Comparison of the Effects of Different Routes of Antipsychotic Administration on Pharmacokinetics and Pharmacodynamics

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Clinicians face a dilemma when choosing between short-acting atypical antipsychotics and long-acting conventional antipsychotics. Atypical antipsychotics offer better safety and efficacy, while depot formulations of conventional antipsychotics provide more reliable drug delivery, reduced differences in peak and trough plasma levels of drug, and greater dosing precision. Risperidone was recently approved by the U.S. Food and Drug Administration as the first atypical long-acting antipsychotic medication, given as biweekly gluteal injections. This long-acting formulation is synthesized using a microsphere encapsulation process, and gradual hydrolysis of the copolymer encapsulating the drug provides a steady release of medication. Consistent with other long-acting medications, plasma drug level fluctuation is reduced more with long-acting than with oral risperidone. Analyses are currently underway to further examine safety outcomes with long-acting risperidone.

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In treating schizophrenia, the value of maintenance pharmacotherapy with conventional neuroleptics is well accepted,[1] although elevated risks of persistent drug-induced movement disorders such as tardive dyskinesia with the continuous use of conventional antipsychotics have been an ongoing concern. Fortunately, progress in short-acting pharmacotherapy led to the introduction of "atypical" antipsychotics, with reduced liability for reversible drug-induced motor side effects such as extrapyramidal side effects and persistent movement disorders such as tardive dyskinesia. However, clinicians face a dilemma when choosing between short-acting atypical antipsychotics, with superior safety and efficacy, and long-acting conventional antipsychotics, which provide reliable drug delivery and reduced pharmacokinetic variability.

WHY DEPOT ANTIPSYCHOTICS?

More Reliable Delivery

For medication to be effective over the long term, patients must appreciate the benefit gained from accepting and maintaining adherence over years. While patients with medical and mental illnesses may be similarly nonadherent to medication regimens, disease characteristics such as impairment of cognition and insight in the persistently psychotic patient can influence overall compliance.[2,3] In schizophrenia, more than 50% of patients may be nonadherent to medication regimens as early as 1 month postdischarge, with fewer than 30% compliant at 2 years.[4] In our state hospital population, 3-month nonadherence rates with oral atypicals are 50% and partial adherence rates are 80%. Complete adherence is seen in fewer than 15% of patients by 3 months postdischarge from an acute care unit with, admittedly, too short a length of stay.[5]

Critically, physicians are often incorrect in assessing compliance in the majority of patients, with errors being evenly split between false-positives and false-negatives.[6] More concerning, patients themselves may not learn to adhere to medication regimens even after repeated relapse.[6] Depot therapy allows the clinician to more accurately assess the status of antipsychotic treatment and response, since a known amount of drug is being administered with guaranteed compliance.

Table 1. Modeling Depot Neuroleptics: The Common Thread[a]

Fluphenazine, flupenthixol, and haloperidol simulations illustrate kinetics based on "flip-flop" model

    Terminal log-linear phase determined by Ka, since Ka is considerably smaller than Ke

    Time to steady state tied to rate-limiting pharmacokinetic step

    Concentrations and clearance tied to:

$$Cp_{(t)} = \frac{f \propto D \propto Ka}{Vd \propto (Ka - Ke)} \propto [e^{(-Ke \propto t)} - e^{(-Ka \propto t)}]$$

[a]Adapted from Ereshefsky et al.[7] Abbreviations: Cp = plasma concentration, D = dose, f = bioavailability, Ka = absorption rate, Ke = elimination rate, t = time, Vd = volume of distribution.
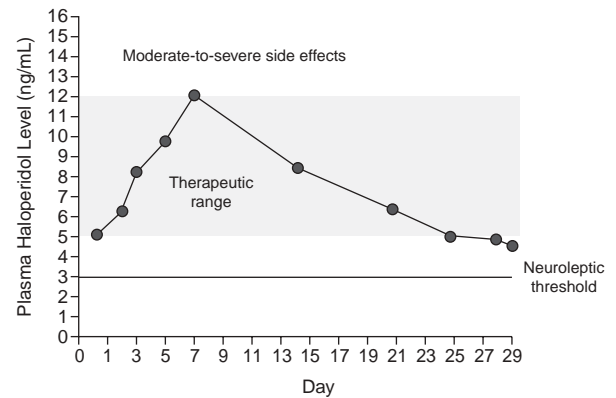
Figure 1. Plasma Concentration of Fluphenazine Decanoate Over Time[a]

[a]Reprinted with permission from Ereshefsky et al.[8] Fluphenazine dose (25 mg) was administered by intramuscular injection. Fluphenazine decanoate injections routinely lead to a rapid rise in plasma levels within 24 hours following dose administration. These rapid increases in concentration have been associated with extrapyramidal symptoms, and especially dystonia.

