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Use of Risperidone in Children with Autism, Bipolar Disease, or Schizophrenia Marcia L. Buck, Pharm.D., FCCP

On October 6, 2006, the Food and Drug Administration (FDA) announced the approval of risperidone, an atypical antipsychotic, as the first drug to treat irritability and aggression in children with autism. On August 22, 2007, the FDA-approved indications for risperidone were expanded to include treatment of bipolar disorder in children 10 years of age and older and schizophrenia in patients 13 years of age and older.¹ While risperidone has made a significant improvement in the lives of many children, it is associated with a number of potentially serious adverse effects. The decision to initiate therapy should only be made after careful consideration of the benefits and risks and a thorough discussion with the patient's family. This issue of *Pediatric Pharmacotherapy* will provide an overview of the studies conducted with risperidone in children and review its pharmacokinetics, drug interactions, and adverse effects.

Mechanism of Action

As with other antipsychotics, the exact mechanism of action for risperidone is not fully understood. Therapeutic effects are thought to result from risperidone's combined antagonist activity at dopamine type 2 (D₂) and serotonin type 2 (5HT₂) receptors. In addition to having high affinity for these receptors, risperidone also has antagonist activity at α_1 and α_2 -adrenergic and histaminergic (H₁) receptors. It has low to moderate affinity for serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity for dopamine D₁ and haloperidol-sensitive sigma site receptors, and no affinity for cholinergic muscarinic or β -adrenergic receptors.^{2,3}

Clinical Studies in Children

Since the initial approval of risperidone by the FDA in 1993, several hundred papers have been published describing its use in children and adolescents. They range from isolated case reports to well-designed multicenter controlled

clinical trials, and address use not only in autism, bipolar disorder, and schizophrenia, but also in Tourette's syndrome, tic disorders, oppositional defiant disorder, conduct disorder, anorexia nervosa, and other conditions.

Two recent studies highlight its benefits in children with autism.^{4,5} In 2002, McCracken and colleagues, representing the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, published the results of their multicenter risperidone trial in *The New England Journal of Medicine*.⁴ A total of 101 children (5-12 years of age) with autism were randomized to receive either risperidone (0.5 to 3.5 mg/day) or placebo. Primary outcome measures were scores on the irritability subscale of the Aberrant Behavior Checklist (ABC) and scores on the Clinical Global Impressions-Improvement (CGI-I) scale.

At 8 weeks, the risperidone group had a 56.9% reduction in their irritability subscale score, compared to only a 14.1% reduction in the placebo group ($p < 0.001$). The rate of an overall positive response, defined as at least a 25% decrease in the irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69% in the risperidone group, compared to 12% in the controls ($p < 0.001$). Two-thirds of the patients with a positive response to risperidone maintained that benefit at 6 months.⁴

Shea and colleagues conducted an 8-week controlled study in 79 children (5-12 years) with autism or pervasive developmental disorders.⁵ The children were randomized to receive risperidone (0.1 mg/kg/day titrated up to 0.6 mg/kg/day) or placebo. Symptoms were assessed using the irritability score on the ABC, the Nisonger Child Behavior Rating Form, and the CGI-Change scale (CGI-C). The risperidone-treated patients had a significantly greater

decrease in their irritability score compared to placebo (64% versus 31%). The treatment group also had a greater degree of improvement in their remaining ABC scores and the Nisonger form. Eighty-seven percent of the risperidone patients had improvement of their CGI-C scores, compared to only 40% in the placebo group. More children in the risperidone group experienced adverse effects, but most were mild and responded to dosage adjustment. Weight gain was higher in the risperidone group (2.7 kg versus 1 kg). There were no differences in extrapyramidal symptoms between the groups.⁵

The efficacy of risperidone in adolescents with newly-diagnosed schizophrenia was assessed by Zalsman and coworkers in an open-label 6 week trial.⁶ Eleven patients (15-20 years of age) were assessed with the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), and the CGI-Severity scale. The average dose of risperidone was 3.14 ± 1.60 mg/day. The average improvement in PANSS score was 28%, BPRS was 30.11%, and CGI-Severity score was 31.36% (all $p < 0.01$ compared to baseline). Negative signs were not significantly improved. Adverse reactions included extrapyramidal effects, somnolence, depression, and weight gain.

Biederman and colleagues recently evaluated risperidone in 30 children (ages 6-17 years) with manic, mixed, or hypomanic bipolar disorder.⁷ In this 8-week open-label study, 70% of the children achieved a CGI-I score ≤ 2 . The average dose was 1.25 ± 1.5 mg/day. Adverse effects included a four-fold increase in serum prolactin levels and an average weight gain of 2.1 ± 2.0 kg.

