Future of Depot Neuroleptic Therapy: Pharmacokinetic and Pharmacodynamic Approaches

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The future of depot neuroleptic therapy is discussed in terms of pharmacokinetic and pharmacodynamic research opportunities. Analytic methods for neuroleptic assays, including chromatographic, radioreceptor, nuclear magnetic resonance, and radioimmunoassay techniques, are briefly reviewed. Elucidation of depot neuroleptic multicompartment kinetics utilizing nonlinear mixed-effects modeling and the usefulness of these data in interpreting plasma levels are discussed. The clinical significance of plasma monitoring of depot fluphenazine, including the development of dosage conversion guidelines, is presented. The relationships between haloperidol and its metabolite reduced haloperidol (RH) are discussed in terms of dosage form and response. Clinical advantages resulting from the availability of more depot neuroleptics are discussed.
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One of the most common reasons for the readmission of psychiatric patients to the hospital stems from the lack of medication compliance. The introduction of injectable depot neuroleptics in the early 1960s provided clinicians with a method of accurately assessing medication compliance in the mentally ill patient. Several studies have suggested that depot neuroleptics reduce the frequency of relapse or length of hospital stay when compared to oral agents.[1-3] However, other investigators have reported that depot neuroleptics did not reduce the number of relapses among schizophrenics when compared with oral medications.[4] It is beyond the scope of this article to review all the comparative studies; the reader is referred to the articles by Kane and Johnson in this issue.[5,6]

The major perceived use of depot neuroleptics currently is in cases of patient refusal or failure to take oral medication as prescribed.[1] Injectable depot therapy bypasses absorption variability, gut wall metabolism, and first pass extraction by the liver. This method of drug administration is useful with patients who absorb inadequate amounts of drug from oral therapy, resulting in subtherapeutic plasma levels.[7]

Assessment of the action of drugs in psychiatric disorders is complicated because drug effects are only one of several inputs to the brain. Many environmental factors, including drugs, affect the brain's biochemical responses. Behavior is the outcome of a complex interplay of genetics, prior skills, events stored as memories, and biochemical factors. When a drug is added to this complicated set of interactions, there may be initially only a minor change in behavior. Substantial changes in behavior, however, can occur over extended periods of time.

The longitudinal course of drug response is partially dependent on individual pharmacodynamic and pharmacokinetic factors. Pharmacokinetic studies of drugs are needed to investigate how bioequivalence, therapeutic efficacy, and drug distribution characteristics influence the patient's response. Failure to consider pharmacokinetics explains much of the disparity in results found among clinical studies. These principles and their applications will play an important role in the future use of long-acting neuroleptic drugs.

OVERVIEW OF DEPOT NEUROLEPTICS

The synthesis of long-acting neuroleptics is accomplished by an esterification of fluphenazine or other hydroxyl-containing neuroleptics to a long-chain fatty acid. These esters are usually dissolved in sesame seed oil, coconut oil, or Viscoleo. Medications such as fluspirilene are not esterified, but are formulated as an aqueous microcrystalline suspension with slow release properties.[8] The medication, in oil or suspension, when injected into muscle, forms a reservoir of slowly released drug. The esterified compounds are reportedly taken up into fat stores in various body areas, except the brain and spinal cord, within days.[2] The drug is slowly and steadily released from the depot and hydrolyzed by plasma esterases to the parent compound,[1] although preliminary reports suggested that fluphenazine decanoate was released "erratically, in spurts," from the injection site.[9]

At the present time, fluphenazine enanthate and decanoate are the only long-acting depot neuroleptics available in the United States. An increase in the number of depot neuroleptics available will lead to potentially improved patient care for the following reasons:

1. Easier conversion from oral to depot medication without switching drug class.

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TABLE 1. Comparison of Depot Neuroleptics

