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Clinical Pharmacokinetics of the Depot Antipsychotics

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Summary

The clinical pharmacokinetics of the 4 depot antipsychotics for which plasma level studies are available (i.e. fluphenazine enanthate and decanoate, haloperidol decanoate, clopenthixol decanoate and flupenthixol decanoate) are reviewed. The proper study of these agents has been handicapped until recently by the necessity of accurately measuring subnanomolar concentrations in plasma. Their kinetic properties, the relationship of plasma concentrations to clinical effects, and conversion from oral to injectable therapy are discussed.

The depot antipsychotics are synthesised by esterification of the active drug to a long chain fatty acid and the resultant compound is then dissolved in a vegetable oil. The absorption rate constant is slower than the elimination rate constant and therefore, the depot antipsychotics exhibit 'flip-flop' kinetics where the time to steady-state is a function of the absorption rate, and the concentration at steady-state is a function of the elimination rate.

Fluphenazine is available as both an enanthate and decanoate ester (both dissolved in sesame oil), although the decanoate is more commonly used clinically. The enanthate produces peak plasma concentrations on days 2 to 3 and declines with an apparent elimination half-life (i.e. the half-time of the apparent first-order decline of plasma concentrations) of 3.5 to 4 days after a single injection. The decanoate produces an early high peak which occurs during the first day and then declines with an apparent half-life ranging from 6.8 to 9.6 days following a single injection. After multiple injections of fluphenazine decanoate, however, the mean apparent half-life increases to 14.3 days, and the time to reach steady-state is 4 to 6 weeks. Withdrawal studies with fluphenazine decanoate suggest that relapsing patients have a more rapid plasma concentration decline than non-relapsing patients, and that the plasma concentrations do not decline smoothly but may exhibit 'lumps' due to residual release from previous injection sites or multicompartment redistribution. Cigarette smoking has been found to be associated with a 2.33-fold increase in the clearance of fluphenazine decanoate. In 3 different studies, fluphenazine has been proposed to have a therapeutic range from < 0.15 to 0.5 ng/ml with an upper therapeutic range of 4.0 ng/ml. Plasma concentrations following the decanoate injection are generally lower than, but clinically equivalent to, those attained with the oral form of the drug.

Haloperidol decanoate plasma concentrations peak on the seventh day following injection although, in some patients, this peak may occur on the first day. The apparent elimination half-life after multiple injections is approximately 3 weeks and the time to reach steady-state is approximately 3 months. The reduced metabolite of haloperidol is

present in significant quantities in humans following oral therapy; however, this has not been reported in pharmacokinetic studies with the depot preparation. The therapeutic range for haloperidol has been reported to be 3 to 40 ng/ml in several studies, but these studies did not measure the reduced metabolite. It has been suggested that the presence of high concentrations of the reduced metabolite may affect the response to haloperidol.

Clopenthixol is only active as the cis *(Z) isomer, which is the form of the drug present in the decanoate preparation. Peak plasma concentrations are usually reached between 4 and 7 days after injection. Following multiple injections, the apparent elimination half-life is 19 days. No correlation between plasma concentrations and clinical response has been reported, but concentrations have been observed to range from 10 to 100 ng/ml following a wide range of dosages and injection intervals.*

Flupenthixol is available as either the palmitate or decanoate ester, although most pharmacokinetic studies have used the decanoate formulation. Like clopenthixol, flupenthixol is only active as the cis *(Z) isomer which is the form present in the decanoate preparation. Peak plasma concentrations occur on approximately the seventh day following injection, and no pharmacokinetic differences have been observed between the 2% and 10% concentrations of the drug. Following a single injection, an apparent elimination half-life of 8 days was reported, whereas after multiple injections, the apparent half-life was 17 days. Following withdrawal, no statistically significant differences were noted between relapsing and non-relapsing patients, but there was a trend towards lower trough concentrations in the relapsing group. There was also a shorter apparent half-life in the relapsing group when compared with the non-relapsing patients. No correlations between plasma concentrations and clinical response were found.*

Most methods for converting oral preparations to depot injections have been empirically developed. One study that did examine plasma concentrations and clinical effects during conversion of oral fluphenazine to the decanoate found that 1.2 to 2.5 times the oral dose (mg/day) given weekly resulted in a smooth transition between dosage forms. Fluphenazine plasma concentrations on the decanoate were lower during the first 3 weeks in comparison with oral fluphenazine therapy. It is recommended that the initially effective dose be reduced or the injection interval increased after 4 to 6 weeks to prevent possible accumulation of drugs as plasma concentrations approach steady-state. The recommended dose of haloperidol decanoate is 20 times that of the daily oral dose (mg/day) given monthly, but this should be reduced to a factor of 15 in geriatric patients. Flupenthixol 10mg given orally daily is proposed to be equivalent to 25mg of the decanoate given weekly. The use of the mean conversion ratios as a starting point for an individual patient's conversion is appropriate, but wide interindividual variations in pharmacokinetics require plasma level monitoring and careful clinical observation of the patient.