Pharmacokinetics

Risperidone is well absorbed after oral administration, with an absolute bioavailability of 70%. Administration with food does not affect the rate or extent of absorption. Peak concentrations occur 1 hour after an oral dose. Risperidone is rapidly distributed, with a volume of distribution of 1 to 2 L/kg, and is highly bound to plasma proteins. It is extensively metabolized via hydroxylation by CYP2D6 to 9-hydroxyrisperidone. This metabolite has similar pharmacologic activity to the parent compound, reaching a peak plasma concentration approximately 3 hours after the dose in extensive metabolizers and 17 hours post-dose in poor metabolizers. A minor metabolite is produced through N-dealkylation.^{2,3}

In adults, the apparent half-life of risperidone is 3 hours in extensive metabolizers and 20 hours in poor metabolizers. The half-life of 9-

hydroxyrisperidone is approximately 20 hours in extensive metabolizers and 30 hours in poor metabolizers. In a recent study of risperidone pharmacokinetics in 19 children (4-15 years of age), the average half-life for the parent compound was 3.0 ± 2.3 hours.⁸

Drug Interactions

Risperidone concentrations may be increased when administered with azole antifungals (fluconazole, itraconazole, ketoconazole), cimetidine, clozapine, lamotrigine, protease inhibitors (such as indinavir or ritonavir), ranitidine, selective serotonin reuptake inhibitors (such as fluoxetine or paroxetine), thioridazine, or verapamil. In the case of drugs that act as CYP2D6 inhibitors, concentrations of risperidone may initially increase, but the reduced production of 9-hydroxyrisperidone may offset the overall effect of the drug interaction.^{2,3}

Co-administration of carbamazepine, phenobarbital, phenytoin, rifampin and other drugs that induce CYP2D6 may decrease serum risperidone concentrations. With carbamazepine, risperidone concentrations may be decreased by up to 50%. In cases where the interacting drug cannot be discontinued, the risperidone dose may need to be increased to produce optimal effect. Because of its antagonist activity at dopaminergic receptors, risperidone may antagonize the effects of levodopa or other dopamine agonists. Concomitant administration of risperidone and valproate may result in up to a 20% increase in serum valproate concentrations.^{2,3}

Adverse Effects

In pediatric clinical trials, the most common adverse effects associated with risperidone were somnolence (in 67% of patients), fatigue (42%), increased appetite (49%), upper respiratory tract infection (34%), increased salivation (22%), constipation (21%), dry mouth (13%), dystonia, tremor, and Parkinsonian/extrapyramidal symptoms (8-12% each), dizziness (9%), tachycardia and dyskinesia (7% each), confusion and weight gain (5% each).²

Weight gain is a relatively common adverse effect with atypical antipsychotics. This effect may limit the utility of therapy in some patients, as effective symptom control may only be achieved at the cost of obesity and limited mobility. Weight gain was reported in 7.4% of 391 children receiving risperidone who were monitored as part of an observational cohort study in New Zealand.⁹

In 2002, Ratzoni and colleagues compared weight changes in 50 adolescents treated for 12 weeks with olanzapine, risperidone, or haloperidol.¹⁰ They reported an average weight gain of 3.9 ± 4.8 kg in the teens given risperidone and an increase of 7.2 ± 6.3 kg in the patients given olanzapine. In contrast, the haloperidol group had only a 1.1 ± 3.3 kg increase. Extreme weight gain, defined by the authors as an increase of 7% body weight or greater, occurred in 19 of the olanzapine patients (90%), 9 of the risperidone patients (43%), and only one of the haloperidol patients (12%).

In a similar study, Fleischhaker and colleagues reported a relatively small increase in weight with clozapine and risperidone, compared to olanzapine.¹¹ A total of 45 hospitalized children were placed into one of the three treatment groups for 6 weeks. At the end of the study, the average change in weight was 2.5 ± 2.9 kg in the clozapine group, 2.8 ± 1.3 kg in the risperidone group, and 4.6 ± 1.9 kg in the olanzapine group.

Endocrinologic adverse effects are a known complication of the atypical antipsychotics. Hyperglycemia has been reported with all the agents in this class, and in some cases has resulted in ketoacidosis, hyperosmolar coma, and death. Children receiving risperidone should be routinely monitored for symptoms of polydipsia, polyuria, polyphagia, or weakness. In those with additional risk factors for diabetes, such as obesity or a positive family history, periodic fasting blood glucose measurements are recommended.^{2,3}

