

PHARMACOKINETICS OF THREE DIFFERENT INJECTABLE ZUCLOPENTHIXOL PREPARATIONS

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Abstract

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1. The zuclopenthixol concentrations in serum has been investigated in man and dog after injection of three different zuclopenthixol preparations. These were zuclopenthixol dihydrochloride in aqueous solution, zuclopenthixol acetate in oil and zuclopenthixol decanoate in oil.
2. The pharmacokinetic profiles of the three injectable zuclopenthixol preparations are very different. Maximum serum levels are obtained after about 1 hour for zuclopenthixol dihydrochloride, after 36 hours for zuclopenthixol acetate and after one week for zuclopenthixol decanoate.
3. The different pharmacokinetics of the three injectable zuclopenthixol preparations are reflected in their clinical properties.

Keywords: formulations, intramuscular injection, neuroleptic, serum levels, zuclopenthixol.

Abbreviations: area under serum concentration curves (AUC), hour (h), milliliter (ml), nanogram (ng).

Introduction

The neuroleptic drug, zuclopenthixol, has for some years been available as two injectable preparations (in addition to oral preparations). These two preparations are an aqueous solution of zuclopenthixol dihydrochloride for acute treatment of psychotic patients, and a solution of the decanoic acid ester of zuclopenthixol in a thin vegetable oil (Viscoleo[®]) mainly for maintenance treatment (Fredricson Overø, 1980; Jørgensen and Fredricson Overø, 1980; Aaes-Jørgensen et al, 1983; Jørgensen et al, 1985). Aqueous injectables of neuroleptics are often used in the initial treatment of acutely disturbed psychotic patients. The duration of effect of such preparations is relatively short, therefore several injections are often given daily to a patient in the acute phase of treatment.

In order to obtain a preparation with a relatively rapid onset of action combined with a duration of effect of some days a new formulation, the acetate acid ester of zuclopenthixol in a thin vegetable oil, Viscoleo, has been developed.

In clinical studies zuclopenthixol acetate in Viscoleo was shown to have an onset of clinical

effect (calming effect) within few hours, and a duration of effect of 2-3 days (Amdisen et al, 1986 and 1987). Furthermore drugs dissolved in a vegetable oil are well tolerated at the injection site, whereas aqueous solutions of neuroleptics cause local muscle damage at the injection site (Svendsen and Blom, 1984).

The purpose of the present paper is to compare the serum level profiles obtained with the three different injectable preparations of zuclopenthixol.

Methods

Healthy Volunteers

Seven male and two female healthy volunteers, 21-41 years (mean 27 years), participated in the study on zuclopenthixol dihydrochloride in aqueous solution.

Patients

Eighteen male acutely disturbed psychotic patients, aged 20-51 years (mean 31 years), were included in the study of zuclopenthixol acetate in Viscoleo (Amdisen et al, 1986). Seven female schizophrenic patients, aged 37 - 83 years (mean 63 years), in maintenance treatment were included in the zuclopenthixol decanoate study (Aaes-Jørgensen et al, 1983). The studies were carried out in accordance with the Helsinki Declaration II. All patients gave informed verbal consent after the purpose of the study had been explained to them.

Dogs

Four purebred Beagle dogs of either sex weighting 9-15 kg were on different occasions given intramuscular injections of the three injectable zuclopenthixol preparations.

Drugs

The three compounds used in the studies are shown in Fig. 1. The available preparations were: Zuclopenthixol dihydrochloride, aqueous solution corresponding to 1% zuclopenthixol base. Zuclopenthixol acetate, 5% in Viscoleo. Zuclopenthixol decanoate, 20% in Viscoleo.