Neuroleptics	Fatty Acid Chain	Vehicle	Dosage and Interval	Single-Dose Kinetics		
				Plasma Levels	Time to Peak (days)	Half-Life (days)
Fluphenazine	Decanoate	Sesame oil	12.5-100 mg, 1-4 weeks	0.5-3.0	0.3-1.5	6-9
Fluphenazine	Enanthate	Sesame oil	12.5-100 mg, 1-2 weeks	NA	2	3.5-4.0
Haloperidol	Decanoate	Sesame oil	20-400 mg, 4 weeks	3.0-10.0	3-9	21
Flupenthixol	Decanoate or palmitate	Viscoleo	10-50 mg, 2-4 weeks	0.5-2.0	11-17	17
Clopenthixol	Decanoate	Viscoleo	50-600 mg, 1-4 weeks	0.5-9.0	4-7	19
Perphenazine	Enanthate	Sesame oil	50-200 mg, 1-4 weeks	2.0-10.0	2-3	3.5-4.5
Pipotiazine	Palmitate	Sesame oil	25-600 mg, 4 weeks	NA	NA	NA
	Undecylenate	Sesame oil	2-200 mg, 1-4 weeks	NA	NA	NA
Fluspirilene	None	Aqueous suspension	2-30 mg, 1-4 weeks	NA	NA	NA

2. Flexible selection of depot agent to minimize side effects.
3. Increased selections for alternative therapies of the refractory patient.
4. Decreased costs of depot therapy secondary to competition in the marketplace.
5. More widespread use of depot therapy, leading to increased clinical experience and to decreased morbidity and health care costs.

Table 1 summarizes the studies examining the pharmacokinetics of depot neuroleptics available worldwide.[10-16] Most of the clinical studies with the various depot neuroleptics have compared their side effect profile to that of fluphenazine decanoate or simply reported the various sedative, autonomic, and extrapyramidal symptoms (EPS) occurring in the study population. Fluphenazine enanthate was reported to cause increased extrapyramidal and motor side effects compared to fluphenazine decanoate during a 7-month double-blind study with 50 schizophrenic outpatients.[17] Haloperidol decanoate was reported to cause sedation in 4 of 38 patients.[18] In a larger study of haloperidol decanoate involving 239 chronic schizophrenic patients, 27% had autonomic side effects or EPS.[19] Fluspirilene and clopenthixol decanoate were compared to fluphenazine decanoate, and their sedative effects ("somnolence," "drowsiness") were found to be similar.[20,21] In a report on 10 schizophrenics, 5 displayed akathisia and pseudoparkinsonism after administration of perphenazine enanthate.[22] Extrapyramidal symptoms with pipotiazine palmitate and undecylenate were reported to range between 10% and 43% among the patients in the various published studies.[23]

In several studies, all of the extrapyramidal side effects were adequately treated with antiparkinsonian agents. There were no reports of abnormal effects on liver, renal, or other organ systems, as measured by routine laboratory analysis. The most serious problem that can occur with a long-acting neuroleptic is the neuroleptic malignant syndrome (NMS). Because of the apparently long half-life of the injected drug, it can be difficult to effectively treat patients in whom this syndrome develops. Of the 12 deaths patients treated with fluphenazine decanoate.[24] Finally, it has been reported that the relative occurrence of tardive dyskinesia is not specifically related to any particular neuroleptic agent.[25] Careful epidemiologic studies to accurately assess the effects of drug product selection and plasma levels on the incidence of tardive dyskinesia have not been performed to date. Additional carefully controlled studies that consider pharmacokinetic and pharmacodynamic variables need to be performed as new depot agents become available.

NEUROLEPTIC ASSAY

A prerequisite to the study of the pharmacokinetics of neuroleptic agents is the ability to measure the clinically relevant subnanomolar quantities of drug in biological fluids. In general, the best correlation between drug at the site of action within the central nervous system and a peripheral measure is the free (unbound) level of drug within the plasma. Free drug levels are more useful than total drug levels because they measure the drug that is available to diffuse across the blood brain barrier to the site(s) of action.[26] Some studies suggest that models of the amount of drug within the central nervous system have produced better correlations when based on red blood cell levels.[27-29]

Several low-affinity binding sites in plasma are located on albumin. Cholesterol and alpha-1-acid glycoprotein are high-affinity binding sites.[31-32] Alpha-1-acid glycoprotein levels in plasma are important because of the dramatic increase in the concentration of this protein found in patients during stressful events.[33] Perhaps higher total levels of drug, with free levels relatively unchanged, are required during an acute stressful event to maintain a constant amount of drug at the site of action.