Adverse effects from depot antipsychotics are relatively rare, except for extrapyramidal system reactions. The most serious (albeit very rare) problem that can occur with a long acting antipsychotic is the neuroleptic malignant syndrome. Due to their long apparent half-lives after injection, effective treatment of this syndrome following administration of depot antipsychotics can be difficult.

The introduction of depot antipsychotics in the early 1960s represented a major advance in drug delivery systems as they facilitated drug administration in psychiatric patients who are non-compliant with oral therapy. One of their major advantages is that injections can be given on a weekly to a monthly basis, and dosages and administration intervals can be individually titrated. However, despite the worldwide use of the depot antipsychotics, very few reports have extensively investigated their pharmacokinetic properties. To properly study the pharmacokinetics of these agents,

the accurate quantitation of subnanomolar concentrations is required. The paucity of pharmacokinetic literature on depot antipsychotics stems from the inability of investigators to accurately measure low plasma concentrations of the drugs (below 1 ng/ml).

This article reviews the available literature on the pharmacokinetics of the depot antipsychotics. Only those drugs for which plasma level studies are available will be evaluated, i.e. fluphenazine enanthate and decanoate, haloperidol decanoate, clopenthixol decanoate, and flupenthixol decanoate. Each drug's pharmacokinetic properties, the relationship of their plasma concentrations to clinical response and adverse effects, and the conversion from oral to injectable treatment will be examined. At present, there is little pharmacokinetic information available on other depot antipsychotics such as pipothiazine palmitate, fluspirilene and perphenazine enanthate, and these agents will not be discussed.

1. Fundamental Pharmacokinetic Properties

The depot antipsychotics are synthesised by esterification of their hydroxyl group to a long chain fatty acid. The esters are then dissolved in either sesame seed oil, coconut oil, or Viscoleo® (a vegetable oil). Only fluspirilene is not esterified, but is formulated as an aqueous suspension (Simpson, 1984). Once the drug is injected into muscle, it is then slowly released from the site. The diffusion and availability of free drug released from the oily depot site is most likely the initial rate-limiting kinetic step (Dreyfuss et al., 1976a) since enzymatic hydrolysis from the ester occurs rapidly. Therefore, the apparent rate of elimination is controlled by the absorption (release) rate and not by the rate of hepatic metabolism (Ereshefsky et al., 1984a; Jørgensen, 1980a). When the absorption rate constant is less than the elimination rate constant, a 'flip-flop' model results (Gibaldi and Perrier, 1982). The time necessary to achieve steady-state plasma concentrations is dependent on the absorption rate of the depot antipsychotic and may take up to 3 months, yet plasma concentrations are still proportional to clearance.

Injectable depot administration bypasses oral absorption variability, gut wall metabolism, and first-pass extraction by the liver. Active drug becomes available as plasma esterases hydrolyse the esterified compound (see fig. 1). The sesame oil vehicle may retard this hydrolysis resulting in a prolonged duration of action (Dreyfuss et al., 1976a; Jørgensen, 1972). The free drug is then available to distribute (Ereshefsky et al., 1984a) across the blood brain-barrier to the site of action, be metabolised to active or inactive metabolites, or bind to other tissues. Once sufficiently polar metabolites are formed, they are eliminated by biliary or renal excretion.

1.1 Fluphenazine Enanthate and Decanoate

Fluphenazine enanthate and decanoate are both formulated in sesame oil; however, their pharmacokinetic profiles are quite different.

1.1.1 Disposition Studies

Studies determining fluphenazine enanthate and decanoate kinetics originally used radioactively-labelled compound or a radioimmunoassay (RIA) method (Curry et al., 1979a; Midha et al., 1980; Wiles et al., 1980). However, the RIA methods weakly crossreact with metabolites and the radiolabelled detection method was unable to distinguish between parent drug and metabolites. Recently, high-performance liquid chromatography (HPLC) [Harris et al., 1982] and high-performance thin-layer chromatography (HPTLC) [Davis and Fenimore, 1983] have been developed which have lower limits of sensitivity of approximately 0.2 ng/ml.