Dosage

The zuclopenthixol preparations were all given as intramuscular injections (doses in Table 1)

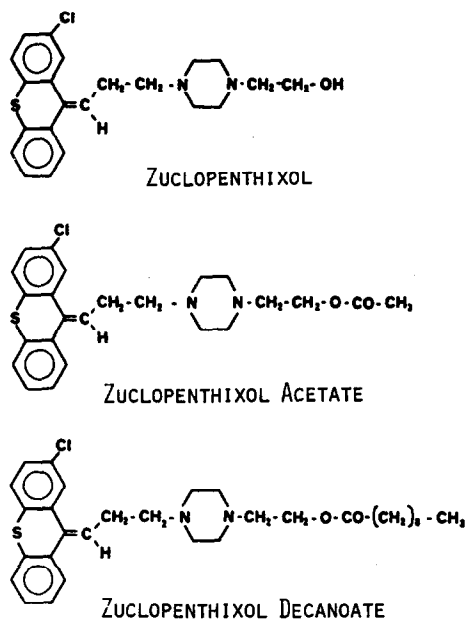


Fig. 1 Formulas of zuclopenthixol and the acetic and decanoic acid esters.

Table 1

Dose of Zuclopenthixol Dihydrochloride to Volunteers and Dogs
and of Zuclopenthixol Esters to Patients and Dogs

	Volunteers/ Patients	Dogs
Zuclopenthixol, dihydrochloride	5 mg	1 mg/kg
Zuclopenthixol, acetate	50-150 mg	5 mg/kg
Zuclopenthixol, decanoate	50-800 mg	10 mg/kg

Blood sampling

From the volunteers given zuclopenthixol dihydrochloride blood samples were drawn before injection and 0.25, 0.50, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours after injection. From the patient studies blood samples were drawn during a period of 3 days after injection of zuclopenthixol acetate (Amdisen et al, 1986) and during a dosage intervals of 2 weeks for the patients treated with zuclopenthixol decanoate (Aaes-Jørgensen et al, 1983).

In the dog studies blood was obtained before and 0.25, 0.50, 1, 2, 4, 6, 9, 12, 24, 48 and 72 hours after zuclopenthixol dihydrochloride injection, before and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours after zuclopenthixol acetate injection, before and 1, 4, 8, 24 hours and 2, 4, 7, 10, 14, 17, 21 and 28 days after zuclopenthixol decanoate injection.

After clotting the blood samples were centrifuged, serum was separated and kept deep frozen until analysis.

Drug Estimation

The concentrations of zuclopenthixol in serum were determined by a high performance liquid chromatographic method with a lower limit of sensitivity of about 0.5 ng/ml (Aaes-Jørgensen, 1980).

Statistical Analysis

Standard Pearson parametric correlation analysis was performed for variables. 1) Serum concentration and dose. 2) AUC and dose.

Results

Serum Levels, Dogs:

The average serum levels of zuclopenthixol measured in dogs are shown in Fig. 2. After injection of zuclopenthixol dihydrochloride in aqueous solution the absorption was very fast, the peak level being obtained already 1 hour after injection, whereafter the zuclopenthixol concentration declined rather rapidly.

Zuclopenthixol acetate in Viscoleo was absorbed more slowly, the maximal serum concentration was found 1-2 days after injection, then the curve declined slowly, and zuclopenthixol was detectable until 7 days after injection.

Zuclopenthixol decanoate as a very lipophilic substance is slowly released from the oil depot. Maximum concentration was obtained after 4 days in the dogs, then the curve declined very slowly, zuclopenthixol being measurable until 28 days after injection.

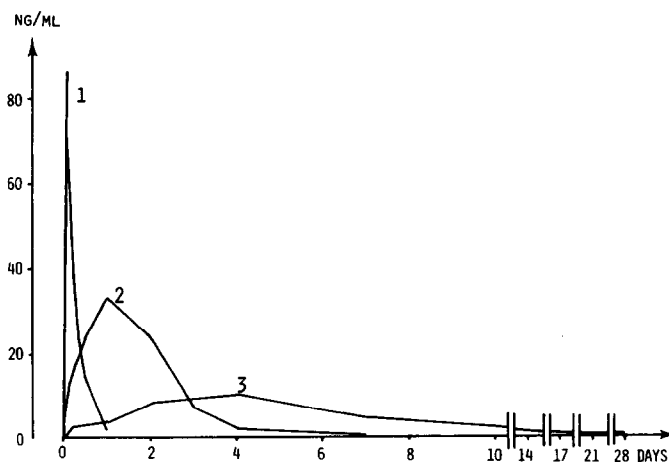


Fig. 2. Average levels of zuclopenthixol in dogs injected zuclopenthixol dihydrochloride in aqueous solution N = 4 (1), zuclopenthixol acetate in oil N = 4 (2) and zuclopenthixol decanoate in oil N = 2 (3).