Figure 2. Plasma Concentration of Haloperidol Decanoate Over Time[a]

[a]Adapted from Ereshefsky.[9] Haloperidol was administered every 28 days; mean monthly dose = 243 mg.

Improved Pharmacokinetic Profile Over Oral Therapy

Thus far, long-acting antipsychotics in the United States have been delivered via intramuscular injection using depot formulations that utilize an oil-based vehicle and an esterified drug. Fluphenazine and haloperidol decanoate both use sesame seed oil as the vehicle, with the antipsychotic esterified at the drugs' benzylic ketone. The rate-limiting step in the kinetics of these drugs is the slow rate of absorption from the injection site. Hence, the observed terminal phase decline in plasma levels of fluphenazine decanoate corresponds to a half-life of 8 to 14 days, rather than the elimination half-life of 15 to 24 hours. Similarly, for haloperidol decanoate, the observed terminal half-life is 19 to 21 days rather than 15 to 24 hours. This pharmacokinetic action is called "flip-flop kinetics" (Table 1) and is the basis for understanding appropriate dosing with the older depot medications.

Peak levels occur much sooner with fluphenazine decanoate, at around 24 hours postinjection (Figure 1),[8] as compared with C_{max} occurring at 5 to 8 days with haloperidol decanoate (Figure 2).[9] Steady state is reached within 4 to 5 times the rate-limiting half-life with these medica-

tions, so differing dosing strategies can be used, including an initially higher or loading dose, followed by a much lower maintenance dose. Alternately, oral supplementation while the dose of depot builds to effective steady-state plasma levels can be utilized, with the caveat that oral adherence is implicit.

More Predictable Pharmacokinetics

First, in comparison to oral compounds, reductions in the large differences between C_{max} (peak) and C_{min} (trough) plasma levels within a single dosing interval for depot antipsychotics are observed. Since side effects are often related to the daily peak concentration of oral medication, and compliance can be in turn related to side effects,[10] treatment adherence may be improved by a change to depot drug delivery. Second, improved bioavailability may allow for a lower total drug dose that provides similar clinical outcomes and, most importantly, greater dosing precision, since intersubject variability is reduced due to the avoidance of first-pass hepatic metabolism.

Depot dosing can lower the rate of reversible motor side effects when compared with oral therapy by constraining the peak levels below the moderate-to-severe threshold of reversible motor side effects, corresponding to dopamine-2 (D_2) receptor occupancies exceeding 80%.[11] The work of Kapur and colleagues[11] suggests that occupancy rates need to equal or exceed 60% for D_2 receptors for part of each oral dosing interval, while reversible motor side effects are frequently observed with sustained D_2 occupancies of > 80%. Because of a depot drug's sustained-release characteristics, trough concentrations at the end of 1 month for haloperidol decanoate treatment, as an illustration, can result in an effective D_2 occupancy rate of approximately 60% or more, while reducing peak concentrations to considerably lower than those experienced with equally

effective oral therapy. Despite these possible advantages, only typical antipsychotics have been marketed in long-acting injectable formulations. These agents lack the relatively more potent effects on the serotonin-2A receptor seen with the atypicals, decreasing their overall effectiveness in treating the spectrum of symptoms associated with schizophrenia. Depot neuroleptics also cause negative effects on basal ganglia function and reversible motor side effects even at their minimum effective dose, as evidenced by neuroleptic threshold effects observed at low doses.[12]

An additional advantage for depot products in reducing relapse may be due in part to their extended pharmacokinetic properties, beyond the simple assurance that medication is always in the patient's body. Indeed, discontinuation studies have suggested that relapse reductions extending into the second year are due to the very slow withdrawal of medication.[13] This finding is supported by positron emission tomography (PET) raclopride displacement data suggesting that D_2 receptor occupancies are "therapeutic" ($\geq 60\%$) 2 months after haloperidol decanoate discontinuation and as high as 35% 6 months postdiscontinuation.[14] However, conventional oral agents, which lack the effects associated with atypical agents such as receptor effects on serotonin and indirect actions on glutamate, appear to have higher relapse rates than do atypicals such as risperidone, as demonstrated in a recent study by Csernansky and colleagues.[15] Therefore, atypical antipsychotics in long-acting form would have all of the advantages of conventional depot therapy plus the enhanced efficacy and tolerability associated with their novel pharmacology.

