecate) and different authors (Curry et al. 1978, 1979; Nasrallah et al. 1978; Wiles 1979; Wiles and Gelder 1979) have reported the presence of peak concentrations on the day of injection. The last mentioned authors, who carried out the most thorough investigation, found that in 18 patients from different hospitals the mean time of the peak concentration was 3.3 h and that the peak height was 1.2 – 12.6 times the pre-injection concentration. A clinical report has indicated that these early peaks may be of practical importance in causing side effects on the day of injection (Curry et al. 1979).

The general appearance of the serum concentration curves after injection of *cis*(Z)-flupentixol decanoate in Viscoleo together with the time of peak around 7 days after injection clearly demonstrate the depot properties of the *cis*(Z)-flupentixol decanoate preparation as also reported earlier (Jørgensen 1980; Stauning et al. 1979). The depot effect in all probability depends on a slow release of *cis*(Z)-flupentixol decanoate from the oil vehicle, as we know from animal studies that the hydrolysis of the decanoic ester is rapid (Jørgensen et al. 1971), and thus cannot be the rate limiting step. Since the slowest in a series of processes is the one determining the declining part of the serum concentration curve, the estimated disappearance half-lives refer to release of ester from the depot and are not elimination half-lives. The shortest disappearance half-lives of 5.3 and 11.3 days (Nos. 1, 7) were found in patients in whom the concentrations after the last injection rather rapidly went below the limit of sensitivity of the radioimmunoassay whereas the longest half-lives of 112.6 and 69.2 days (Nos. 3, 6) were found in cases where the serum concentration could be measured for a long time after the last injection. Thus a probable explanation for the large variability in the disappearance half-lives is that the release from the oil vehicle is not a monoexponential process, but that some part of the ester is released relatively rapidly whereas some persists in the muscle for a very long time. From this it follows that the magnitude of the disappearance half-life which one estimates will depend on the part of the curve used, and that the validity of this half-life is questionable. Using concentration data obtained at day 14, 21 and 28 after dosing to steady-state, Jørgensen and Fredricson Overø (1980) have calculated relatively short half-lives for *cis*(Z)-flupentixol palmitate and clopenthixol decanoate in Viscoleo (17.3 and 19.2 days, respectively).

The area under the serum concentration curve (AUC) calculated from time 0 to infinity with single dose administration and for a dosage interval with repeated dose administration at steady-state is an expression of the systemic availability of drug from an administered drug preparation. By definition IV injection gives 100 % systemic availability, so the bioavailability of *cis*(Z)-flupentixol from tablets is seen to be about 40 % (Table 4). This reduced bioavailability could be due to incomplete absorption after oral administration. However, since absorption has been shown to be complete in rats (Jørgensen et al. 1969) a more probable explanation is that *cis*(Z)-flupentixol is partly metabolized on passage through the gut wall and the liver during absorption (first-pass metabolism). The bioavailability after oral administration tends to be lower than the mean bioavailability figure of 55 % found in volunteers (Jørgensen 1980), but the difference is not significant. The AUC values after the fourth injections of the depot preparation (Table 4) are surprisingly low, as IM injection should also give complete bioavailability. However, the precondition for using the AUC from a single dosage interval is that the patient is at steady-state, and this does not seem to be the case at the fourth injection, because part of the oil depot releases the drug with a very long half-life. Based on the bioavailability figure of 40 % for oral administration, and the precondition that IM depot injection gives complete bioavailability, the pharmacokinetically equivalent doses would be: 10 mg flupentixol orally per day corresponds to 40 mg *cis*(Z)-flupentixol decanoate IM every fortnight (at steady-state).

All the nine patients who entered the trial were chronic schizophrenics, which is clearly demonstrated by the data given earlier in this paper. Moreover, nearly all the patients had been treated with neuroleptics for a fairly long time. They therefore seemed to be representative of the patient who is a candidate for maintenance treatment and also for long-acting neuroleptics. Such aspects must be considered relevant in respect of the heterogeneity of schizophrenic patients treated with neuroleptics. For a critical review on such aspects see May and van Putten (1978). Three out-patients belonged to the very strictly defined subgroup for depot neuroleptics. They did not differ in kinetic parameters from the chronic in-patients.