Risperidone can also increase serum prolactin levels, leading to suppression of hypothalamic gonadotropin-releasing hormone. As a result, patients may develop galactorrhea, amenorrhea, gynecomastia, or impotence. Long-standing increases in prolactin release can also lead to decreased bone density and could potentially affect growth. Utilizing data from the RUPP study, Anderson and colleagues compared serum prolactin levels in 42 children given risperidone and 36 controls at 8 weeks, 6 months, and 22 months.¹² At 8 weeks, the prolactin level was 39.0 ± 19.2 ng/mL in the risperidone group, compared to 10.1 ± 8.8 ng/mL for controls ($p < 0.0001$). Prolactin levels remained significantly higher in the risperidone-treated patients at 6 and 22 months. Despite the increase, none of the patients developed adverse effects. Based on combined data from premarketing studies, the manufacturer reports only a 0.8% incidence of galactorrhea and a 2.3% incidence of gynecomastia in pediatric patients given risperidone.^{2,3}

Prolactin production also appears to be correlated with the rate of risperidone metabolism.¹³ In a recent study of 25 children (5 to 15 years of age) receiving risperidone who were genotyped for CYP2D6 polymorphisms, those with the ultrarapid metabolizer phenotype had the highest concentrations of 9-hydroxyrisperidone and the highest prolactin levels. There was no relationship between prolactin level and patient age. Despite the elevated prolactin levels in these patients, none experienced adverse effects.

Although less common than with traditional antipsychotics, there have been reports of neuroleptic malignant syndrome (NMS) and tardive dyskinesia with risperidone use. The risk for these reactions increases as the dose of risperidone is increased and receptor-site specificity is lost. Neuroleptic malignant syndrome typically manifests as hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. Some patients may develop rhabdomyolysis leading to myoglobinuria and acute renal failure.^{2,3} Patients and family members should understand the presenting symptoms of NMS and be aware of the need to seek immediate medical attention.

Tardive dyskinesia (TD) is associated with long-term use of antipsychotics. Involuntary movements associated with TD may not fully reverse with drug discontinuation. Although rare with the atypical antipsychotics, TD has been reported with their use. In a meta-analysis of 10 long-term pediatric studies, Correll and Kane found only 3 cases of TD reported with atypical antipsychotics, resulting an annualized rate of 0.42% (95% CI 0.087-1.24).¹⁴ Other rare, but serious, adverse effects associated with risperidone include orthostatic hypotension, seizures, depression, arrhythmias, and hypersensitivity reactions.^{2,3}

Dosing Recommendations

Prior to initiating risperidone, behavioral symptoms, as well as growth (height, weight, and sexual maturation), heart rate and blood pressure, and activity level should be assessed to establish a baseline. In patients with risk factors for diabetes, a fasting blood glucose should be obtained, if possible. Patients and family members should be counseled about the benefits and risks of risperidone therapy and the signs and symptoms of serious adverse effects which require medical attention. Parents should be prepared for the potential increase in appetite produced by risperidone and have a plan for managing their child's food intake.

The recommended starting dose for risperidone in children with autism is 0.25 mg/day for children 15 to 19 kg and 0.5 mg/day for children \geq 20 kg. Therapy is typically initiated as a single daily dose in the morning or evening. The dose may be increased by 0.25 to 0.5 mg at a minimum interval of every 2 weeks. The effective dose range provided by the manufacturer is 0.5 to 3 mg/day. In patients who develop somnolence with once-daily dosing, the dose may be divided and administered twice daily. Risperidone doses should be reduced in patients with underlying renal or hepatic disease.^{2,3}

In children and adolescents with bipolar mania or schizophrenia, the recommended starting dose is 0.5 mg/day, with titration by 0.5 to 1 mg daily until symptom control and/or a target dose of 1 to 6 mg is achieved. In adults, the recommended dose for initiation of risperidone is 2 mg/day with daily titration in 1 to 2 mg increments. The effective dose range for adults is 1 to 6 mg for bipolar disease and 4 to 16 mg for schizophrenia.^{2,3}

Availability

Risperidone (Risperal[®]; Janssen) is available in 0.25, 0.5, 1, 2, 3, and 4 mg standard oral tablets and orally disintegrating tablets, as well as a 1 mg/mL oral solution. The orally disintegrating tablets may be taken with or without water. The orally disintegrating tablets contain aspartame and should not be given to patients with phenylketonuria. The oral solution is available in 30 mL bottles with a calibrated pipette. The solution may be given with water, coffee, orange juice, or milk. It is not compatible with cola or tea.

Risperidone is also available in an injectable form, in 12.5, 25, 37.5, and 50 mg kits. The kit contains a prefilled syringe and diluent.³

Summary

Risperidone can have a significant impact on reducing irritability and aggression in children with autism, as well as improving symptoms in children with bipolar disease and schizophrenia. While it has the potential to provide considerable benefit for these pediatric patient populations, it is also associated with serious adverse effects. As a result, the benefit to risk profile must be evaluated for each child and his or her family prior to initiating treatment.

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Formulary Update

There was no Pharmacy and Therapeutics Committee meeting in December. Meetings will resume in January.

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