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# Comparison of Serum Levels After Intramuscular Injections of 2% and 10% Cis(Z)-Flupentixol Decanoate in Viscoleo® to Schizophrenic Patients

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**Abstract.** The serum concentrations of cis(Z)-flupentixol after injection of 2% and 10% cis(Z)-flupentixol decanoate in Viscoleo® (Depixol® injection, Fluanxol® Depot) have been investigated in a crossover study with eight schizophrenic patients. No statistically significant difference was found between the two preparations when the data from individual days or areas under the serum concentration curves were considered. For the individual patients a difference was found between the two treatments in six cases; one preparation gave the higher serum concentration in four cases and the other preparation in two cases. Thus, the difference found within individual patients reflects the intraindividual variation rather than a difference between preparations. The maximum serum concentration was seen at 4 or 7 days after injection. The maximum/minimum fluctuation ratio indicates that dosage intervals longer than 2 weeks seem reasonable for most of the patients. The similarity in the serum concentrations, no matter which concentration of flupentixol decanoate solution was given, indicates that a dispersal and possibly a metabolic breakdown of the oil depot takes place in the muscle.

**Key words:** Long-acting neuroleptics – Flupentixol – Decanoate – Serum levels

The IM depot preparation of flupentixol [cis(Z)-flupentixol decanoate in Viscoleo®, Depixol® injection, Fluanxol® depot 20 mg/ml] was introduced as a 2% solution in the late sixties and a number of clinical trials established its value in the maintenance treatment of schizophrenic patients (Gottfries, 1971; Gross and Kaltenbäck, 1972; Carney and Sheffield, 1973; Gottfries and Green, 1974). Some patients need rather high doses of flupentixol decanoate so that large volumes of the depot preparation have to be injected. Consequently, a more concentrated solution containing 10% cis(Z)-flupentixol decanoate in Viscoleo® (Depixol®-Concentrate injection, Fluanxol® Depot 100 mg/ml) was developed. The clinical usefulness of the more concentrated solution was demonstrated by Bjerke et al. (1972), Engstrand (1974), Astrup et al. (1974), and Wadzisz (1977). Pharmacologically it was demonstrated that the 10% solution possessed depot properties to the same extent as the 2% solution, but these studies did not allow a discrimination between the two preparations (Svendsen, unpublished data). It has therefore been of interest to investigate the possibility of a difference in bioavailability (serum concentration profile as well as amount of drug absorbed) between the two preparations of flupentixol when injected into the same patient.

## Materials and Methods

*Patients.* Ten psychiatric patients were accepted to take part in the study. They were selected on the criterion that a stable period of observation of 3 months could be expected. One patient dropped out of the study because she had a cerebral stroke and one patient was excluded because of great irregularity in blood sampling. The remaining eight patients were all women, 42–72 years of age and weighing 47–88 kg. Six of them were schizophrenics and two had atypical psychosis (schizoaffective). Duration of disease was 7–42 years. All had had at least 1 year of mental stability on flupentixol decanoate injections prior to the study and all were somatically healthy. Six patients received antiparkinson medication, two were given diuretics, and one received disulfiram, imipramine, and lithium.

*Dosage.* The experimental period consisted of two 2-week dosage intervals during which blood samples were drawn from the patients. Prior to the blood sampling intervals the patients were kept on the same preparation as that given in the first sampling interval during two dosage intervals of 2 weeks. Five patients started on 10% flupentixol decanoate solution (PJ, ES, GB, LÅ, and BC) and three on 2% solution (BB, EH, and GM). All patients except ES (40 mg)

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and GM (30 mg) received 100 mg flupentixol decanoate every 2 weeks.

*Blood Sampling.* Blood samples of 20 ml were drawn by venepuncture on day 0 (day of injection) before injection, and then on days 2, 4, 7, 10, and 14 of each sampling interval, between 8:30 and 11:30 a.m. The samples were allowed to clot and then centrifuged. Serum was removed and stored frozen (−18°C) for up to 2 months before analysis.

*Drug Estimation.* The serum concentrations of cis(Z)-flupentixol, the active drug in the cis(Z)-flupentixol decanoate preparation, were estimated by a sensitive radioimmunoassay (Jørgensen, 1978). The limit of sensitivity was about 0.3 ng/ml. The inactive metabolites, flupentixol sulphoxide and N-dealkyl flupentixol, and the decanoic ester were not coestimated to any significant degree. None of the other drugs given to the patients interfered with the assay.

