Review

Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications

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Abstract. The authors review the literature regarding the pharmacokinetics of long-acting injectable neuroleptic drugs (LINS). There are important differences between LINS and oral neuroleptics that affect their pharmacokinetics. By avoiding first pass metabolism in gut and liver, LINS result in lower circulating concentrations of metabolites than are found after oral administration. In addition, LINS take more time to reach a stable steady state than their oral counterparts. The clinical significance of these pharmacokinetic properties is discussed. The authors recommend that when patients are being changed from oral neuroleptics to LINS, that this conversion be done gradually over several months.

Key words: Schizophrenia - Neuroleptics - Pharmacokinetics - Long-acting neuroleptics

Long-acting injectable neuroleptics (LINS) provide a method for medicating schizophrenic patients without requiring that they take pills on a regular basis. The injection is administered intramuscularly once every 1-4 weeks depending on the particular drug selected. The drug is slowly released from the injection site, providing a reasonably steady plasma level over the entire interval, a property which has led to these drugs being heavily utilized by clinicians. Indeed, some view these medications as being preferable to oral neuroleptics for the large proportion of chronic schizophrenic patients who require long-term maintenance therapy (Freeman 1980). This is because LINS provide a partial solution to the problem of noncompliance which can seriously compromise the treatment of schizophrenic patients. This advantage of depot drugs is best demonstrated in studies such as those conducted by Johnson and his coworkers (1984) under conditions that resemble most closely those that exist in community clinics. In these studies, patients with histories of poor compliance are included in the population and the amount of contact between patients and staff are limited. In the larger, more carefully controlled investigations (Hogarty et al. 1979; Schooler et al. 1980) patients with serious compliance problems - that is, the individuals most likely to benefit from treatment with LINS - are commonly not included. In addition, the amount of contact between treating staff and patient usually exceeds that available in community programs. However, a careful look at the later studies indicates that there may be advantages for LINS even under these carefully controlled conditions. In both the Schooler and Hogarty studies there were no differences in outcome between oral and depot fluphenazine at the end of 1 year. The Hogarty study also included a second year during which patients receiving fluphenazine decanoate demonstrated a lower risk of relapse than those assigned to oral fluphenazine. Moreover, the best outcomes were found for patients who received fluphenazine decanoate supplemented by a form of social therapy. These results suggest that LINS may be the preferred route of neuroleptic administration for patients who are selected for being reliable and stable and who are treated in a setting enriched with social therapies.

There are two important differences between LINS and oral neuroleptics which affect their pharmacokinetics. LINS avoid first pass metabolism in gut and liver, conceivably resulting in lower circulating concentrations of the metabolites than are found after oral administration, and LINS have longer accumulation half-lives than their oral counterparts and therefore require more time to reach a stable steady state and a longer time to disappear from plasma after the termination of treatment. These properties of LINS can also become serious problems. The prescribing clinician has less flexibility: the long time taken to achieve steady state may mean that the patient's condition may not be controlled adequately during the initial stages of treatment. Conversely, the slow disappearance of drug from plasma when therapy is stopped may be a problem if the patient experiences serious side effects. These characteristics of LINS suggest that a knowledge of their pharmacokinetics may be even more important for depot than oral drugs.

This review will document the evidence supporting these differences in kinetics and will focus largely on the implications of these differences as they affect clinical practice.

Explanation of slow-release characteristics

There are two possible explanations for the slow-release characteristics of LINS. The first is that the rate of release is dependent upon the rate of hydrolysis of the esterified drug by esterases in muscle tissues or blood. The second is that the rate limiting factor is the rate of diffusion of the esterified neuroleptic from the oil vehicle. Data from animal studies indicate that the latter explanation is correct. For example, Aaes-Jorgensen and co-workers (1977) found that after intramuscular injection of clopenthixol decanoate...
in dogs, there appeared to be a slow, monoexponential release of radioactivity from the depot with a half-life of 4–5 days. By contrast, in vitro experiments showed that hydrolysis of the ester group to yield clopenthixol occurred rapidly in blood and a variety of tissue preparations, including muscle. In similar experiments in dogs, Dreyfuss and coworkers (1976a) found that 18.6% of radioactivity remained at the injection site 35 days after the intramuscular injection of fluphenazine decanoate. On the other hand, after the intravenous injection of FD to dogs, thin layer chromatography showed that most of the drug in plasma was in the unesterified form, indicating rapid hydrolysis of the decanoate ester by blood esterases in vivo (Dreyfuss et al. 1976b). By contrast, experiments in which fluphenazine decanoate was incubated with plasma or tissue preparations suggested that the rate of hydrolysis in vitro was very slow. At present, it is not clear why there is a discrepancy between the apparent rates of hydrolysis of fluphenazine decanoate in vitro and in vivo.