No consistent association between serum flupentixol values and results from the rating scales could be demonstrated. However, that is not surprising because the chronic patients chosen for this study were already in a stable phase in the long-term neuroleptic treatment programme. Such patients usually demonstrate only slight variations in the target symptom profile and side effects, except at changes of the treatment programme or if a release occurs. It is also well known that many such patients usually do not show any symptom change during a time-limited drug withdrawal period. The wash-out period was restricted with that knowledge in mind. Therefore no relapse symptoms appeared nor did any target symptom decrease when the patients were given the neuroleptic agent, i.e., flupentixol, again.

The effect of neuroleptic treatment on the serum prolactin level has been studied extensively during the past decade. It has been shown that acute treatment with a neuroleptic drug leads to pronounced increase in the prolactin level (Meltzer et al. 1976; Langer et al. 1977; Wiles et al. 1976), whereas old patients treated for a very long time showed almost normal

prolactin levels (Beumont et al. 1974; Rivera-Calimlim et al. 1976; Kolakowska et al. 1976a). This effect may be combination of tolerance development (Naber et al. 1979) and structural changes in the brain. We did not find a significant correlation between increase in prolactin during treatment and concentration of neuroleptic drug, although we found that the neuroleptic treatment leads to increase in prolactin. The fact that no correlation was found between change in prolactin and change in clinical parameters may be due to the selection of very stable patients. However, this finding is in accordance with previous investigations (Rivera-Calimlim et al. 1976b; Bjerkenstedt et al. 1977; Bjørndal et al. 1980). The reason may also be that prolactin and schizophrenia are linked to separate dopamine systems, which are differently influenced by neuroleptic drugs.

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References

Beumont PVJ, Corker CS, Friesen HG, Kolakowska T, Mandelbrot BM, Marshall J, Murray MAF, Wiles DH (1974) The effects of phenothiazines on endocrine function: II. Br J Psychiatry 124:420–430

Bjerkenstedt L, Eneroth P, Härnryd C, Sedvall G (1977) Effects of melperone and thiothixene on prolactin levels in cerebrospinal fluid and plasma of psychotic. Arch Psychiat Nervenkr 224:281–293

Bjørndal N, Bjerre M, Gerlach J, Kristjansen P, Magelund G, Oestrich IH, Wæhrens J (1980) High dosage haloperidol therapy in chronic schizophrenic patients: A double-blind study of clinical response, side effects, serum haloperidol and serum prolactin. Psychopharmacology 67:17–23

Curry SH, Whelpton R, De Schepper PJ, Vranckx C, Schiff AA (1979) Kinetics of fluphenazine after fluphenazine dihydrochloride, fluphenazine enanthate and decanoate administration to man. Br J Clin Pharmacol 7:325–331

Curry SH, Altamura AC, Montgomery S (1979) Unwanted effects of fluphenazine enanthate and decanoate. Lancet 331–332

Dysken MW, Javaid JI, Chang SS, Schaffer C, Shabid A, Davis JM (1981) Fluphenazine pharmacokinetics and therapeutic response. Psychopharmacology 73:205–210

Eggert Hansen C, Rosted Christensen T, Elley J, Hansen LB, Kragh-Sørensen P, Larsen N-E, Naestoft J, Hvidberg EF (1976) Pharmacokinetic studies of perphenazine. Br J Clin Pharmacol 3:915–923

Forsman A, Øhman R (1977) Applied pharmacokinetics of haloperidol in man. Curr Ther Res 21:396–411

Guy W (1976) ECDEU Assessment Manual for Psychopharmacology. DHEW Publication No (ADM) 76-338. National Institute of Mental Health, Rockville

Johnstone EC, Crow TJ, Frith CD, Carney MWP, Price JS (1978) Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. Lancet 848–851

Jørgensen A, Hansen V, Dahl Larsen U, Rauf Khan A (1969) Metabolism, distribution and excretion of flupentixol. Acta Pharmacol Toxicol 27:301–313

Jørgensen A, Fredricson Overø K, Hansen V (1971) Metabolism, distribution and excretion of flupentixol decanoate in dogs and rats. Acta Pharmacol Toxicol 29:339–358

Jørgensen A (1978) A sensitive and specific radioimmunoassay for *cis*(Z)-flupentixol in human serum. Life Sci 23:1533–1542

Jørgensen A (1980) Pharmacokinetic studies in volunteers of intravenous and oral *cis*(Z)-flupentixol and intramuscular *cis*(Z)-flupentixol decanoate in Viscoleo. Eur J Clin Pharmacol 18:355–369

