Risperdal Consta™: The First Long-Acting Atypical Antipsychotic Agent

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OVERVIEW OF OLDER AND NEWER AGENTS

Schizophrenia, with its accompanying signs and symptoms of delusions, hallucinations, disorganized thoughts, inappropriate affect, and impaired psychosocial functioning, is considered one of the more complex psychiatric disorders to treat. One reason for this difficulty is the tendency for patient noncompliance with medication regimens. This trend of nonadherence to therapy is sometimes influenced by “poor insight, negative attitude or subjective response toward medication, previous nonadherence, substance abuse, shorter illness duration, inadequate discharge planning or aftercare environment, and poor therapeutic alliances.”

Adverse drug effects (ADEs) from medications, especially extrapyramidal symptoms, neuroleptic dysphoria, akathisia, sexual dysfunction, and weight gain, may also have a negative effect on patient adherence. In 1993, Weiden and Olfson estimated that the annual cost of schizophrenia relapse, mostly a result of noncompliance, exceeded $2 billion annually.

Traditionally, noncompliant patients with schizophrenia have been treated with injections of long-acting depot formulations of the conventional (first-generation) antipsychotic agents, allowing for scheduled observation of medication delivery at prescribed intervals, typically every two to four weeks, depending on the pharmacokinetics of the agent used. To date, only two conventional antipsychotic agents—haloperidol (e.g., Haldol®, Ortho-McNeil) and fluphenazine (Prolixin®, Apothecan)—have been available in the depot formulations within the U.S. Chemically, their formulations are biodegradable esters of the original medication (i.e., pro-drugs) dissolved in an oil-based vehicle that, when injected intramuscularly, is slowly released from the injection site and hydrolyzed.

The advantages of conventional depot formulations include reduced fluctuations in serum concentration, the avoidance of first-pass metabolism, and the certainty of medication delivery. Some disadvantages include extrapyramidal symptoms and the need for patients to be stabilized with oral therapy before conversion to the depot product.

In October 2003, the Food and Drug Administration gave Janssen Pharmaceutica approval to market Risperdal Consta™ (risperidone), the first second-generation (“atypical”) antipsychotic agent available in a long-acting injectable formulation. For many years, both physicians and patients have preferred using the newer agents because of their improved side-effect profile. Risperdal Consta™ is a novel, delayed-release formulation because it is not an esterified oil-and-water formulation; it is formulated in microspheres contained in an aqueous solution that releases the medication slowly over time.

CHEMICAL AND PHYSICAL PROPERTIES

Risperidone belongs to the benzisoxazole class of antipsychotic agents. According to the manufacturer, this agent is practically insoluble in water. New technology allows the use of static-flow methods to integrate risperidone into D, L-lactide-co-glycolide, a commonly used medical copolymer matrix. After the microspheres are formed, they are run through a sieve to ensure a particle size of 25 to 150 micrometers. The microspheres must be reconstituted into an aqueous solution before they are injected.

PHARMACOLOGY AND MECHANISM OF ACTION

Risperidone is a potent inhibitor of the serotonin_{2A} and dopamine_{2} receptors. The mechanism by which risperidone treats the symptoms of psychosis is believed to be related to its actions on the serotonin and dopamine systems. Risperidone also has enhanced affinity for alpha_{1}, alpha_{2}, and histamine_{1} receptors.

PHARMACOKINETICS

Absorption

Initially after the risperidone injection, less than 1% of the drug is released. Two to three weeks later, gradual hydrolysis allows for a steady release of the drug. For this reason, patients should take oral antipsychotic drugs for the first three weeks of long-acting risperidone therapy.

Effective plasma concentrations are reached by the third to fourth weeks; they are sustained through the sixth week and then slowly start to decrease between the sixth and eighth weeks. A steady state is achieved after four injections at two-week intervals and is maintained for four to six weeks after the last injection.