Pharmacokinetic descriptions of neuroleptic drugs involve the use of multicompartment models. From the plasma, usually termed the central compartment, unbound drug may be actively or passively transported into "deeper" compartments (e.g., skeletal muscle, brain tissue, or fat). Until these deeper compartments equilibrate with the free drug in the central compartment, the medica-

of action. Furthermore, when the administration of the drug is discontinued, these deep compartments will leach the active drug out through the central compartment and back to the site of action.[34] Therefore, effects secondary to oral or depot neuroleptic therapy can persist for weeks and months after the discontinuation of routine therapy.

As a general rule, three drug plasma levels must be obtained in a standard kinetic analysis to define each compartment. For a neuroleptic drug that has at least three significant compartments, nine levels drawn at appropriate times would be required to define one individual's pharmacokinetic parameters.[34] Analysis of the kinetics of depot neuroleptics is complicated, since prolonged studies are required. One method of obtaining more information in a shorter time with fewer levels is to use a nonlinear mixed effects model (NONMEM) for analysis of the data. NONMEM requires knowledge of how much drug was given, and the times of administration and plasma level sampling.[35,36]

Assays of the neuroleptics are usually performed either by physical detection of the drug by high performance liquid chromatography (HPLC),[37,38] gas liquid chromatography (GLC),[39,40] high performance thin layer chromatography (HPTLC),[41] or by radioimmunoassay (RIA).[38,42,43] An *in vitro* measure of neuroleptic activity can also be approximated by determining the total amount of dopamine-blocking activity by its competition with a radioactively labelled ligand bound to dopamine receptors (radioreceptor assay, RRA).[36,44-46] Alternately, biological responses *in vivo* have been measured by assaying prolactin.[47,48]

In addition to a reliable, sensitive, and specific assay method, blood collection procedures must be stringently controlled. Because these drugs are present in such low concentrations, small changes in the collection procedure may result in a dramatic change in the assay result. One example of a poorly controlled collection procedure is to draw a sample into a vacuum collection tube capped with a plastic stopper. These stoppers, however, contain a plasticiser that causes redistribution of the drug into erythrocytes, which will be spun out of the sample when centrifuged. A second example is photo-oxidation of the drug by exposure to ultraviolet light prior to assay. Both examples result in lower drug levels measured than actually exist in the sample.

Once these sampling procedures have been perfected, reproducible separation of the drug from contaminants must be performed with a high extraction efficiency, monitored by the use of an internal standard. A clinically usable assay should have a coefficient of variation (both intra- and interassay) of less than the minimum change in plasma level that might yield a clinical effect (e.g., 10%-20%). Many methods of detection, such as electron capture, scintillation, and nitrogen or fluorescent detection, have been employed; the small quantity of drug present in clinical samples makes this a critical procedure. Our laboratory currently employs an HPTLC assay for fluphenazine consisting of extraction, followed by paraffin oil treatment of the chromatography plates to permit increased resonance within the molecule, then ultraviolet development and fluorescent scanning with computerized quantification.[41] We have found this to be an extremely reliable and efficient method of detecting subnanomolar quantities of fluphenazine.[49] An advantage of HPTLC over GLC or HPLC is that many samples may simultaneously be run on a single plate, providing excellent speed and efficiency. An additional advantage is that HPTLC is a closed system and the plates may be stored for future reanalysis; in contrast, GLC and HPLC are open systems, in which the sample is lost following chromatographic separation and detection.[50]

RIAs potentially offer the most efficient detection of drug, but there are still problems with specificity. The appropriate antibody must be produced to measure only the drug to be examined, and not the metabolites or other contaminants in the sample. To do this, one must have a reliable, sensitive, and specific assay (such as HPTLC or HPLC) to standardize the RIA.[38,42,43]

