

## RISPERDAL CONSTA<sup>®</sup>

Graylands Hospital Drug Bulletin 2003 Vol 11 No 2 May ISSN 1323-1251

- ★ Risperdal Consta<sup>®</sup> has recently been approved by the Therapeutic Goods Administration (TGA) and is the first long-acting, injectable atypical antipsychotic to be available in Australia.
- ★ The manufacturers expect the product to be commercially available from June. However, it is not available on the Pharmaceutical Benefits Scheme (PBS) at present.
- ★ The Western Australian Drugs & Therapeutics Committee (WADTC) considered the evidence available for Risperdal Consta<sup>®</sup> and recommended against its general formulary listing (i.e. that the drug should NOT be added to the formulary of any metropolitan or regional hospital).
- ★ Guidelines as produced by the WADTC for the appropriate use of this product must be followed. Applications for the initial use of Risperdal Consta<sup>®</sup> must be made in writing to the Area Clinical Director of Mental Health Services or equivalent. Continued use of the drug after 4 months is dependant upon the demonstration of clinical benefit and absence of extrapyramidal side effects.
- ★ Current approximate prices of a single Risperdal Consta<sup>®</sup> vial for fortnightly administration, are as follows: 25mg = \$200.00, 37.5mg = \$300.00, 50mg = \$400.00, compared with \$3.13 for a 200mg vial of zuclopenthixol decanoate.

### PLACE IN THERAPY

Risperdal Consta<sup>®</sup> will be appropriate for use in patients with schizophrenia who have documented *significant* adverse consequences due to non-compliance with oral antipsychotics **AND** in whom a reasonable trial of a typical depot drug eg. zuclopenthixol, flupenthixol, has been associated with intolerable side effects.

Until data of a better quality and comparative nature are available, a trial of a typical depot antipsychotic should be undertaken before Risperdal<sup>®</sup> injection is considered.

Risperdal<sup>®</sup> (risperidone) is an atypical antipsychotic that is well known in psychiatric practice in Australia. It is an antagonist at dopamine D<sub>2</sub> and 5HT<sub>2</sub> receptors and has shown efficacy against both positive and negative symptoms of schizophrenia (1).

Risperdal Consta<sup>®</sup> is presented as a prolonged release powder and solvent for

suspension, and is indicated for the treatment of schizophrenia and related psychoses.

### Pharmacokinetic Properties

When reconstituted, the long-acting formulation is an aqueous suspension containing risperidone in a matrix of glycolic acid-lactate copolymer. Once injected, gradual hydrolysis of the

copolymer allows a slow, steady release of risperidone (2).

After an intramuscular injection with long-acting risperidone, there is a 1% initial release of the drug, then a lag time of three weeks. The main release of risperidone starts after three weeks, is maintained from weeks four to six, then subsides by week seven (3). For this reason, oral supplementation may be necessary during the first three weeks of treatment with Risperdal Consta<sup>®</sup> (see **Oral Supplementation**).

Once ceased, therapeutic plasma concentrations of risperidone remain until four to six weeks after the last injection and elimination is complete approximately seven to eight weeks after the last injection (3).

Absorption of risperidone from the long-acting formulation is complete. No accumulation was observed in patients who were injected with 25-50mg fortnightly for twelve months (3).

#### **Strengths Available & Product Contents**

There are three strengths of Risperdal Consta<sup>®</sup> available; 25mg, 37.5mg & 50mg.

Each pack contains a vial of risperidone powder, a pre-filled syringe with 2mL of solvent, two Hypoint<sup>®</sup> 20G needles for reconstitution and one Needle-Pro<sup>®</sup> 20G needle for deep intramuscular gluteal injection.

#### **Administration**

The risperidone powder may only be suspended with the solvent provided and must be administered using all the needles provided.

A particular reconstitution technique must be adhered to, to ensure correct suspension of the risperidone and also to ensure the correct dose is given to the patient.

Before giving an injection of long-acting risperidone, the person administering it must be familiar with the correct technique. It is recommended that training be implemented prior to its use.