Distribution

The volume of distribution of long-acting risperidone is 1 to 2 liters/kg after absorption occurs. Risperidone is approximately 90% protein-bound, primarily to albumin and alpha_{1}-acid glyco-
DRUG FORECAST

protein, whereas 9-hydroxyrisperidone (9-OH) risperidone, an active metabolite, is 77% protein-bound.6

Metabolism and Elimination
Risperidone is metabolized extensively through the liver, primarily by the CYP450 2D6 isoenzyme to 9-OH risperidone.6,7 Potent inhibitors or inducers of this metabolizing enzyme may affect the plasma levels of risperidone. The activity of the metabolite is similar to that of risperidone, and the antipsychotic activity of the medication is believed to be a result of both agents.6 Animal studies have shown that risperidone penetrates the blood–brain barrier better than its metabolite does.7

The long-acting injection has an apparent half-life of three to six days, including dissolution of the microspheres and absorption of the drug.6 Risperidone and its metabolites are excreted primarily through the urine and, to a lesser extent, via the feces.6

In clinical trials, no accumulation of risperidone was noticed after long-term use; it is completely cleared from the body seven to eight weeks after the final injection.6 The microsphere matrix breaks down as a result of hydrolysis to lactic and glycolic acids, and the final end-products are carbon dioxide and water.11

ADVERSE EFFECTS
On the basis of the two published clinical trials that we reviewed (see later in this article), the most commonly reported ADEs have been insomnia and anxiety.12,13 Other ADEs with a reported incidence of greater than 5% were agitation, headache, rhinitis, dizziness, and hyperkinesias. Extrapyramidal symptoms, such as tremors, involuntary muscle movements, hyperkinetias and hypokinesias, and hypertension, were more frequent with risperidone 50 mg than with 25 mg or placebo. The occurrence of these symptoms, or of ADEs related to them, appears to be dose-related; a higher risk of symptoms was associated with the 50-mg dose (incidence, 8%–27%), compared with the relatively lower risk with 25 mg (incidence, 4%–21%), a rate similar to that with placebo.

During the clinical trials, the amount of weight gained was low. In the 12-week trial, the mean increases from baseline weights were 0.5 kg (1.1 pounds) in the patients receiving risperidone 25 mg and 1.2 kg (2.6 pounds) in patients receiving 50 mg. In the 12-month trial, the increases were 1.7 kg (3.7 pounds) for the 25-mg group of patients and 2.6 kg (5.7 pounds) for the 50-mg group.9,12,13 No significant laboratory, cardiovascular, or electrocardiographic changes were reported in the studies. There was a low risk of orthostasis and possible tachycardia.9 In unpublished studies, the incidence of treatment-related ADEs, perhaps associated with prolactin, appeared to be less than 2%, and there was little evidence correlating elevated prolactin levels and prolactin-related ADEs.9

The reporting of psychosis as an ADE in clinical trials may also reflect untreated psychopathology, in contrast to new psychotic symptoms. In the 12-month trial, 14.5% of the patients reported depression.23

There was a low incidence of pain at the injection site initially, and the incidence of pain decreased as therapy progressed.12,13

INDICATIONS AND USES
Long-acting risperidone is indicated for the treatment of schizophrenia.6

Dosage and Administration
General Recommendations
With traditional depot antipsychotic agents, patients generally need to be stabilized with an established oral therapy regimen before a switch to the depot formulations; however, patients may begin therapy with long-acting risperidone without this requirement.10 Patients should begin oral antipsychotic treatment at the same time as the first injection, continue for at least three weeks, and then begin to taper the oral medication.10

At this time, the available dosages include 25-, 37.5-, and 50-mg single-dose units, which are given as an intramuscular gluteal injection every two weeks.6

Clinical guidelines for initiating risperidone long-acting injection therapy have been proposed in an earlier paper devoted to dosing.10 Patients who are new to risperidone therapy may begin receiving Risperdal Consta™ after an initial oral test dose of 1 to 2 mg for two days. This dose shows only the patient’s immediate sensitivity to the medication, and it should not be assumed that no adverse reactions to the medication will occur on the basis of the test dose.

After the two days of oral test dosing, patients may begin receiving risperidone 25 mg every two weeks; they should continue oral antipsychotic treatment for the first three weeks. Patients who are stabilized with oral antipsychotic therapy may start long-acting risperidone at any time. After the first three weeks, the oral medication may be tapered over three to four days or more slowly, if necessary. Patients who have been receiving conventional depot formulations for at least six months should simply switch to long-acting risperidone at the next scheduled injection.

Unlike risperidone, which does not accumulate in the body, the conventional formulations sometimes do accumulate, and it may take one to two months for the first medication to be cleared.10 The problem of accumulation, associated with keeping the patient on oral antipsychotic treatment past the recommended three-week period and the possible long washout period for the older antipsychotic depot injections, should prompt clinicians to carefully monitor for any new-onset ADEs during these switching (crossover) periods (e.g., new or worsening extrapyramidal symptoms). They must take into account that the patient is receiving two antipsychotic agents with demonstrated risks of ADEs; these risks may increase with the combination therapy until the first agent is completely removed from the treatment regimen and has completely cleared from the body before it can be determined whether the ADE is related to long-acting risperidone.