Jørgensen A, Fredricson Overø K (1980) Clopenthixol and flupentixol depot preparations in outpatients schizophrenics, III. Serum levels. Acta Psychiat Scand Suppl 279:41–54

Kazuko I, Narischige T, Moinoru I (1976) Determination of prolaction levels in blood by radioimmunoassay (double antibody system). Internal Department No 1. Faculty of Medicine. Toho University, Japan. Preclinical Report

Kendall MG, Stuart A (1973) The advanced theory of statistics, vol 2. Charles Griffin & Co Ltd, London

Kolakowska T, Wiles DH, Gelder MG, McNeilly AS (1976) Clinical significance of plasma chlorpromazine levels. Plasma levels of the drug, some of its metabolites and prolactin in patients receiving long-term phenothiazine treatment. Psychopharmacology 49:101–107

Langer G, Sachar EJ, Halpern FS, Gruen PH, Solomon M (1977) The prolactin response to neuroleptic drugs. A test of dopaminergic blockade: Neuroendocrine studies in normal men. J Clin Endocrinol Metab 45:996–1002

May PRA, Van Putten T (1978) Plasma levels of chlorpromazine in schizophrenia. Arch Gen Psychiatry 35:1081–1087

Meltzer HY, Fang VS (1976) The effect of neuroleptics on serum prolactin in schizophrenic patients. Arch Gen Psychiatry 33:279–286

Molnar G, Gupta RN (1980) Plasma levels and tricyclic antidepressant therapy. Part 2. Pharmacokinetic, clinical and toxicologic aspects. Biopharm Drug Disp 1:283–305

Muusze RG, Visser-Van der Weel AJ, Verzijden R, Oei TT (1977) Fluorimetrische bepaling op de dunne laag van de bloodkoncentratie van thioxanthenen (Sordinol en Fluanxol) na orale en intramusculaire (depot) toedining. Bulletin van de coördinatiecommissie biochemisch inderzoek van de psykiatrische instituten van de nationale ziekenhuisraad 10:1–8

Møller Nielsen I, Pedersen V, Nymark M, Franck KF, Boeck V, Fjalland B, Christensen AV (1973) The comparative pharmacology of flupentixol and some reference neuroleptics. Acta Pharmacol Toxicol 33:353–362

Naber D, Fischer H, Ackenheil M (1979) Effect of long-term neuroleptic treatment on dopamine tuberoinfundibular system: Development of tolerance? Commun Psychopharmacol 3:59–65

Nasrallah HA, Rivera-Calimlim L, Rogot AD et al. (1978) Fluphenazine decanoate: Plasma concentrations and clinical response. Psychopharmacol Bull 14:46–47

Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812

Rivera-Calimlim JL, Lal S, Ettigi P, Hontela S, Muller HF, Friesen HG (1976a) Effect of acute and chronic neuroleptic therapy on serum prolactin levels in men and women of different age groups. Clin Endocrinol 5:273–282

Rivera-Calimlim L, Nasrallah H, Strauss J, Lasagna L (1976b) Clinical response and plasma levels: Effect of dose, dosage schedule, and drug interactions on plasma chlorpromazine levels. Am J Psychiatry 133:646–652

Schneider K (1959) Psychischer Befund und psychiatrische Diagnose. Klinische Psychopathologie, 5. Aufl., Leipzig, Thieme

Simpson GM, Angus JWS (1970) A rating scale for extrapyramidal side effects. Acta Psychiat Scand Suppl 212:11–19

Stauning JAa, Kirk L, Jørgensen A (1979) Comparison of serum levels after intramuscular injection of 2% and 10% *cis*(Z)-flupentixol decanoate in Viscoleo to schizophrenic patients. Psychopharmacology 65:69–72

Wiles DH, Kolakowska T, McNeilly AS, Mandelbrot BM, Gelder MG (1976) Significance of plasma chlorpromazine levels, I. Plasma levels of the drug, some of its metabolites and prolactin during acute treatment. Psychol Med 6:407–415

Wiles DH (1979) Tardive dyskinesia and depot fluphenazine. Br J Psychiatry 382–383

Wiles DH, Gelder MG (1979) Plasma fluphenazine levels by radioimmunoassay in schizophrenic patients treated with depot injections of fluphenazine decanoate. Br J Clin Pharmacol 8:565–570

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