LONG-ACTING RISPERIDONE

Until recently, clinicians had to make a choice between the better safety and efficacy profiles of newer oral agents or the better delivery features of a conventional depot neuroleptic. While atypical antipsychotic medications provide improved safety and efficacy outcomes, further improvements may be possible by combining an atypical profile with long-acting administration. Certainly in cases complicated by substance abuse, reduced disease insight, and reduced psychological reserve against stress, reliable medication delivery can become a significant intervention. Long-acting risperidone has been investigated under the paradigm of gluteal injections every 2 weeks and offers clinicians and patients the first atypical long-acting medication.

Technology
Unlike the traditional esterification of conventional antipsychotics to achieve a long-acting injectable formulation, long-acting risperidone is synthesized by a microsphere encapsulation process using static flow methods to incorporate risperidone inside a glycolide/lactide matrix, a commonly used medical polymer. Microspheres are formed in a static flow chamber with subsequent movement through fibratory sieves to ensure uniform risperidone concentration within the particle and overall particle size (25–150 μm). Microspheres exist as a powder after solvent removal and are reconstituted to an aqueous suspension prior to gluteal injection using a customized needle (external diameter of 22 gauge, internal diameter of 20 gauge).

After the injection of the drug, relatively little of the total risperidone contained within the microsphere preparation is released. A clinically negligible amount of drug is released immediately, primarily that covering the surface of the microspheres. A latency period for absorption is then observed. Gradual hydrolysis of the copolymer occurs, steadily releasing risperidone over the next several weeks to produce active moiety plasma levels equivalent to steady-state oral dosing. The final end products of long-acting risperidone are risperidone and naturally occurring glycolic and lactic acids, which are metabolized to carbon dioxide and water.
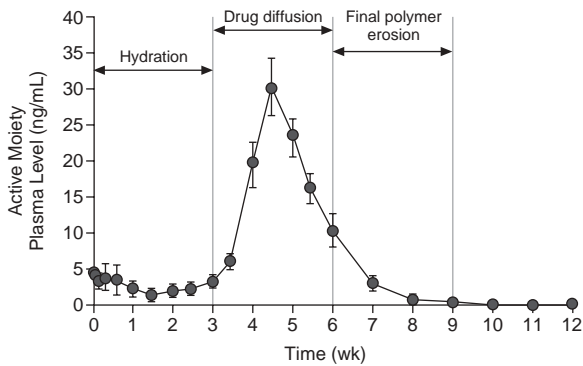
Pharmacokinetics of Risperidone
The pharmacokinetics of risperidone are quite straightforward. It is metabolized principally by the cytochrome P450 (CYP)2D6 enzyme to the active metabolite 9-OH risperidone. Since both risperidone and 9-OH risperidone are pharmacologically active, the sum of the 2 concentrations is used as the active moiety in most pharmacokinetic studies. Moreover, even in patients with CYP2D6 drug interactions or in those with genetic poor or intermediate metabolizer status (gene polymorphism), the sum of risperidone + 9-OH risperidone, i.e., the active moiety concentration, is no different than the concentrations seen in those with extensive metabolizer status. The ratio of risperidone to 9-OH risperidone can be very different, and in limited metabolic studies, appears to have little safety consequence.[16]

Animal studies suggest that the blood-brain barrier may be preferentially penetrable to risperidone over 9-OH risperidone, with blood/brain ratios of 0.22 and 0.04, respectively.[17] This difference in penetrability may provide clinical importance to the differences between the short- and long-acting formulations in the steady-state percentage of active moiety remaining as unchanged risperidone.