Plasma Concentration Profiles

Fluphenazine enanthate apparently produces a slowly rising concentration that peaks at 2 to 3 days, whereas the decanoate has an earlier peak concentration which occurs within 1 to 2 days (see fig. 2). Like other phenothiazines, fluphenazine has a large

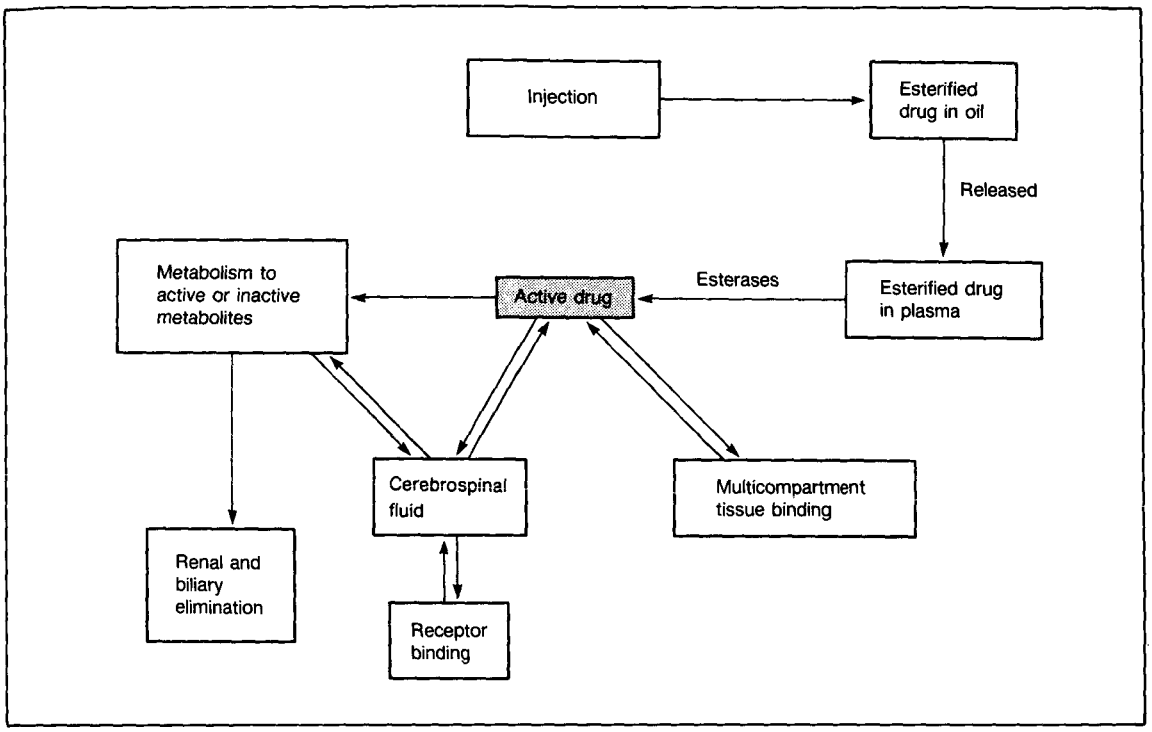

Fig. 1. Disposition of depot antipsychotics.

number of metabolites; however, only the sulphoxide and 7-hydroxyfluphenazine metabolites have been studied (Whelpton and Curry, 1976). The apparent elimination half-lives (i.e. half-times of the apparent first-order decline of plasma concentrations) of fluphenazine enanthate (Curry et al., 1979a) and decanoate (Ereshefsky et al., 1984a) range between 3.5 and 4 days and 6.8 and 9.6 days, respectively, after single injections of 25mg. However, when fluphenazine decanoate plasma concentrations were measured in 4 patients maintained for over 5 weeks on weekly injections, their mean apparent half-life was calculated to be 14.3 ± 2.2 days. This increase in apparent half-life from single to multiple injection is perhaps due to redistribution from tissue storage sites or residual drug absorption from multiple depot injection sites (see fig. 1). There was no measurable evidence of the esterified compound in plasma, urine or faeces; however, conjugated forms of fluphenazine, fluphenazine sulfoxide and 7-hydroxyfluphenazine were found in the urine. Fluphenazine and 7-hydroxyfluphenazine were found in faeces, but not their conjugates. 7-Hydroxyfluphenazine glucoronide has been reported to be excreted in the bile of dogs and subsequently hydrolysed in the gastrointestinal tract (Whelpton and Curry, 1976).

Cerebrospinal fluid fluphenazine concentrations measured in 6 schizophrenics were 38% of the plasma concentrations (Wiles and Gelder, 1980).