*Data Treatment.* To make a statistical treatment possible, the measured concentrations (Table 1) were normalized by calculating each concentration in percent of the basal minimum concentration (mean of the concentrations measured on day 0 and 14 in the first sampling interval). As the statistical tests used are paired tests, it is a precondition that the data originate from exactly the same day in the two intervals. Due to some irregularity in blood sampling this was not the case for all data and an interpolation has been made to supply the missing data for the statistical analysis. The statistical tests used were a paired Student's *t*-test, a Wilcoxon matched-pairs signed-ranks test, and a sign test, which were made with the normalized data obtained on each individual blood sampling day with the two preparations and also the areas under the serum concentration curves calculated for the individual patients in the two intervals (Table 1). In addition to this, a paired Student's *t*-test was performed to compare the normalized data of the whole interval within each patient.

The areas under the serum concentration curves (AUC) were calculated by the trapezoidal rule. Based on dose and AUC we calculated the systemic clearance (dose/AUC) as an expression of total elimination of drug from the body.

**Table 1.** Measured serum concentrations of cis(Z)-flupentixol (ng/ml), calculated areas under the serum concentration curve (AUC) (ng/ml days), and systemic clearance (1/min)

| Patient | Serum concentrations in the first interval | | | | | | Serum concentrations in the second interval | | | | | | AUC | | Systemic clearance | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 0 | Day 2 | Day 4 | Day 7 | Day 10 | Day 14 | Day 0 | Day 2 | Day 4 | Day 7 | Day 10 | Day 14 | 1 interval | 2 interval | 1 interval | 2 interval |
| BB | 8.2 | 8.6 (3)[a] | 9.4 | 9.3 | 10.5 | 8.0 | 9.4 | 10.2 | 10.7 | 10.4 | 8.6 | | 129 | 138 | 0.40 | 0.37 |
| PJ | 8.4 | 9.0 (3)[a] | 9.3 | 9.0 | 7.6 | 5.8 | 9.1 | 13.3 | 13.0 | 9.8 | 8.2 | | 114 | 147 | 0.45 | 0.35 |
| ES | 3.0 | 3.4 (3)[a] | 3.7 | 4.9 | 4.3 | 3.2 | 3.9 | 4.5 | 6.0 | 5.0 | 3.4 | | 55 | 65 | 0.37 | 0.31 |
| GB | 6.2 | 7.0 (3)[a] | 7.8 | 9.8 | 9.2 | 6.1 | 9.7 | 11.8 | 12.3 | 9.1 | 8.5 | | 113 | 141 | 0.45 | 0.36 |
| EH | 12.6 | 11.4 (3)[a] | 10.4 | 11.0 | 12.6 | 13.2 | 14.4 | 16.9 | 19.8 | 17.6 | 16.4 | | 166 | 238 | 0.31 | 0.27 |
| LÅ | 10.0 | 11.0 (3)[a] | 12.9 | 14.6 | 12.1 | 8.7 | 11.3 | 14.1 | 19.0 | 12.0 | 11.3 | | 166 | 188 | 0.31 | 0.27 |
| GM | 3.4 | | 6.4 | 5.2 | 3.8 | 2.9 | 2.2 | 2.6 | 3.4 | 3.0 | 2.1 | | 64 | 39 | 0.24 | 0.39 |
| BC | 6.6 | 12.2 | 15.4 | 13.2 | | 5.5 | 12.3 | 19.1 | 11.4 | 8.0 | 5.7 | | 154 | 152 | 0.33 | 0.34 |

[a] Figures in brackets indicate that the corresponding serum concentration did not originate from the sampling day given in the heading of this column but on the day corresponding to the figure in the bracket

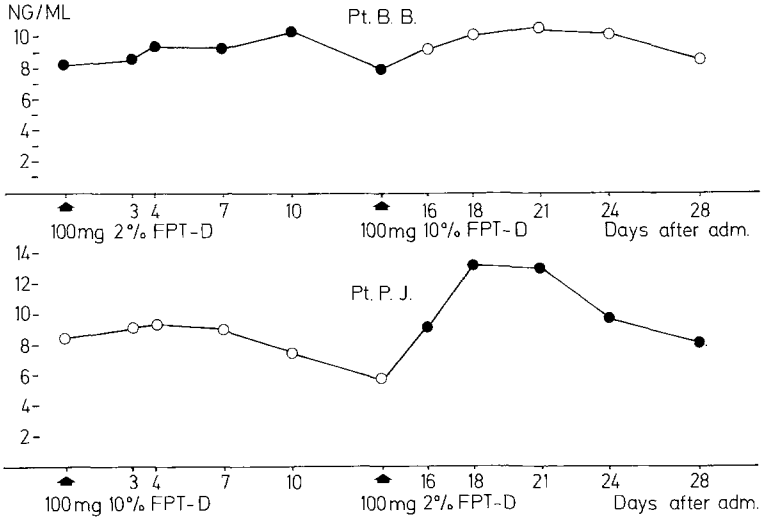


**Fig. 1**
Serum concentrations of cis(Z)-flupentixol in two patients repeatedly administered 100 mg cis(Z)-flupentixol decanoate in Viscoleo® IM