Patients who are considered to have been stabilized with multiple antipsychotic drugs should be carefully assessed before they are switched to injectable risperidone. A common cause of monotherapy failure—and thus the apparent need for a second antipsychotic drug—is noncompliance with the initial regimen. When these patients are switched to long-acting risperidone, the number of medications that they have been taking can be decreased before risperidone therapy is begun, or the medications can be tapered one at a time.

The product’s labeling recommends
that the starting dose for long-acting risperidone be based on the total dose of the antipsychotic medications that the patient was taking before the switch. In addition, patients who begin risperidone 50 mg every two weeks should be carefully monitored after they have discontinued their other medications to determine whether the risperidone dose should be decreased.

Given the comparable efficacy of both the 25- and 50-mg doses and the reduced side-effect profile of the 25-mg dose, we recommend a fair trial of risperidone 25 mg every two weeks for eight to 12 weeks before increasing the dose to 37.5 or 50 mg. This plan has several advantages:

- The risk of adverse reactions is minimized.
- Patients who will respond to the 25-mg dose can be identified, although the clinician may have already assumed and determined that the patient would automatically require a higher dose, based on prior or unsuccessful treatments.
- Treatment would be less expensive.

Physicians should inform patients who are experiencing excessive sedation with their current antipsychotic therapy that risperidone is usually less sedating. These patients may feel somewhat more energized, but they may also report trouble sleeping, given the reduced sedation with risperidone. If this is the case, the physician may prescribe a hypnotic agent with antihistamine-like effects or a benzodiazepine for a period of time. Patients who are taking concomitant anticholinergic medications with their current antipsychotic regimen, as a consequence of observed extrapyramidal symptoms, should be reassessed to determine whether they need to continue anticholinergic therapy after discontinuing the former medication regimen.

Missed doses are a concern with all medications, but especially with antipsychotic therapy. After a patient has received four two-week injections of risperidone, a steady state should have been achieved. If a patient misses a scheduled dose after a steady state is reached, the dosage does not need to be adjusted as long as the next dose is given by three to six weeks after the last injection. If more than six weeks has elapsed since the last dose or if the patient has not received enough injections to have reached a steady state, a dose should be administered immediately and the patient should resume oral therapy for three weeks.

Patients who are considered to be stabilized with long-acting risperidone may periodically experience “breakthrough” symptoms. Oral supplementation may be needed in the event of breakthrough psychosis. If the symptoms persist, the physician should consider increasing the dose of injectable risperidone. When it is necessary to adjust the dosage, it should be increased by 12.5 mg. The maximum approved dose is 50 mg every two weeks. Studies have shown that there is no additional benefit above this dose, but an increased risk of side effects does exist.

**Special Populations**

No specific dosage adjustments are needed for elderly patients. The recommended starting dose is 25 mg every two weeks.

Because the long-acting formulation of risperidone has not been studied in patients with impaired renal or hepatic function, it is suggested that the doses of oral risperidone be carefully titrated for these patients before they are switched to the injection. The recommended titration is oral risperidone 0.5 mg twice daily for one week, with an increase to either 1 mg twice daily or 2 mg once daily during the second week. If patients tolerate the 2-mg dose, they can start the long-acting injection at 25 mg every two weeks. Studies of oral risperidone in patients with hepatic dysfunction have shown an increased amount of free risperidone, which may lead to an enhanced effect.

**DRUG INTERACTIONS, CONTRAINDICATIONS, AND PRECAUTIONS**

Although drug interactions associated with Risperdal Consta™ have not been studied in humans, several potential interactions are known. Fluoxetine and paroxetine have been shown to increase plasma concentrations of risperidone.

For patients who have been stabilized with risperidone, the dose should be decreased two to four weeks before therapy is begun with either agent. If patients have been following an established fluoxetine or paroxetine regimen, they should begin with a lower dose of risperidone (25 mg) every two weeks.

Because risperidone is metabolized via the CYP450 2D6 isoenzyme pathway, dosage adjustments are needed when patients are using other medications that are metabolized in the same way.

Patients who are following an established risperidone regimen may require a dosage increase or oral supplementation if they begin therapy with known CYP450 inducers, such as the anticonvulsants carbamazepine (e.g., Carbatrol®, Shire) and phenytoin (Dilantin®, Pfizer), barbiturates, or the bactericide rifampin. When patients discontinue one of these medications, the risperidone dose should be decreased two to four weeks before they stop taking the other medication.