#### **Commencing Long-Acting Risperidone**

Patients with no previous history of risperidone use, should be pre-treated with oral risperidone prior to the first injection of long-acting risperidone to assess tolerability and efficacy.

The recommended starting dose of long-acting risperidone is 25mg by deep intramuscular injection every two weeks.

The preparations cannot be halved or altered in anyway to obtain different strengths. The syringes used are not calibrated. Due to the nature of the suspension (consists of microspheres), giving half the volume does not equate to half the dose being given.

#### **Dose Increases**

Some patients may benefit from the higher doses. Dose increases should only be considered after a minimum of four weeks of treatment at a particular dose. The maximum dose should not exceed 50mg every two weeks.

If further sedation of a patient is required, it is recommended that an additional agent be used (eg. benzodiazepine) rather than increasing the dose of the long-acting risperidone (3).

#### **Oral Supplementation**

Where appropriate, oral supplementation with risperidone at the stabilised dose should be continued for three weeks after the first injection of long-acting risperidone. Oral risperidone should be ceased after this.

After the first three weeks, oral risperidone up to 4mg/day may be used temporarily to supplement therapy while establishing the patient's optimum long-acting risperidone dose. If oral supplementation is required continuously, the dose of long-acting risperidone should be reassessed.

#### **Plasma Concentrations**

In the phase-III clinical trials where safety and efficacy were examined, no relationship between the plasma concentrations and change in PANSS (Positive and Negative Syndrome Scale)

and total ESRS (Extrapyramidal Symptom Rating Scale) scores was seen (3).

### **Special Patient Populations**

The only recommended dose for elderly patients is 25mg every two weeks (3).

One study compared the safety and efficacy of long-term use of long-acting risperidone in 57 patients over the age of 65 versus 725 patients of all ages. It found that after 12 months, the long-acting risperidone formulation was just as efficacious and well tolerated in elderly patients as it was in the total group of patients of all ages (4).

The long-acting risperidone formulation has not been studied in patients with hepatic and renal impairment. It should therefore be used with caution. The manufacturer suggests if it is to be used in this patient population, to start with oral risperidone 0.5mg twice daily for one week then increasing to 1mg twice daily or 2mg once daily. If an oral dose of 2mg daily can be tolerated, an injection of 25mg long-acting risperidone can be given every two weeks (3).

The long-acting risperidone formulation has not been studied in patients under the age of 18 years.

### **Pregnancy and Breastfeeding**

The safety of risperidone for use in pregnancy has not been established and should only be used if the benefits outweigh the risks.

Both risperidone and its active metabolite 9-hydroxyrisperidone are excreted into human breast milk. Data from one case report (5) indicated that the total estimated infant exposure was approximately 4% of the oral maternal dose. This is well below the "10% level of concern" recommended for safe breastfeeding with many drugs. However, the short and long-term effects of risperidone exposure on cognitive development in infants are unknown. Clinical experience with this drug is extremely limited at present, therefore it cannot be recommended for use in breastfeeding mothers.

### **Side Effects**

#### Extrapyramidal Side Effects (EPSE)

Two 1-year trials were conducted investigating efficacy and safety of long-acting risperidone. In these trials, severity of extrapyramidal symptoms at doses of 25-50mg was generally mild at baseline and did not change significantly or was reduced during the course of the trial (2,6). The incidence of extrapyramidal disorder in the first trial ranged from 4-8% (2), and from 6-7% in the second trial (6).

#### Weight Gain

In one of the 1-year trials, an overall average weight gain of 2.3kg was reported across all doses (6). In the other trial, average weight gain in the 25mg group was 0.5kg and 1.2kg in the 50mg group, compared with a loss of 1.4kg in the placebo group (2).

#### Pain at Injection Site

In one trial, only 2% of patients spontaneously reported pain at injection site (6), while in the other study, pain at injection site varied from 3-10% (2).

#### Other Side Effects

Other side effects reported by  $\geq 10\%$  of patients in any group were anxiety, insomnia, psychosis, agitation, depression, headache, hyperkinesia, rhinitis and dizziness (2,6).