## Results

The measured serum concentrations in the eight patients appear in Table 1 and two typical serum concentration curves are shown in Fig. 1. It appears that most of the patients show maximum serum concentration at 4 or 7 days after injection. A very atypical decreasing serum concentration course is seen with patient EH in the first sampling interval. Since the serum concentration profile for this patient in the second sampling interval is the same as that seen for the other patients, the odd profile in the first sampling interval may be due to accidentical injection into tissues with a poor blood supply. It is notable that this patient was the fattest patient in the group (body weight 88 kg, height 161 cm).

The interindividual variation in fluctuation of the serum concentration appears in Fig. 2. It appears that the maximum/minimum fluctuation varies from about 1 to 3.5 in a dosage interval. The curves for the mean concentrations calculated for each preparation are seen to fluctuate with ratios of 1.7 and 1.5, respectively, for the 2% and 10% preparations. The maximum serum concentration of the mean curves is seen on day 4 and day 7 after injection.

The statistical comparison of the data on each individual day in the two intervals did not show a significant difference between the two preparations of cis(Z)-flupentixol decanoate. A comparison of the areas under the serum concentration curves gave the same result. Thus it can be concluded that there is no statistically significant difference between the two preparations in the present study. The comparison performed on the individual patients showed that there was a significant difference between the concentrations measured in the two intervals for six of the eight patients, while no difference was seen for the last two patients (LÅ and BC). For four of the patients (PJ, ES, GB, and GM) the 2% serum concentration curve was significantly higher than the 10% curve, while the

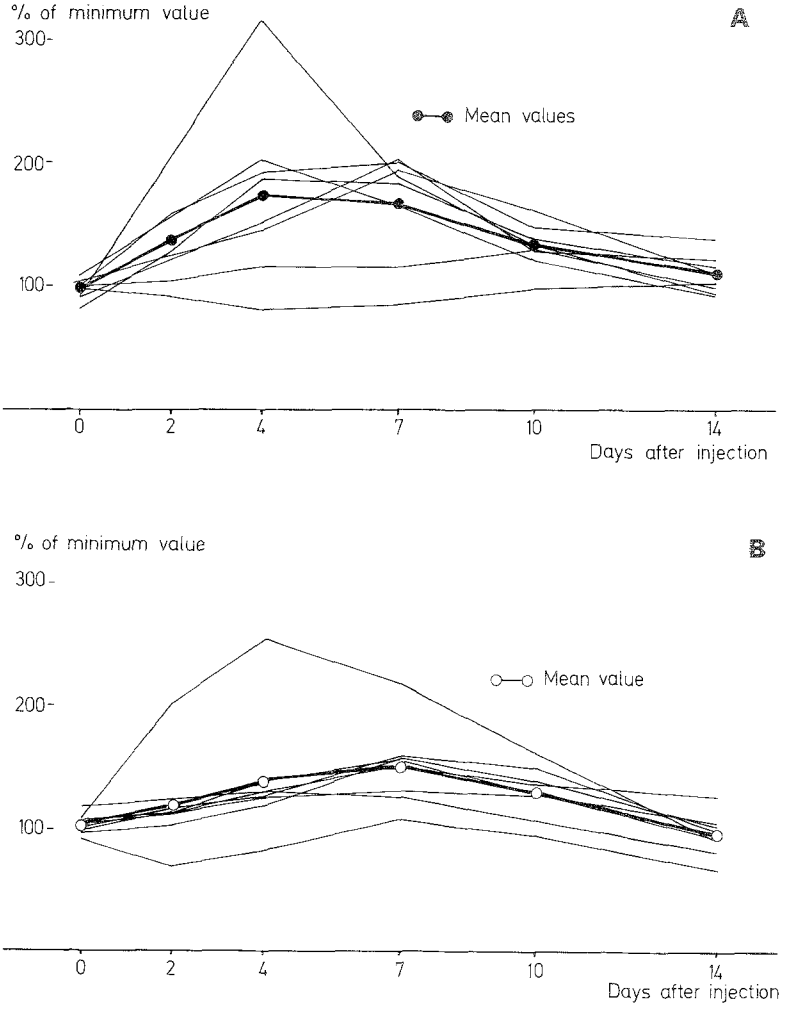


**Fig. 2 A and B**
Serum concentrations of cis(Z)-flupentixol in patients after repeated IM injection of cis(Z)-flupentixol decanoate in Viscoleo® given in percent of the basal minimum concentration, which is calculated as the mean of the serum concentrations on day 0 and 14 of the first sampling interval. **A** 2% cis(Z)-flupentixol decanoate. **B** 10% cis(Z)-flupentixol decanoate ($N = 8$)