**CLINICAL EFFICACY**

Two published clinical trials have assessed the safety and efficacy of Risperdal Consta. Other studies have been presented at scientific meetings, but they are not included in this review.

**Kane et al.**

A 12-week, multiple-site, randomized, double-blind, parallel-group, placebo-controlled trial was conducted to compare placebo with long-acting, injectable risperidone at 25, 50, and 75 mg. Hospitalized patients and outpatients between ages 18 and 55 who had Positive and Negative Syndrome Scale (PANSS) scores of 60 to 120 were included in the study. Patients were excluded from the study if:

- they had received a depot antipsychotic medication within the past 120 days.
- a diagnosis of substance abuse or tardive dyskinesia was confirmed.
- there was a history of neuroleptic malignant syndrome or electrocardiogram (ECG) abnormalities.
- they were pregnant or lactating.
- they were at risk for violent behavior.
- they had current suicidal ideations.
- they were hypersensitive or allergic to risperidone.

A “clinical improvement” was defined as a decrease in PANSS scores by at least
20% from the baseline score to the endpoint. ADEs were recorded at the baseline evaluation and every two weeks. A “serious event” was defined as death or a life-threatening event that required or prolonged hospitalization or that caused disability or incapacity, congenital anomalies, or birth defects. Extrapyramidal symptoms included hyperkinesias, hypertonia, tremor, hypokinesia, and involuntary muscle movements. The injection site was checked weekly and before and after each injection.

Of the 554 patients screened for the trial, 400 were randomly assigned to receive either placebo (n = 98) or risperidone 25 mg (n = 99), 50 mg (n = 103), or 75 mg (n = 100). Patients with at least one assessment after the baseline examination were evaluated to determine the drug’s efficacy (n = 370). Sixty-eight percent of the patients who received placebo and 51% of those receiving risperidone discontinued the trial prematurely.

At the baseline evaluation, mean PANSS scores ranged from 80.1 to 82.3. All patients who were receiving risperidone showed a decrease in their PANSS scores (−6.2 to −8.5), whereas patients receiving placebo had increased scores (+2.6) at the endpoint. Clinical improvement was noticed in 47% of the patients receiving risperidone 25 mg, in 48% of those receiving 50 mg, in 39% of those receiving 75 mg, and in 17% of the patients receiving placebo.

ADEs were reported by 80% to 83% of the patients, and more serious ADEs were observed in the placebo group (23.5%) than in the treatment groups (13%–15%). Specifically, extrapyramidal symptoms were seen in 13% of patients receiving placebo and in 10% receiving 25 mg, in 24% receiving 50 mg, and in 29% receiving 75 mg of risperidone per dose.

Minor increases in weight were recorded in the treatment groups, ranging between 0.5 and 1.9 kg, or between 1.1 and 4.2 pounds for the 25- and 50-mg doses, respectively (P < .001).

Although concomitant medications were used by more than 80% of the patients, their use increased with higher doses of risperidone. Of the patients in the 25-mg group, 12% received anti-parkinson medications; in the placebo group, 13% received them; and in the 50- and 75-mg groups, 23% received them. Sedatives were used by 51% of the placebo patients, by 43% of the 25-mg patients, and by 57% of the 75-mg patients.

Antidepressants were used in 12% of the placebo patients, in 15% of the 25-mg treatment group, in 18% of the 50-mg group, and in 20% of the 75-mg group.

The authors concluded that long-acting risperidone was well tolerated and more efficacious than placebo in reducing the signs and symptoms of schizophrenia. Of the three doses studied, the 25-mg dose seemed to have the best risk–benefit profile. Long-acting risperidone combined the effectiveness and tolerability of the atypical agents with the improved bioavailability and ensured delivery of the injectable formulations.

**Fleischhacker et al.**

Investigators conducted an open-label, 12-month, international trial to assess the long-term safety and tolerability of long-acting risperidone injection at doses of 25, 50, and 75 mg in patients who were considered clinically stable in their current regimens of antipsychotic therapy. Enrolled patients underwent a two-week run-in period in which risperidone 1–6 mg was allowed and all other antipsychotic medications were discontinued. After the run-in period, patients were assigned to receive the injection according to their current oral dosages as follows: patients taking 2 mg or less, 25 mg; patients taking 2 to 4 mg, 50 mg; and patients taking 4 to 6 mg, 75 mg.

