Eur. J. Clin. Pharmacol. 18, 355–360 (1980)

European Journal of Clinical Pharmacology

Pharmacokinetic Studies in Volunteers of Intravenous and Oral Cis (Z)-Flupentixol and Intramuscular Cis (Z)-Flupentixol Decanoate in Viscoleo®

A. Jørgensen

Biochemical Department, H. Lundbeck & Co., Copenhagen, Denmark

Summary. Serum concentrations of cis (Z)-flupentixol have been estimated in three male human volunteers who received cis (Z)-flupentixol by intravenous infusion, flupentixol (cis (Z)/trans (E) mixture, 1 : 1) orally as single and repeated doses, and i. m. cis (Z)-flupentixol decanoate in Viscoleo®. The intravenous data show that cis (Z)-flupentixol followed a multicompartment model, but it was not possible to fit the data to a two or three compartment model. The concentration curves after oral administration indicated relatively slow absorption with a peak concentration at 3–6 h, except for one case with peak at 1 h. The variation in the dosage interval after one daily oral administration was relatively limited (1.7–3.0 times), which indicates that 24 h is a reasonable dosage interval. Biological half-lives were estimated in different ways and showed some intra-individual variation; the half-life was of medium length (19–39 h). The serum concentrations after intramuscular injection of cis (Z)-flupentixol decanoate clearly demonstrated a depot effect, with a maximal concentration at 3–5 days after injection. The descending part of the serum curves allowed an approximate estimation of half-life of 3–8 days. This was not the elimination half-life, but in all probability the half-life of release of drug from the oil depot which was the rate-limiting step. From the areas under the serum concentration curves the fraction of orally administered cis (Z)-flupentixol available to the organism was calculated to be 55% (range 48–60%). The loss of drug might have been due to imcomplete absorption, but it is more likely that cis (Z)-flupentixol underwent first-pass metabolism in the gut wall and the liver. As the tablets contained about 50% cis (Z)-flupentixol, while the depot preparation contained 74% cis (Z)-flupentixol, the pharmacokinetically equivalent doses are: 10 mg tablet daily corresponds to 25 mg depot weekly. Calculation of systemic clearance gave values of 0.44–0.49 l/min, and an apparent volume of distribution was 12.5–17.2 l/kg.

Key words: cis (Z)-flupentixol; cis (Z)-flupentixol decanoate, serum concentration, biological half-life, pharmacokinetics, first-pass metabolism

The thioxanthene drug, flupentixol, has been extensively used for the treatment of various mental disorders since its introduction in 1965. In the late sixties a decanoic ester dissolved in Viscoleo® was developed and introduced as a depot preparation to be administered by intramuscular injection every two to four weeks. The use of these drugs has been based only on clinical experience, as it was not possible to perform pharmacokinetic studies due to lack of a sensitive analytical method. Studies in animals (Jørgensen et al. 1969, 1971) and man (Jørgensen and Gottfries 1972), mostly with radioactive compounds, gave some valuable information on the basic pharmacokinetics, and clearly demonstrated the depot properties of flupentixol decanoate in oil, but they did not supply the human data which would be useful in clinical practice. The development of a radioimmunoassay for cis (Z)-flupentixol, the neuroleptically active flupentixol isomer (Møller Nielsen et al. 1973; Johnstone et al. 1978), has now made it possible to initiate pharmacokinetic studies of this drug (Jørgensen 1978).

The present report deals with investigation of its basic pharmacokinetics in volunteers after administration of cis (Z)-flupentixol by intravenous infusion and oral administration (single and repeated dosed) and intramuscular injection of cis (Z)-flupentixol decanoate in Viscoleo®.

Materials and Methods

Subjects

Three male volunteers participated in the study:

Initials	Age [years]	Height [cm]	Body weight [kg]
CC	24	186	80
EIL	25	175	70
AJ	38	170	73

Prior to the study they had appeared normal on clinical investigation, including a series of blood tests of bone marrow and hepatic and renal function. The subjects, who were all highly experienced in taking part in this kind of experiments, gave informed verbal consent.

On the days of experiments the food intake of the volunteers was carefully controlled. They were allowed a light breakfast around 7 a. m. Following drug administration no food was allowed for 2 h, after which time standardized meals were given for the rest of the day.

