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Steady-State Serum Concentrations after *cis* (Z)-Flupentixol Decanoate in Viscoleo

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Abstract. Serum concentrations of *cis*(Z)-flupentixol have been measured in patients on *cis*(Z)-flupentixol decanoate injections during successive dosage intervals of 2–4 weeks. The calculation of the fluctuation of the serum concentration in the dosage interval indicates that each individual patient should have his own dosage interval. For the 2-week group a significant correlation was found between weekly dose and preinjection concentration ($r = 0.79$) although an inter-individual variability of $\times 4$ was found. For this group the relative within-patient variation in the pre-injections concentration was calculated to be 9.6%, showing that a constant dosage regimen in the individual patient leads to an almost constant drug load.

Key words: Serum levels – Long-acting neuroleptics – *cis*(Z)-Flupentixol decanoate

Cis(Z)-flupentixol decanoate in Viscoleo (Depixol Inj., Fluanxol Depot) is a depot neuroleptic with a duration of action of 2–4 weeks. Its main indication is maintenance treatment of schizophrenic patients. Since this is a life-long medication it is important to know the within-patient variation of serum concentrations on repeated administration. The present report gives data on this aspect, as well as on variation between patients and the maximum/minimum fluctuation in the dosage interval.

Materials and Methods

Patients. Twenty-three well controlled schizophrenic patients participated in the study. All had been ill for at least 1 year and maintained on IM *cis*(Z)-flupentixol decanoate at a constant dose and injection interval for at least 3 months. The doses given were 10–100 mg every 2 weeks, 20–50 mg every 3 weeks and 10–40 mg every 4 weeks. Patients with concurrent serious organic brain desease, or chronic physical illness were excluded from the study.

Blood Samples. Venous blood samples were withdrawn on a day of depot injection immediately before injection and thereafter on the same day weekly for a period of 6 or 8 weeks. Blood was allowed to coagulate and serum was separated by centrifugation and deep frozen until analysis.

Clinical Assessment. A brief global assessment of the patient's mental state was carried out on each blood sampling day.

Drug Estimation and Data Treatment. Serum concentrations of *cis*(Z)-flupentixol, the active drug in the *cis*(Z)-flupentixol decanoate preparation, were estimated by a specific radioimmunoassay with a limit of sensitivity of 0.2 ng/ml (Jørgensen 1978). The maximum/minimum fluctuation (C_{max}/C_{min}) in the dosage interval was calculated as the ratio of the highest and lowest of the measured values in the interval. The relative within-patient variation in preinjection drug concentration was calculated for each patient from the formula:

$$\frac{\Sigma|\bar{x}\text{-}x|}{n} \cdot \frac{100}{\bar{x}},$$

were x is the measured preinjection concentration, $\bar{x}$ the mean preinjection concentration for each patient and n the number of x's. For correlation analysis we used Pearson's product moment correlation coefficient (Kendall and Stuart 1973).

Results and Discussion

Thirteen patients were on 2-week dosage intervals, four patients on 3-week intervals, and six patients on 4-week intervals. The global assessment of the mental state showed that none of the patients had changed during the study. Data for all patients are shown in Table 1 together with the mean preinjection concentrations. It appears that the preinjection concentrations from the 2-week group varied between 0.06 and 0.26 ng/ml/mg weekly dose. This individual variation of about $\times 4$ must be considered rather limited, and is in agreement with earlier data from two closely related depot neuroleptics (Jørgensen and Overø 1980). In spite of the individual variation a significant correlation was found between dose in mg/week and preinjection concentration (ng/ml) ($P < 0.01$, $r = 0.79$). The use of dose in mg/week/kg body weight or mg/week/sqm body surface gave slightly poorer, but still significant correlations. The preinjection concentrations from the 3- and the 4-week groups showed almost the same individual variation as the 2-week group except for patient No 23 who deviated considerably.

Earlier studies with *cis*(Z)-flupentixol decanoate injections (see, e.g., Stauning et al. 1979) have shown maximum serum concentration at about 7 days after injection in most patients. The weekly collected serum data show that this is also true in the present study. The ratios between maximum and minimum concentrations (C_{max}/C_{min}) are also shown in

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Table 1. Data for all patients studied