Patients were allowed to continue the oral risperidone for up to three weeks and periodically throughout the trial if needed. Patients were included in the trial if:

- they were 18 years of age or older.
- a diagnosis of schizophrenia had been confirmed.
- their condition was stabilized with antipsychotic therapy for at least four weeks.
- their symptoms were determined to be stable.

Patients were excluded if:

- a diagnosis of substance abuse was confirmed.
- they had tardive dyskinesia or a history of neuroleptic malignant syndrome.
- ECG abnormalities were present.
- they were pregnant or lactating.
- a history of severe hypersensitivity or allergy was present.
- they were known to be unresponsive to risperidone.
- clozapine had been administered within the past two months or a depot antipsychotic dose had been given within the previous month.

Patients were assessed for ADEs every two weeks and for severity of extrapyramidal symptoms every month for three months, then every three months.

The researchers assessed the efficacy of the medication every three months using the PANSS scores and every month using the Clinical Global Impression Scale for Severity (CGI–S). Again, clinical improvement was defined as a 20% reduction or more in PANSS scores.

An ECG was performed at screening, at the baseline examination, at six months, and at the endpoint. Similarly, patients’ weights were recorded at screening, at six months, and at the endpoint.

Six hundred sixty-three patients were screened, and 615 received at least one injection. Of these patients, 65% finished the trial; 58% received 25 injections, 23% received 12 to 24 injections, and only 19% received fewer than 12 injections.

PANSS scores decreased for all treatment groups as follows: −8.0 for those receiving 25 mg, −8.3 for those receiving 50 mg, and −3.3 for those receiving 75 mg.

Even though safety and tolerability were the primary objectives of this study, which evaluated long-acting risperidone in a population with schizophrenia that was considered to be clinically stable, more than 50% of the patients in the trial had significantly improved PANSS scores. In addition, a greater percentage of patients were assessed as being “not ill” or “mildly ill” at the end of the trial compared with their baseline evaluations.

ADEs were reported in 85% of the patients; the most common reactions were anxiety (24%), insomnia (21%), psychosis (17%), and depression (15%). Extrapyramidal symptoms were reported in 21% of patients receiving 25 mg, in 27% receiving 50 mg, and in 25% receiving 75 mg.
All patient groups reported weight gain as follows: 1.7 kg (3.7 pounds) in the 25-mg group, 2.6 kg (5.7 pounds) in the 50-mg group, and 1.9 kg (4.2 pounds) in the 75-mg group.

Overall, 88% of patients took concomitant medications; 23% of the 25-mg patients, 34% of the 50-mg patients, and 27% of the 75-mg patients took antiparkinson agents. Sedatives were used by 45% of the patients receiving 25 mg, by 54% of the patients receiving 50 mg, and by 72% of those receiving 75 mg.

The authors concluded that stabilized patients with schizophrenia could be switched successfully from oral to long-acting risperidone.

A total of 65% of the patients completed the study, perhaps because of the low incidence of ADEs. The 75-mg dose was associated with a higher patient dropout rate because of insufficient responses or psychiatric ADEs, compared with the 25- and 50-mg doses.

Long-acting risperidone seemed to prevent hospitalizations; only 18% of the participants required inpatient treatment during the one-year trial period.

COST

The average cost per injection of the 25-mg dose is approximately $220. This charge may vary, depending on the acquisition costs in different health care systems. The cost rises proportionally with increases in the dosage; for instance, the 50-mg dose is approximately $440 per injection.

With two injections of the 25-mg dose costing approximately $440 per month of treatment, and because this dose has proved to be effective, this treatment still appears to be expensive. However, depending on the doses used and the various acquisition charges, this apparently costly treatment option falls into a price range that is similar to many oral atypical antipsychotic medications that are on the market today, if the commonly prescribed doses are used to treat schizophrenia. Thus, if the ensured delivery of risperidone long-acting injection can be used to treat patients who have histories of noncompliance with oral medications, and if this agent can reduce relapse rates and rehospitalizations resulting from a lack of continuous drug therapy, Risperdal Consta™ offers a unique therapeutic option for these patients as well as improved clinical and pharmacoeconomic outcomes. Further research is needed in this area.

CONCLUSION

Risperdal Consta™ is the latest addition to the armamentarium of medications that are used to treat patients with schizophrenia. It is the first atypical agent available in a long-acting, injectable form.

This medication may prove to be a beneficial combination of the efficacy and tolerability of the atypical antipsychotic agent risperidone with the improved delivery system of a long-acting injection. Because noncompliance is a serious problem that affects many chronically ill patients with schizophrenia, Risperdal Consta™ may offer a new and effective treatment alternative.

REFERENCES