Available long-acting injectable neuroleptics

The first available LIN was created when fluphenazine hydrochloride had its side chain esterified with heptanoic acid, producing fluphenazine enanthate (FE). The resulting molecule was not absorbed until it was hydrolyzed by muscle esterases, thus releasing free fluphenazine. Decanoic acid was used later for esterification since hydrolysis of the resulting drug, fluphenazine decanoate (FD), was somewhat slower. Both clinical experience and laboratory evidence (Dreyfuss et al. 1976a, b) have demonstrated that FD has a longer interinjection interval. Not surprisingly, it has replaced FE which is seldom used today. Currently, more than a dozen different LINS are available worldwide. This review will focus on three of the most widely used drugs. However, the emphasis will be on pharmacokinetic principles which are likely to be generalizable to any LIN.

Significance of the oil vehicle

The two oil vehicles which have been most commonly used in formulating depot neuroleptics are sesame oil and viscoleo. The characteristics of the oils are important since one of the important factors contributing to the sustained release of the neuroleptic is the oil/water partition coefficient. In one study (Knudsen et al. 1985) perphenazine decanoate was administered to two patients in both sesame oil and viscoleo. The study concluded that lower, but more even release of the neuroleptic is the oil/water partition coefficient. However, the emphasis will be on pharmacokinetic principles which are likely to be generalizable to any LIN.

Pharmacokinetics of LINS

The fact that the drug is released very slowly from the oily depot has important effects on the pharmacokinetics of LINS. When a drug is administered orally, plasma concentrations rise to a maximum during what is called the “absorption phase” and then decline polyexponentially (in the case of most neuroleptics) in what have been termed the “distribution” and “elimination” phases. In this case, the elimination rate constant and half-life values are often calculated from the “terminal” portion of the log plasma concentration versus time curve. With the development of ultrasensitive analytical methods, however, it has become feasible to monitor plasma levels for several days after the administration of a single oral dose of neuroleptic. In one study, for example, plasma haloperidol levels could be measured for 11 days after the administration of a single oral dose of 5 mg haloperidol to a drug-free healthy volunteer (Hubbard et al. 1987). In this case, the “terminal half-life” was calculated as 21 days, which possibly represented a half-life for redistribution as the drug was slowly released from fat deposits and tissue binding sites. Where LINS are concerned, however, the very slow release of drug means that the absorption of drug from the depot into the bloodstream takes place continually throughout the interval between doses. Thus, the pharmacokinetics of LINS are rate limited by the rate of absorption (release from the depot) rather than the rate of metabolism (Jorgensen 1980; Ereshefsky et al. 1984). In this situation, the decline in plasma concentrations from the peak level reflects the rate of absorption rather than the elimination rate constant. Since the rate of absorption (release) is slower than the rate of elimination, the pharmacokinetics assume what has been termed a “flip-flop” model (Gibaldi and Perrier 1982). Further discussion on the “flip-flop” kinetics of LINS is available elsewhere (Ereshefsky et al. 1984; Jann et al. 1985).

It suffices to say that the polyexponential plasma level decline curve obtained after the administration of LINS is very difficult to interpret unambiguously, particularly in view of the fact that the curve is almost invariably contaminated by interference from drug leaching out of old injection sites and fatty deposits in the body. Under these circumstances it is not surprising that the drug can be detected in the plasma of patients for months after cessation of therapy with LINS (Gitlin et al. 1988). Therefore, a half-life value calculated from the “terminal” portion of the log plasma level time curve of LINS is not an elimination half-life. This situation has resulted in a great deal of confusion and the literature is rife with errors and misinterpretations of the pharmacokinetics of LINS.