Patient No.	Age (years)	Dose (mg/week)	Number of dosage intervals	Mean preinjection conc. ng/ml	Mean preinjection conc. ng/ml/mg	Mean C_{max}/C_{min}	Relative within-patient variation (% of pre-injection concentration)
Patients with 2-week intervals							
1	29	20	3	1.9	0.10	1.9	4.8
2	35	30	3	1.9	0.06	2.2	7.0
3	44	30	3	3.4	0.11	2.3	4.7
4	44	20	3	4.1	0.21	1.4	9.1
5	57	20	4	3.5	0.18	1.5	7.1
6	34	30	3	2.5	0.08	1.9	16.0
7	28	5	3	0.6	0.12	1.1	22.2
8	33	50	3	13.0	0.26	1.1	12.8
9	24	5	3	0.6	0.12	1.3	14.3
10	23	20	3	1.4	0.07	1.8	0.0
11	63	20	4	1.8	0.09	1.8	7.6
12	34	40	4	4.3	0.11	1.7	11.1
13	59	5	4	1.0	0.20	1.8	7.7
Mean (SD)	39 (13)				0.13 (0.06)	1.7 (0.4)	9.6 (5.7)
Patients with 3-week intervals							
14	40	6.7	3	0.6	0.09	2.2	
15	67	16.7	3	1.9	0.11	1.4	
16	60	13.3	1	0.8	0.06	3.4	
17	47	13.3	2	1.1	0.08	4.6	
Mean (SD)	54 (12)				0.09 (0.02)	2.9 (1.4)	
Patients with 4-week intervals							
18	60	5.0	2	1.2	0.24	1.2	
19	50	2.5	2	0.3	0.12	3.0	
20	58	10.0	2	0.7	0.07	5.7	
21	41	7.5	2	0.8	0.11	2.5	
22	50	7.5	2	0.7	0.09	2.0	
23	55	2.5	1	2.0	0.80	1.5	
Mean (SD)	52 (7)				0.24 (0.28)	2.6 (1.6)	

Table 1. The mean ratio from the 2-week group is 1.7, showing that most patients in this group could be treated with longer intervals. A number of patients were maintained successfully on injections every 3 or 4 weeks, and the data show that this frequency of injection was also pharmacokinetically acceptable for those patients except for one from each group (ratios 4.6 and 5.7, respectively). These two patients might benefit from receiving injections with shorter intervals. It should, however, be borne in mind that factors other than purely pharmacokinetic ones (e.g., desired frequency of attendance at the clinic) are also relevant when determining the optimum frequency of injection. It appears from the present study that the minimum duration of action of IM *cis*(Z)-flupentixol decanoate in maintainance treatment of schizophrenia is 2 weeks; but for many patients it may be 4 weeks or longer. An earlier study by Stauning et al. (1979) showed a significant correlation between fluctuations in one dosage interval and the following in individual patients. It is suggested that biological factors unique to each patient may have a marked influence on the duration of action of depot neuroleptics.

The course of the preinjection concentration during three or four 2-week dosage intervals is depicted in Fig. 1 and given in relative values in the last column of Table 1. The variation in the preinjection concentration is seen to be rather limited, with a mean of 9.6%, showing that the release of the drug from the depot is uniform. Clinically speaking, it means that the drug load of the individual patient is constant when the patient is on a constant dosage regimen, at least in a not too long treatment period. Since the present period of measurement was only 1.5–2 months, the study does not allow us to draw conclusions regarding year-long treatment. A slow and gradual change, e.g., due to changes in the patient's physiological condition, would not be discovered in a short-term study like the present one.

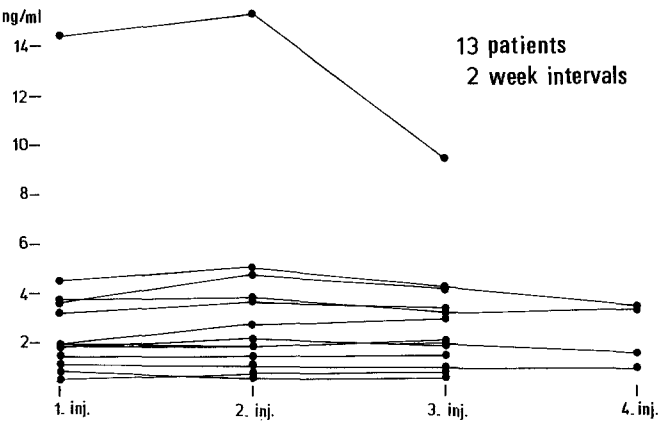

Fig. 1. *Cis*(Z)-flupentixol serum concentrations on the day of injection

References

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

Jørgensen A, Fredricson Overø K (1980) Clopenthixol and flupentixol depot preparations in outpatient schizophrenics. III. Serum levels. Acta Psychiatr Scand 61 (suppl. 279):41–54

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

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

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