Interindividual Variability

Wide interpatient variation in plasma concentrations following a standard dose has been observed with many antipsychotic agents (Cooper, 1978). Similarly, wide interpatient variation in fluphenazine decanoate plasma concentrations was observed in 9 patients following a single 50mg intramuscular dose (Nasrallah et al., 1979). Peak plasma

concentrations were achieved from 1 to 6 hours after the dose and ranged between 3 and 13 ng/ml, with 6 of 9 patients having subsequent rises in their plasma concentrations over the 2-week study. Ereshefsky et al. (1984c) reported that in 42 plasma samples drawn at steady-state, a wide variability existed following doses of 25mg (mean level 0.73 ± 0.71 ng/ml, range < 0.10 to 2.22 ng/ml) and 50mg (mean level 1.45 ± 1.44 ng/ml, range 0.20 to 2.49 ng/ml).

Plasma Concentration-Dose Correlation

Linear least squares regression correlation analysis in 39 patients on decanoate therapy, after 4 or more weekly injections at a constant dose, yielded a high correlation between standard dosages and mean plasma concentrations ($r = 0.96$, $p < 0.01$) at each dose [Ereshefsky et al., 1984a]. The intramuscular route bypasses the variability associated with oral absorption and first-pass metabolism. Thus lower correlations were observed with oral absorption ($r = 0.71$, $p < 0.001$) [Ereshefsky et al., 1984a].

Possible Explanations for the Early Peak with the Decanoate Formulation

Animal studies have confirmed the hypothesis that the rate of release of fluphenazine from the injection site controls the plasma concentration (Dreyfuss et al., 1971). This does not, however, account for the presence of an initial peak with the decanoate. It has been suggested by Altamura et al. (1979) that the early peak seen with the decanoate could reflect the presence of unesterified fluphenazine in the decanoate preparation (3% free fluphenazine) as compared with the enanthate (1% free fluphenazine). However, Curry et al. (1979a) noted that these peak plasma concentrations may be too large to be ascribed to just the presence of unesterified fluphenazine (e.g. a 50mg injection yielded only 1.5mg of unesterified drug).

The conversion from the esterified compound to the active drug *in vivo* is due to enzymatic hydrolysis (Dreyfuss et al., 1976a,b). It appears that hydrolysis at the injection site is not as important as the hydrolytic activity in the plasma. However, others believe that hydrolysis at the site of injection is important (Altamura et al., 1979). If hydrolysis in plasma were the only factor, the early peak seen with the decanoate should also be observed with the enanthate, but the enanthate data does not demonstrate an early peak in the early ^{14}C-labelled recovery studies (Curry et al., 1976).

The decanoate, unlike the enanthate, may bind differently to the muscle favouring exposure to plasma esterases and resulting in the early peak concentrations. Partition studies (Altamura et al., 1979) have demonstrated that the decanoate ester does bind to the soluble fraction of the muscle tissue. However, the decanoate, in contrast to the enanthate, fails to bind to the insoluble fraction of the muscle tissue. This increases the decanoate's accessibility to plasma and muscle esterases in the initial stages following an injection (Altamura et al., 1979).

Further investigation of both the *in vitro* stability and *in vivo* esterase and absorption mechanisms are required to explain how the observed initial peak concentrations are achieved with the decanoate formulation.

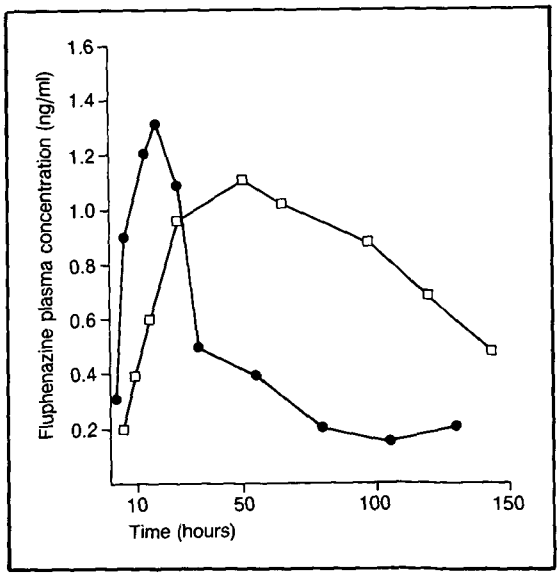

Fig. 2. Plasma concentrations of fluprenazine enanthate (□——□) and decanoate (●——●) after single injections of 25mg (after Curry et al., 1978 and Ereshefsky et al., 1984a).

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