opposite was the case for the remaining two patients (BB and EH). Because of this it can be concluded that the difference between the preparations found in the individual patients is due to intraindividual variation and not to a difference between the two preparations.

## Discussion

The serum level curves obtained in the present study differ appreciably from previously published serum curves obtained after injection of tritium-labeled flupentixol decanoate (Jørgensen and Gottfries, 1972). The difference is easily explanable, however, by the fact that in this earlier study the serum level measurement was a nonspecific determination of total radioactivity, which included unhydrolyzed ester, flupentixol metabolites, and tritiated water in addition to the active drug cis(Z)-flupentixol, which is the only compound measured in the present study.

Based on the assumption that a maximum/minimum fluctuation of a factor of two or less is clinically desirable it may be seen that administration of flupentixol decanoate in intervals of 2 weeks is very satisfactory. The fluctuation is in fact so small in most of the patients that it seems reasonable to try longer dosage intervals. One patient (BC) shows a fluctuating serum concentration curve in both intervals and the dosage interval should perhaps be shortened for this particular patient. A significant correlation was found between the fluctuation in the first and the second sampling interval with the individual patients ($R = 0.77$, $P < 0.05$) indicating that the fluctuation is to a high degree patient related.

The similarity in serum concentrations after injection of the 2% and the 10% solution of cis(Z)-flupentixol decanoate in Viscoleo® indicates that the liberation of ester from the depot is not only due to simple diffusion of substances from a spherical oil depot to a water phase, where the ester is rapidly removed because of hydrolytic cleavage and distribution into the tissues. The fivefold greater volume with the 2% solution as compared to the 10% solution does not lead to a fivefold larger surface, which could counterbalance the fact that the concentration gradient is five times higher with the 10% solution. Thus, in addition to diffusion of flupentixol decanoate from the oil phase to the water phase of the body, a general dispersal of the oil depot into smaller units and possibly a metabolic breakdown of the oil seem to play major roles for the pharmacokinetic properties of IM injected cis(Z)-flupentixol decanoate in Viscoleo®.

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## References

Astrup, C., Grimsgård, A., Hebnes, K., Kruse-Jensen, A., Lid, M.: A study of flupenthixol decanoate and pipothiazine undecylenate in schizophrenics. Acta Psychiatr. Scand. **50**, 481–491 (1974)

Bjerke, K., Faurby, A., Kirk, L.: Et års klinisk erfaring med Flupenthixol-dekanoat 10% (Lu 7105) i høj dosering. Nord. Psyk. Tidsskr. **26**, 363 (1972)

Carney, M. W. P., Sheffield, B. F.: The long-term maintenance treatment of schizophrenic out-patients with depot flupenthixol. Curr. Med. Res. Op. **1**, 423–426 (1973)

Engstrand, E.: Klinisk undersøkelse av flupenthixol dekanoat 10% (Lu 7105). Nord. Psyk. Tidsskr. **28**, 539–545 (1974)

Gottfries, C. G.: Klinisk prövning av flupenthixol decanoat som depå-neuroleptikum. Nord. Psykiatr. Tidsskr. **25**, 296–303 (1971)

Gottfries, C. G., Green, L.: Flupenthixol decanoate in treatment of outpatients. Acta Psychiatr. Scand. (Suppl.) **255**, 15–24 (1974)

Gross, H., Kaltenbäck, E.: Klinische Erfahrungen mit Flupenthixol-Decanoat (Fluanxol-Depot®) bei chronischen Psychosen. Wien. Klin. Wochenschr. **84**, 80–84 (1972)

Jørgensen, A., Gottfries, C. G.: Pharmacokinetic studies on flupenthixol and flupenthixol decanoate in man using tritium labelled compounds. Psychopharmacologia **27**, 1–10 (1972)

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

Wadzisz, D. F. J.: The clinical use of Depixol Concentrate in chronic schizophrenia. Paper read at Begian/Dutch Symposium on Depot Thioxanthenes, Copenhagen, Denmark. October 4, 1977

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