The neuroleptic RRA, although a substantial improvement over many of the quantitative assays in terms of measurement of total biological effects, has numerous limitations. These include low sensitivity, nonspecific protein binding limiting the sample aliquot, and the use of caudate tissue instead of limbic tissue, the presumed site of neuroleptic action. Maximum sensitivity achieved with the RRA usually is >1 ng/ml for neuroleptic agents. In the case of fluphenazine, because of its high affinity binding to dopamine receptors, a sensitivity of 0.5 ng/ml is achievable (personal communication, Charles L. Bowden, January 10, 1983). This approximates the sensitivity of most quantitative analytic processes. Another approach, the measurement of prolactin increase as a function of the plasma concentration of a neuroleptic, has not provided consistent correlations with clinical effect.[47,48] Further development of analytic techniques should allow us to clarify the role of neuroleptic metabolites and drug response.[51,52]

Another area in which dramatic progress in assay technology is being made is in the use of quantitative nuclear magnetic resonance (QNMR). QNMR is a technique using a strong magnetic field and a perpendicular radio frequency field to cause the fluorine nuclei in a neuroleptic to absorb energy quantifiably. QNMR may permit us to measure the drug at the site of action. This might be done by a device that looks similar to a computerized axial tomography (CAT) scanner. Refinement of this technique may permit quantification and detection of the molecular interaction at the site of action in the brain, e.g., protein, tissue, or receptor binding. Improvements in QNMR resolution might yield the capability to produce sectional images of the drug's distribution and binding within the body (personal communication from David Young, December 5, 1983).[53]

Because of the specialization and sophistication of the personnel and equipment needed to perform these types of

FIGURE 1. Pharmacokinetic variables that affect the amount of active drug able to bind to the site of action.

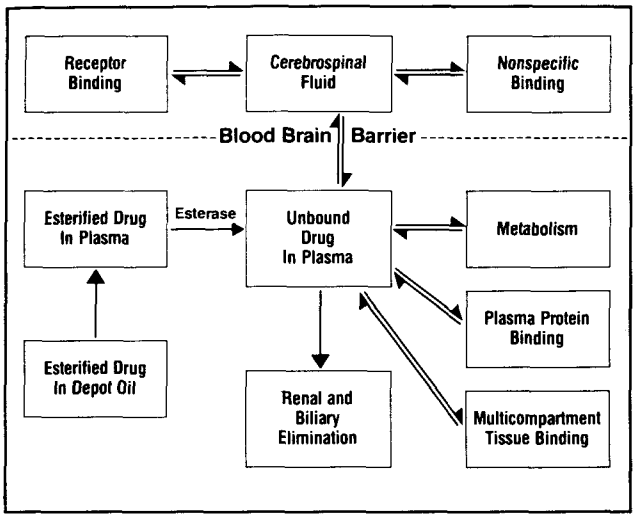
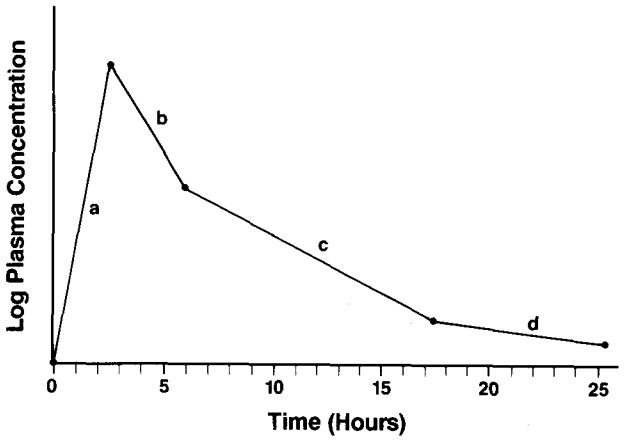


FIGURE 2. Idealized plasma level versus time curve for a single oral dose of a neuroleptic, illustrating absorption phase (a), distribution into equilibrating compartments (b), metabolic elimination (c), and leakage back into plasma from equilibrating compartments (d).



as a cost-effective solution to the growing demand for psychotropic drug assay. These centers should utilize methods that have a large sample capability and rapid turnaround time.