Dosing and Blood Sampling

Intravenous Infusion. Each subject was given an intravenous infusion of cis (Z)-flupentixol dihydrochloride (corresponding to 1 mg cis (Z)-flupentixol dissolved in 100 ml sterile saline) through a Butterfly® infusion set inserted into a cubital vein. The infusion was given at a constant rate for 60 min, starting between 8 and 9 a. m. on the day of the experiment. The ECG was recorded continuously and the blood pressure was measured every 10 min during the infusion and just after it ceased. Blood samples were taken from the contralateral arm 0, 20, 40 and 60 min after starting the infusion. At the end of the infusion, 11 blood samples were collected in the subsequent 48 h. Serum was separated by centrifugation and was kept frozen until analysed.

Oral Administration. A single dose of Fluanxol® tablets 8 mg (corresponding to cis (Z)-flupentixol 4 mg) was given to each subject together with 50–100 ml tap water between 8 and 9 a. m. For repeated administration of Fluanxol® tablets the subjects received 1 mg once daily for three days, followed by 1.5 mg (corresponding to cis (Z)-flupentixol 0.75 mg) for eleven days. Blood samples were collected 0, 1, 2, 3, 4, 6, 8, 10, 12, 15, 24 and 48 h after administration of the single dose or the last dose on repeated administration. Serum separated by centrifugation was stored frozen until analysis.

Intramuscular Administration. 2% Fluanxol® Depot 0.5 ml, (cis (Z)-flupentixol decanoate 10 mg in Viscoleo®, corresponding to cis (Z)-flupentixol 7.4 mg) was administered to each subject by deep intramuscular injection in the gluteus muscle on the first experimental day between 8 and 9 a. m. Blood samples were collected 0, 1, 4 and 8 h and 1, 3, 5, 7, 9, 11, 14, 17, and 21 days after the injection. Serum was separated by centrifugation and stored frozen until analysis.

Drug Analysis

The serum concentration of cis (Z)-flupentixol was determined by a radioimmunoassay with a limit of sensitivity of 0.2–0.3 ng/ml and good specificity with respect to cis (Z)-flupentixol (Jørgensen 1978). The major metabolites of flupentixol are N-dealkyl flupentixol and flupentixol sulphoxide (Jørgensen et al. 1969), which are available as a cis (Z)/trans (E) mixture and as a pure cis (Z)-isomer, respectively. These metabolites interfere with the assay of cis (Z)-flupentixol to the extent of 2% and 1%, respectively. As the metabolites are found in human plasma in the same or lower amounts than of parent compound (Muusze et al. 1977), the cross-reactivity can be considered as of no practical importance. The two metabolites have no pharmacological effect (Christensen, personal communication) and are in all probability of no therapeutic interest. In case of administration of Fluanxol® tablets, the subjects 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. The trans (E)-isomer has been shown to have very little pharmacological effect (Møller Nielsen et al. 1973) and to be without clinical activity in schizophrenia (Johnstone et al. 1978). 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 administration of cis (Z)-flupentixol decanoate in Viscoleo® (Jørgensen 1978). The within-assay standard deviation is 6–7%, and the between-assays standard deviation is about 20%. Due to this difference, all samples from the same subject were analysed in the same assay.

Data Treatment

The intravenous data were treated according to a two compartment open model as described by Jørgensen and Hansen (1976), with weights of 1, $1/y_i$ and $1/y_i^2$

given to the squares of the deviations $(y_i - y)^2$. The data were also subjected to a kind of peeling technique, as the concentration figures originating from the β-term in the equation describing the two compartment model were subtracted for from the original concentration data. The resulting concentration data were then treated according to a two compartment open model. The areas under the serum concentration curves (AUC) after intravenous infusion were calculated by the trapezoidal rule from the start of infusion until 48 h, and by the formula C_{48}/β from 48 h to infinity. The β-values were obtained from the data treatment according to the two compartment open model. The β-value also permitted calculation of the biological half-life ($t_{½} = 0.693/\beta$)

The concentrations measured in the period 8–24/48 h after oral administration allowed graphical estimation of the biological half-life ($t_{½}$). The areas under the serum concentration curves after the single oral dose were estimated according to the trapezoidal rule in the time period 0–48 h, and by the formula $C_{48} \cdot t_{½}/0.693$ from 48 h to infinity. For subject CC, in whom no $t_{½}$ could be determined, the β obtained from the infusion study was used for calculation of the AUC from 48 h to infinity. The area under the serum concentration curve in the dose interval after repeated administration ($AUC_{0-24\,h}$) was determined by the trapezoidal rule.