Serum Levels. Volunteers and Patients

Because of linear pharmacokinetics of zuclopenthixol (Aaes-Jørgensen et al, 1981; Bjørndal and Aaes Jørgensen, 1982 and 1984; Jørgensen and Fredricson Overø, 1980; Aaes-Jørgensen et al, 1983; Jørgensen et al, 1985) it was possible to adjust the data from volunteers and patients to doses of 50 mg zuclopenthixol, 100 mg zuclopenthixol acetate and 100 mg zuclopenthixol decanoate. The average serum levels are shown in Fig. 3.

Maximal serum level was obtained 1 hour after the zuclopenthixol dihydrochloride injection, about 36 hours after the zuclopenthixol acetate injection, and one week after the zuclopenthixol decanoate injection. For zuclopenthixol acetate C_{max} and dose correlated significantly, $r = 0.77$, $p < 0.001$.

The curve from the zuclopenthixol decanoate patients is a very flat curve obtained from patients in steady state treatment. Significant correlations were found between dose and serum concentrations measured on individual days, $r = 0.69 - 0.92$, $p < 0.001$.

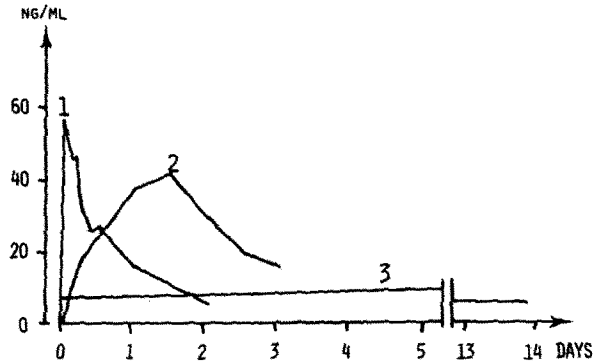


Fig. 3. Average serum levels of zuclopenthixol in 9 volunteers given zuclopenthixol dihydrochloride in aqueous solution (1), 18 patients given zuclopenthixol acetate in oil (2), and in 7 patients given zuclopenthixol decanoate in oil (3). Curve 2 is reproduced from Amdisen et al (1986) with permission of the copyright holder. Curve 3 is reproduced from Aaes-Jørgensen et al (1983) with permission of the copyright holder.

Area under Serum Concentration Curves, Patients

The areas under the serum concentration curves (AUC) calculated according to the trapezoidale rule have also been shown to correlate significantly to the dose of zuclopenthixol acetate and zuclopenthixol decanoate. For zuclopenthixol acetate AUC was estimated from zero to 72 hours after injection, the AUC's versus dose are given in Fig. 4. For the zuclopenthixol decanoate patients dosed every two weeks significant correlation was also found for AUC's versus dose, Fig. 5.

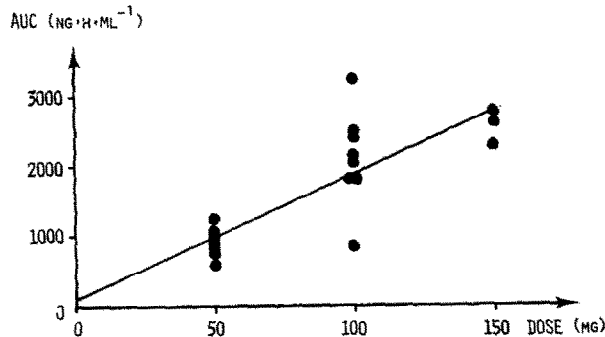


Fig. 4. Correlation between dose of zuclopenthixol acetate in Viscoleo and AUC, $r = 0.80$, $p < 0.001$. Reproduced from Amdisen et al (1986) with permission of the copyright holder.