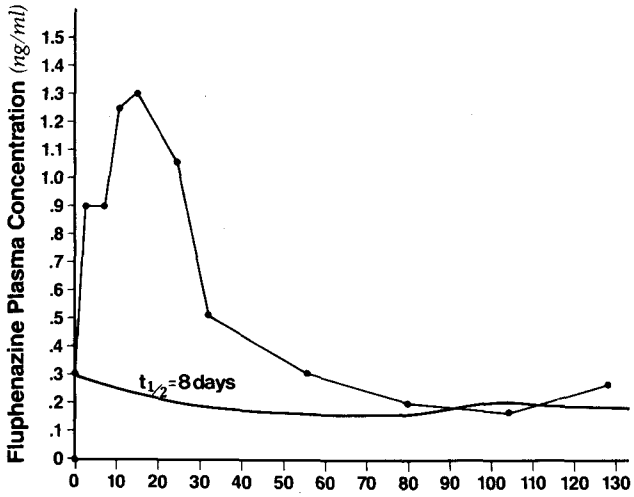
PHARMACOKINETIC AND PHARMACODYNAMIC APPLICATIONS

Pharmacokinetics is the study of drug absorption, distribution throughout the body, metabolism, and eventual elimination.[54] Pharmacodynamics is the study of the biochemical and physiological effects of drugs and, most importantly, their mechanisms of action. A clearer understanding of the unique advantages and disadvantages of depot neuroleptics versus oral therapy requires further study of the interplay between drug concentration at the site of action over time. Drug effects on receptors, such as kindling phenomena, denervation hypersensitivity, and down regulation, also need further study.

Depot neuroleptic pharmacokinetic variables that interrelate with brain effects are illustrated in Figure 1,[55] which shows that once the drug is absorbed from its injection site, redistribution and extensive binding to tissue and protein occur. As stated, the fraction of the free drug in plasma is the only portion that can equilibrate with cerebral spinal fluid and brain tissue. Therefore, it is essential in any study where only total plasma levels are measured that the protein binding be constant over the entire concentration range for the drug. Nonlinear protein binding, as with valproic acid, decreases the usefulness of total plasma levels.[56] Figures 2 and 3 depict the relevant pharmacokinetic parameters obtained from the plasma level versus time curves for both oral and depot neuroleptic therapy. As Figure 3 shows, for the depot neuroleptic, absorption from the injection site may be the rate-limiting step. The typical "decay phase" of the depot curve provides an estimate of the rate of absorption

rate of elimination. This "flip-flop" model is useful for the understanding and application of depot neuroleptic pharmacokinetics to patient care. It also must be reemphasized that these highly lipophilic compounds do not possess simple one-compartment pharmacokinetic characteristics. Drugs that are highly ionized or hydrophilic usually follow a single-compartment kinetic model, where the kinetics can be characterized over the entire concentration time curve as a biexponential function (absorption and elimination). For depot neuroleptics and other lipophilic drugs, multicompartment kinetic models are necessary. The measured decay phase half-life of neuroleptic agents is longer during studies performed at steady state (once plateau concentrations have been reached) than during single-dose studies. An early illustration of multicompartment effects was the description of chlorpromazine urinary metabolite detection after cessation of chronic therapy for up to 6 months.[57]

FIGURE 3. Detail of a patient's plasma level versus time curve following the injection of a single 25 mg dose of fluphenazine decanoate.



The valid study of the relationships between plasma levels and clinical effects depends on the methods used for analysis of the drug, the pharmacokinetic derivation of the individual parameters, clinical assessments, statistical analysis, and the nature of the psychiatric illness. The response that is the best measure of neuroleptic effectiveness is relative improvement, rather than absolute severity of symptoms. For this reason, it is recommended that correlations be based on the difference between the patient's baseline severity of illness and severity at the time of the plasma level determination. This is especially important in evaluating drug effects in a population in which large numbers of minimal and nonresponders are anticipated. If a patient's psychotic symptoms were considered extremely severe on admission and have improved to a "moderately ill" rating, then a definite clinical benefit has resulted from the treatment. On the other hand, if a patient was moderately ill on admission and remains moderately ill, no clinical benefit has resulted. Both patients are considered moderately ill, but one has responded to treatment, while the other has not.[58] Acutely psychotic patients, although more difficult to enroll in studies of plasma level-response relationships, are the best candidates in whom to obtain clinical correlations. Chronically ill patients with multiple dependencies and personality characteristics related to institutionalization are less suitable for clinical response studies. A response study should use a fixed-dose design, in which patients are randomly assigned to various dosages that result in a uniform distribution from subtherapeutic to supratherapeutic levels. In the past, most of the plasma level response studies were technically flawed by the use of a variable dose titration scheme. However, the ethical difficulties in using acutely psychotic patients as subjects in this type of fixed-dose design are apparent.