Provided that the kinetics do not differ between single and repeated doses, the areas under the serum concentration curves can also be used for calculation of β and then $t_{½}$ by using the formula: $AUC_{0-24\,h}$ (rep. dose) $= AUC_{0-24\,h} + C_{24}/\beta$ (single dose) (AUC-values and C_{24} calculated for a 1 mg dose).

From the terminal ends of the serum concentration curves after intramuscular injection, a rough estimate of β and hence the half-life was possible. The areas under the serum concentration curves were determined by the trapezoidal rule from time 0 to time (T) of the last measurable serum sample (11, 17, and 21 days, respectively, for the three subjects), and by C_T/β from this time to infinity.

From the areas under the serum concentration curves after oral and parenteral administrations, the systemic availability of cis (Z)-flupentixol given orally as Fluanxol® tablets could be calculated.

The systemic clearance, Cl_s, which is an expression of the overall elimination of drug from the organism, was calculated by the formula: $Cl_s = \frac{\text{Dose}}{\text{AUC}}$. The apparent volume of distribution in the β-phase ($(V_d)_\beta$) was calculated from the data after intravenous infusion by the formula $(V_d)_\beta = \text{Dose}/\beta \cdot \text{AUC}$.

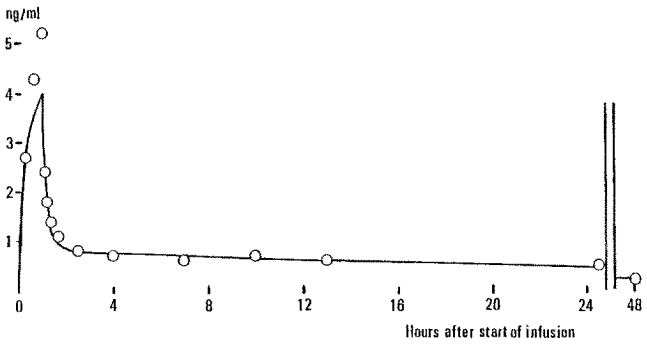

Fig. 1. Serum concentrations of cis (Z)-flupentixol after intravenous infusion of cis (Z)-flupentixol 1 mg in subject CC. Open circles indicate measured concentrations. The curve was estimated according to a two compartment open model (weight $1/y_i^2$)

Table 1. Estimated half-lives of cis (Z)-flupentixol

Subject	Two compartment curve fitting	Graphical estimation from the terminal parts of the oral curves		From AUC values	Mean (SD)
		Single dose	Repeated dosage		
CC	24	–	14	20	19 (5)
EIL	22	18	17	25	21 (4)
AJ	33	27	36	58	39 (14)

Results

Although the doses were kept at a very low level in the present study, the three volunteers all experienced unpleasant side effects, such as sedation and restlessness. The side effects appeared 4–8 h after the intravenous infusion and the single oral dose, on Days 3 to 9 after depot injection and more or less continually in a very weak form during the last week of repeated oral doses.

The serum concentrations measured after intravenous infusion of cis (Z)-flupentixol clearly demonstrate that the pharmacokinetics of cis (Z)-flupentixol must be described by a multicompartment model. Treatment of the intravenous data according to a two compartment open model showed that use of weights 1 and $1/y_i$ for the squares of the deviations gave a poor fit and high standard deviations of the model parameters. The use of weight $1/y_i^2$, which seems most reasonable as no indication of different relative standard deviations at different concentration levels is indicated in the analytical assay, gave an estimation of the model parameters with reasonable standard deviations. However, a plot of the data and the computer estimated curves shows that the two

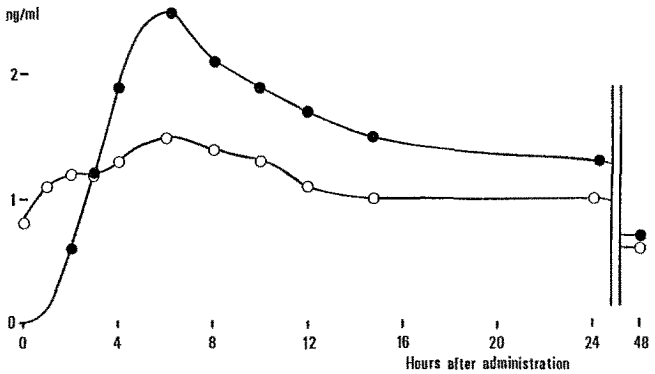

Fig. 2. Serum concentrations of cis (Z)-flupentixol after oral administration of flupentixol tablets (Fluanxol®) to subject AJ. Closed circles: single dose of flupentixol 8 mg. Open circles: Repeated administration of flupentixol 1.5 mg once daily