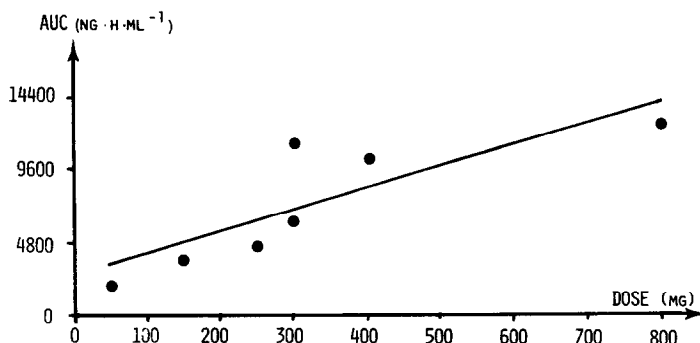


Fig. 5. Correlation between dose of zuclopenthixol decanoate and AUC, $r=0.83$, $p<0.05$. Reproduced from Aaes-Jørgensen et al (1983) with permission of the copyright holder.

Discussion

The pharmacokinetics of zuclopenthixol have been shown to be linear both after oral administration of zuclopenthixol and after parenteral administration of zuclopenthixol esters in Viscoleo. Thus significant and high correlations between administered dose and serum levels was obtained in patients given zuclopenthixol tablets (Aaes-Jørgensen et al, 1981; Bjørndal and Aaes-Jørgensen, 1982 and 1984), and in patients given zuclopenthixol decanoate intramuscularly at intervals of 2 or 4 weeks (Jørgensen and Fredricson Overø, 1980; Aaes-Jørgensen et al, 1983; Jørgensen et al, 1985). As significant correlations between dose and serum level on individual days were obtained it is not surprising that significant correlations between dose and AUC were obtained too. The interindividual variation in serum zuclopenthixol levels was after both oral and intramuscular administration limited to a factor 2-4.

The curve shapes of the three injectable zuclopenthixol preparations are very different. The aqueous solution of zuclopenthixol dihydrochloride and the oil solution of zuclopenthixol acetate are both used for treatment of acutely disturbed psychotic patients, where a rapid onset of clinical effect is desired.

Zuclopenthixol in aqueous solution is absorbed very fast and the concentrations also decline relatively fast, i.e. the clinical effect (wanted calming effect) of an aqueous solution is rather short lasting. For this reason a new injection has to be given rather soon - often after 4-8 hours.

Zuclophenthixol acetate is released from the oil vehicle by diffusion, whereafter the ester bond is rapidly hydrolysed and the active drug, zuclophenthixol, is released. The increase in serum concentration is relatively fast, and a clinical effect is obtained few hours after the injection (Amdisen et al, 1986 and 1987). Maximum serum level appears after about 36 hours, followed by a slow decrease. It is interesting that the sedation, which is a wanted effect in the initial treatment of acutely disturbed psychotic patients, reaches its maximum about 8 hours after the injection, i.e. more than 24 hours earlier than the maximum serum level (Amdisen et al 1987). The clinical effect lasts for 2-3 days. At this time a new injection can be given or the patient can be switched to oral or depot treatment.

The principle for the depot formulation of zuclophenthixol is the same as for the acetate preparation for acute treatment. But because of the longer chained fatty acid (decanoic acid) the release of drug from the oil is much slower. The serum concentration increases slowly and reaches maximum about one week after injection, whereafter the concentration decreases slowly. The duration of clinical effect of zuclophenthixol decanoate in Viscoleo is 2-4 weeks and thus very suitable for maintenance treatment.

Conclusion

With the three different injectable zuclophenthixol preparations it is possible to treat patients in different phases of their psychoses with the same active drug. The differences in the pharmacokinetics between the three injectable zuclophenthixol preparations are reflected in different clinical properties. A rapid onset of effect is obtained with the aqueous solution of zuclophenthixol and with zuclophenthixol acetate in oil. The duration of effect of zuclophenthixol acetate is 2-3 days, whereas the duration of effect of zuclophenthixol in aqueous solution is some hours. For zuclophenthixol decanoate the duration of action is 2-4 weeks.

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