A parallel strategy for the elucidation of clinical response, adverse effects, and plasma level relationships is the use of large numbers of patients in naturalistic environments, rather than a few patients in a clinical research center. Many of the flaws and biases present in small populations (e.g., inadequate statistical power and lack of a uniform distribution of patients who have drug levels above and below the therapeutic range) are easily avoided by using large populations of patients. The problems inherent in the analysis of data obtained from a naturalistic environment are overcome by the use of a NONMEM technique to develop response and kinetic relationships. We are using NONMEM-assisted analysis and subnanomolar quantification of psychotropic drugs in a naturalistic environment to develop models of response. The application of these techniques is illustrated below by data on kinetics for fluphenazine decanoate and metabolite relationships for haloperidol.

METABOLITE RELATIONSHIPS FOR HALOPERIDOL

reduced metabolite (hydroxyhaloperidol) shows the benefit of collaboration between members of our interdisciplinary research group.[59] Our initial RIA procedure did not discriminate between the parent and metabolite moiety. Clinical response studies indicated that two compounds were being detected on the basis of the pharmacokinetic profile. Subsequent review of our analytic techniques revealed that our antibody, prepared from the oximoconjugate of haloperidol, was co-specific for both haloperidol and reduced haloperidol. We then developed a procedure utilizing selective succinylation of the hydroxyl group, followed by silica gel chromatographic separation and reassay.[60]

Our studies with oral haloperidol indicate that reduced haloperidol concentrations range between zero and twice the parent level.[60] When patients are given intravenous haloperidol in a cardiac intensive care unit, no detectable reduced haloperidol is found. We speculate that the use of haloperidol decanoate may similarly result in a different parent-to-metabolite relationship. The dopaminergic antagonist activity of reduced haloperidol is 20% and 25% of that of haloperidol, as measured by apomorphine-induced stereotypy in rats and in calf caudate RRA, respectively. No reduced haloperidol was observed after intraperitoneal injection of haloperidol in these rats. In addition, the effects on weight gain, appetite, and spontaneous motor activity were different in rats administered these two compounds intraperitoneally.[51] The differing biological activities of reduced haloperidol and the parent compound may partially explain our initial findings in schizophrenic patients who were poor responders to oral haloperidol therapy.[52]

The NONMEM analysis of our data on 41 schizophrenic patients is now in progress. This retrospective data set includes 66 plasma levels and clinical global impressions rating scales.[52] Pearson product-moment correlation analysis yielded the following: dose vs. the summed plasma concentrations of haloperidol + reduced haloperidol, $r = 0.69$ ($t = 5.42$, $df = 64$, $p < .01$); dose vs. plasma concentration of haloperidol, $r = 0.76$ ($t = 5.99$, $p < .01$); and dose vs. plasma concentration of reduced haloperidol, $r = 0.57$ ($t = 4.60$, $p < .01$). A log-linear correlation analysis showed weaker relationships, with the exception of dose vs. plasma concentration of reduced haloperidol, $r = 0.71$ ($t = 5.59$, $p < .01$). Two groups of patients were identified based on our earlier work[60]: those with reduced-haloperidol/haloperidol ratios > 1 (N = 17, Group 1) and reduced-haloperidol/haloperidol ratios < 1 (N = 24, Group 2). Age, sex, and diagnosis were not found to differ significantly between the two groups. Significant differences identified between Groups 1 and 2, respectively, were as follows: haloperidol dosage = 44.5 ± 22.9 vs. 35.4 ± 17.6 mg/day (grouped Student's t-test, ($t = 2.20$, $df = 64$, $p < .05$); reduced haloperidol plasma concentration = 40.3 + 24.9 vs. 10.6 ± 14.3 ng/ml ($t = 2.75$, $p < .01$); severity of illness = 4.50 ± 1.18 vs. 3.68 ± 1.11, $t = 2.75$, $p < .01$); and therapeutic effect = 3.36 ± 0.95 vs.

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