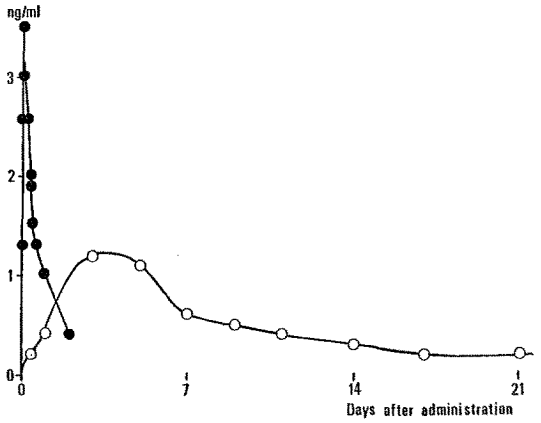

Fig. 3. Serum concentrations of cis (Z)-flupentixol after oral administration of flupentixol tablets (Fluanxol®) and intramuscular injection of cis (Z)-flupentixol decanoate in Viscoleo® (Fluanxol® Depot) to Subject EIL. Closed circles: flupentixol 8 mg orally. Open circles: cis (Z)-flupentixol decanoate 10 mg intramuscularly

Table 2. Areas under the serum concentration curves (AUC) from time 0 to infinity (i. v. infus., oral single dose, i. m. depot) or time 0 to 24 h (oral repeated dose) in ng · h/ml · mg and percentage bioavailability of oral cis (Z)-flupentixol.

AUC values					Per cent of oral cis (Z)-flupentixol available for the organism
Subject	i. v. infus.	oral single dose	oral repeat. dose	i. m. depot	
CC	34	22	14	28	57
EIL	36	18	19	40	48
AJ	38	24	37	60	60
Mean	36	21	23	43	55

compartment open model is not valid (Fig. 1). It is striking that the curves did not fit the maximum points at 40 and 60 min (during and at the end of infusion, respectively). As the fit to the terminal phase, the β-phase, was good, while the α-phase appeared to be composed of two functions, a type of peeling technique was attempted. We did not succeed, however, with this procedure – the fit to the high serum concentrations was still poor, and in addition the standard deviations of the parameters were rather high. The peeling technique reduced the number of data points and this may have contributed to a great extent to the poor result, but it may also be that more then three compartments are necessary to account for the kinetics of cis (Z)-flupentixol. However, the small number of data points did not permit further computer treatment. Thus the only parameter of value supplied by the treatment of the data according to a two compartment open model was β, from which the half-life was calculated (Table 1). From β, dose and AUC the systemic clearance based on serum concentrations, Cl_s, was calculated to be 0.44 to 0.49 l/min (mean 0.46 l/min), and the apparent volume of distribution in the β-phase $(V_d)_\beta$ was 12.5–17.2 l/kg (mean 14.1 l/kg).

The serum concentration curves obtained after oral administration of a single dose of flupentixol 8 mg and the last of a series of daily doses of flupentixol 1.5 mg in one of the subjects are shown in Fig. 2. The peak concentrations after oral administration were obtained at 3–6 h, except for one subject with a peak at one hour, indicating relatively slow absorption. The biological half-lifes estimated graphically from the terminal ends of the curves varied around one day (range 14–36 h, Table 1). No half-life could be estimated for the single oral dose given to subject CC. The maximum/minimum fluctuation in the 24-h dosage interval was 3.0, 1.8, and 1.7, respectively, for the three subjects.

The areas under the serum concentration curves after single and repeated oral administration can be used to calculate β and hence $t_{1/2}$, as already described. This calculation is based on the assumption that the kinetics of cis (Z)-flupentixol on single

and repeated administration do not differ. The fact that no trend was seen in the difference between the half-lives on i. v. infusion and the two oral treatments supports this assumption. The half-lives calculated from the AUC values are given in Table 1, together with the half-lives obtained in other ways. Some intra-individual variability is seen in the half-lives, but this may be explained by the fact that we have operated close to the limit of sensitivity of the assay method, where the standard deviation is rather high (Jørgensen 1978). The mean half-life for the three subjects ranged from 19–39 h, which may be considered a medium length half-life.