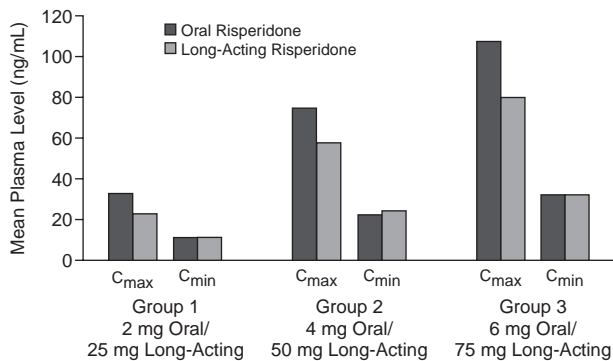### Dosing Considerations Informed by Pharmacokinetics
The results of pharmacokinetic phase 1 and 2 repeated-dose trials support administration of injectable risperidone every 2 weeks to maintain plasma levels of active moiety comparable to levels obtained with repeated oral dosing. The main release of risperidone begins around weeks 2 and 3 postinjection, with rapid buildup of levels occurring during weeks 3 and 4 (Figure 3).[18] Pharmacokinetically defined "therapeutic" levels are maintained during weeks

Figure 3. Single-Dose Pharmacokinetic Profile of Long-Acting Risperidone[a]

[a]Adapted with permission from Lasser et al.[18] Risperidone (lactide coglycolide polymer 75:25 ratio) suspended in 2 mL of an aqueous diluent. N = 26; dose = 50 mg.

Figure 4. Difference in Mean Plasma Levels of Oral and Long-Acting Risperidone[a]
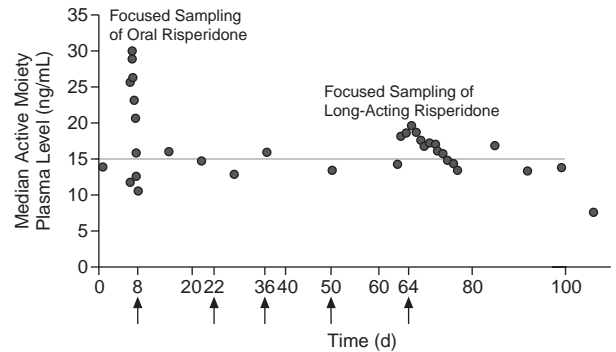

[a]Data from Eerdekens et al.[20] Each group received daily oral doses during weeks 1 through 3, daily doses half the original oral dose during weeks 4 and 5, and long-acting injectable doses every 2 weeks during weeks 2 through 10. Overall, long-acting risperidone reduced mean plasma level fluctuations 36.8%. Long-acting injectable dosing had a significantly (p < .05) lower C_{max} than oral dosing.
Abbreviations: C_{max} = peak plasma level, C_{min} = trough plasma level.

Figure 5. Median Plasma Levels of Oral Versus Long-Acting Risperidone as Seen With Focused Sampling in the 21 Patients in the Lowest Dosage Group[a]
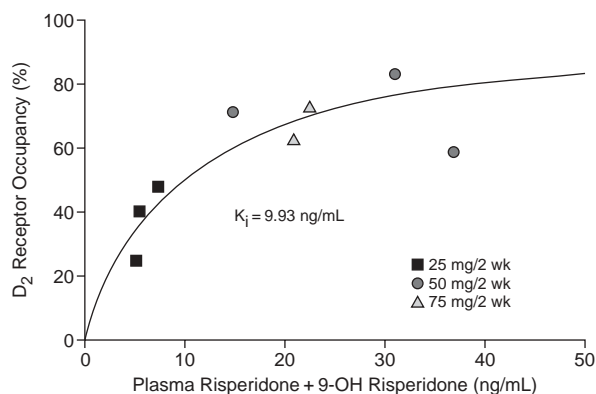

[a]Adapted from Eerdekens et al.[20] Focused sampling is defined as frequent sampling from pre-dose to post-dose trough plasma level. Patients in the lowest dosage group received 2 mg of oral risperidone during weeks 1 through 3, 1 mg of oral risperidone and 25 mg of long-acting risperidone during weeks 4 through 5, and 25 mg of long-acting risperidone during weeks 6 through 15. Arrows indicate the days that long-acting risperidone was administered.

75 mg long-acting = 80.6 ± 40.0 ng/mL [p < .001]; Figure 4).[20] Likewise, median peak plasma concentrations of the active moiety are substantially lower with long-acting versus oral risperidone, as seen with frequent sampling from pre-dose to post-dose trough plasma levels in the 21 patients in the lowest dosage group (Figure 5).