The serum concentrations of cis (Z)-flupentixol after intramuscular injection of cis (Z)-flupentixol decanoate 10 mg in one subject appear in Fig. 3. For comparison, the oral single dose curve has also been drawn on this figure. The serum concentration rose very slowly after the depot injections, reaching the maximum value 3–5 days after injection. Thus, compared to the oral single dose curve with its peak at 3–6 h after administration, the depot effect was very evident. The three blood samples drawn on the day of injection (1, 4, and 8 h after injection) all showed a serum concentration of 0, as did the sample drawn before injection.

The areas under the serum concentration curves (AUC) from time of administration to infinity after single dose administration and with a 24-h interval between repeated oral doses per mg of administered cis (Z)-flupentixol are given in Table 2. Based on these values the fraction of orally administered cis (Z)-flupentixol which reached the systemic circulation in unchanged form, i. e. is available for the organism after Fluanxol® administration, can be calculated. The available fraction was a mean 55% (range 48–60%).

Discussion

Administration of very potent psychotropic drugs like flupentixol to human volunteers in the course of pharmacokinetic studies is faced with certain problems. Due to the high tissue binding of these drugs (mean $(V_d)_\beta$ for flupentixol is 14.1 l/kg), the serum level is low relative to the tissue concentration. Thus, although a sensitive assay technique is available, as in this case, a dose of some magnitude has to be given in order to secure a valid drug estimation, and the volunteers, who seem to be very sensitive to this type of drug, will then suffer side-effects. This occurred in the present study, although we worked with doses giving serum levels close to the limit of determination.

The mean biological half-life in the three subjects (19–39 h), and the rather limited fluctuation between maximum and minimum serum concentration in a 24-h dosage interval on repeated administration, indicates that once a-day treatment is reasonable with cis (Z)-flupentixol given as ordinary tablets. The half-life of 3–8 days found after intramuscular injection of cis (Z)-flupentixol decanoate indicates that the dosage interval for this preparation should be of the order of one week. Against this, however, is the limited fluctuation in serum concentration found by Stauning et al. (1979) with a dosage interval of two weeks. As cis (Z)-flupentixol decanoate is rapidly hydrolysed to liberate cis (Z)-flupentixol (Jørgensen et al. 1971), and the biological half-life of cis (Z)-flupentixol is of the order of 1 to 1.5 days, the half-lives found for cis (Z)-flupentixol decanoate (3–8 days) are not elimination half-lives, but in all probability refer to the release of cis (Z)-flupentixol decanoate from the oil depot as the rate-limiting step.

The fraction of cis (Z)-flupentixol which is sytemically available after oral administration was a mean of 55%. The reduced systemic availability as compared to parenteral administration might be due to incomplete absorption. However, since absorption has been shown to be complete in rats (Jørgensen et al. 1969), a more likely explanation is that cis (Z)-flupentixol is partly metabolized on passage through the gut wall or liver during absorption (first-pass metabolism). As the commercially available flupentixol tablets (Fluanxol® tablets) contain 50% cis (Z)-flupentixol, while the depot preparation (Fluanxol® Depot, Depixol® Inj.) contains 74% cis (Z)-flupentixol, the pharmacokinetic equivalence between the preparations is: a tablet dose of 10 mg daily should be equivalent to a weekly dose of 25 mg of the depot preparation. However, as the serum concentration produced by tablets fluctuates between maxima and minima in 24 h, while the same fluctuation is seen over 2–4 weeks with the depot preparation, the pharmacokinetic equivalence between the tablet and depot forms does not necessarily correspond to clinical equivalence of the two preparations, but it is a useful guideline.

A peak in serum concentration on the day of injection, like that seen for fluphenazine decanoate in sesame oil (Curry et al. 1978, 1979; Wiles and Gelder 1979) is not seen with cis (Z)-flupentixol decanoate in Viscoleo, most probably because the cis (Z)-flupentixol decanoate preparation contains very little free cis (Z)-flupentixol base.

The systemic clearance of 0.46 l/min, calculated on the basis of the serum levels measured after intravenous infusion, are in good agreement with the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.