The mean trough plasma level in these studies was maintained with all cross-formulation comparisons (mean ± SD C_{min}: 2 mg oral = 11.4 ± 3.6 ng/mL, 4 mg oral = 22.3 ± 12.1 ng/mL, 6 mg oral = 32.6 ± 15.7 ng/mL; 25 mg long-acting = 11.3 ± 4.5 ng/mL, 50 mg long-acting = 24.3 ± 16.0 ng/mL, 75 mg long-acting = 32.6 ± 16.5 ng/mL [NS]; Figure 4). Overall, long-acting risperidone reduced mean plasma level fluctuations by an average of 36.8% across the dose range examined.

Supplementation. As mentioned previously, pharmacokinetically defined therapeutic levels of active moiety are obtained at approximately week 3 following initial long-acting risperidone administration. However, as patients will most commonly be stable on treatment with oral risperidone prior to receiving long-acting risperidone, it is not entirely clear whether 3 full weeks of oral supplementation is clinically required. For example, in a 50-week, open-label study,[21] investigators were given the option of not using oral risperidone supplementation after day 15; this naturalistic approach set no specific guidelines or symptomatic requirements regarding oral use during this period (days 15 to 21). Across all dose groups (25, 50, and 75 mg every 2 weeks), approximately two thirds of patients (66%, 70%, and 67%, respectively) used no oral supplementation between weeks 2 and 3. No short- or long-term differences in patient outcome were present

4 through 6, with decline of active moiety levels occurring between weeks 6 and 7. With repeated injection, steady-state levels are usually reached by 6 to 8 weeks from the start of therapy, with significantly reduced peak-trough fluctuations as compared with oral dosing, and oral risperidone is not needed past the initial stabilization phase.[19]

As with conventional depot preparations, significantly lower mean peak active moiety concentrations are seen with long-acting risperidone versus oral risperidone at clinically comparable dosage levels (mean ± SD C_{max}: 2 mg oral = 32.9 ± 9.2 ng/mL, 4 mg oral = 74.1 ± 31.5 ng/mL, 6 mg oral = 107.0 ± 49.0 ng/L; 25 mg long-acting = 22.7 ± 9.2 ng/mL, 50 mg long-acting = 57.3 ± 32.3 ng/mL,

Figure 6. D_2 Occupancy as a Function of Concentration of Risperidone Plus 9-OH Risperidone 14 Days After Administration of Long-Acting Risperidone[a]

$K_i = 9.93$ ng/mL

■ 25 mg/2 wk
● 50 mg/2 wk
△ 75 mg/2 wk

[a]Adapted with permission from Gefvert et al.[22]

between the supplementation groups (2 vs. 3 weeks' oral use), although further controlled examination is needed.

The transition can be made from any antipsychotic to long-acting risperidone microspheres, rather than from prior oral risperidone treatment only. Studies are now planned and ongoing to examine transition strategies from a variety of oral and depot agents to long-acting risperidone. The "loading method" strategy that is used with typical long-acting antipsychotics is not appropriate with long-acting risperidone, given its lack of initial drug release following administration.

D_2 Occupancy Measured by Positron Emission Tomography

A study was performed to measure D_2 occupancy with depot risperidone, using PET-raclopride displacement examination of 8 patients at steady state with doses of 25 (N = 3), 50 (N = 3), or 75 mg (N = 2) of depot risperidone given every 2 weeks (Figure 6).[22] Dose-proportional individual D_2 occupancy was 25%, 40%, and 48% for the 25-mg dose group (active moiety concentration 5.2–7.4 ng/mL); 59%, 71%, and 83% for the 50-mg dose group (active moiety concentration 15.0–37.0 ng/mL); and 62% and 72% for the 75-mg dose group (active moiety concentration 20.9–22.5 ng/mL). Concentrations and PET data were obtained at the end of the second week following 5 biweekly injections. These PET data suggest that doses of long-acting risperidone as low as 25 mg every 2 weeks are likely to be highly efficacious.[23] This is based on anticipated C_{max} levels of ≈30 ng/mL, equivalent to D_2 occupancies of ≈75%.

CONCLUSION

The pharmacokinetics of the release of long-acting antipsychotic therapies have been reviewed within the context of rational dosing strategies for these medications. Long-acting antipsychotics provide more reliable delivery of medication and an improved pharmacokinetic profile, while oral atypical antipsychotics offer better symptom control and less liability for reversible and persistent motor side effects. Long-acting risperidone, the first long-acting atypical, combines the advantages of injectable, delayed delivery administration with the safety and efficacy advantages of the new-generation medications.

Drug names: fluphenazine (Prolixin and others), haloperidol (Haldol and others), risperidone (Risperdal), thiothixene (Navane and others).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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