### **Efficacy**

No data is available at present comparing the efficacy of long-acting risperidone injection with typical antipsychotic depot formulations or any oral antipsychotic medications.

Only two open, long-term trials have been conducted looking at the efficacy of the long-acting risperidone injection. They have not been published as yet, but were presented as posters supported by Jassen-Cilag.

#### Clinical Improvement

One study found the severity of schizophrenia symptoms, as measured by PANSS, was reduced significantly over 50 weeks in patients treated with long-acting

risperidone injection (6). Clinical improvement (a reduction in PANSS of 20% or more) was seen in 56% of patients in both the 25mg and 50mg groups.

The second long-term study also found significant improvements in PANSS total score in patients treated with long-acting risperidone injection (2). Clinical improvement was seen in 47% patients in the 25mg group and in 48% of patients in 50mg group.

### Re-hospitalisation Rates

The issue of whether depot antipsychotics reduce the risk of relapse and subsequent re-hospitalisation remains a controversial one. Studies following patients after discharge, detail a wide range of 1-year rehospitalisation rates. For conventional depot antipsychotics, values quoted range from 13-36% (8,9), for conventional oral antipsychotics from 24-48% (8,10) and for oral atypical agents (excluding clozapine), from 17-44% (8-12).

Chue et al (7) used data from a previously conducted study (6) to assess hospitalisation rates for patients receiving treatment with Risperdal Consta® and found similar values. The 1-year rehospitalisation rate of *in-patients* discharged on risperidone injection was found to be 25.0% (7). *Out-patients* who were started on long-acting risperidone injection had a hospitalisation rate of 15.9% (7). When looking at *all* the patients (in-patients and out-patients), 36% required at least one hospitalisation during the entire trial (7).

### **Storage and Shelf Life**

Each pack of Risperdal Consta® comes with a vial containing risperidone powder and a pre-filled syringe of solvent. The entire pack should be stored in a refrigerator from 2-8°C.

If refrigeration is unavailable, it can be stored at up to 25°C for no more than 7 days prior to administration.

It should not be exposed to temperatures greater than 25°C. Even short exposure to

high temperatures above 30°C will lead to quality defects.

Once reconstituted, the manufacturer recommends the product be used immediately to avoid the possibility of microbiological growth. If not used immediately, administration becomes the responsibility of the user and should not normally be greater than 6 hours after reconstitution.

### **References**

1. Bazire S. Drug treatment options in psychiatric illness. In: Psychotropic drug directory: the professionals' pocket handbook and aide memoire. London: Quay books 2001: 110-111.
2. Kane J, Eerdekens M, Keith S, Lesem M, Karcher K, Lindenmayer JP. Efficacy and safety of Risperdal Consta®, a long-acting injection risperidone formulation. Poster presented at the college of Neuropsychopharmacology 40<sup>th</sup> Annual Meeting December 9-13, 2001, Waikoloa, Hawaii.
3. Risperdal Consta® Product Information. North Ryde: Janssen-Cilag Pty Ltd Australia, March 26, 2003.
4. Gharabawi G, Eerdekens M, Zhu Y, Lasser R. Long-acting risperidone (Risperdal Consta®) for the management of elderly patients with psychotic disorders: a favourable benefit/risk ratio. Poster presented at the First Annual Meeting of the International College of Geriatric Psychoneuropharmacology, December 14-15 2001, Waikoloa, Hawaii.
5. Hill RC, McIvor RJ, Wojnar-Horton RE, Hackett LP, Ilett KF. Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 2000;20(2):285-286.
6. Eerdekens M, Fleischhacker WW, Xie Y, Beauclair L, Sauret H, Chrzanowski W, Martin S, et al. Long-term safety of long-acting risperidone microspheres. Poster presented at the 11<sup>th</sup> Biennial Winter Workshop on Schizophrenia, February 24-March, 2002.
7. Chue P, Devos E, Duchesne I, Leal A, Mehnert A. Hospitalisation rates in patients during long-term treatment with long-acting risperidone injection. Poster presented at the 23<sup>rd</sup> CINP Congress, June 23-17, 2002, Montreal, Canada.
8. Patel NC, Dorson PG, Edwards N, Mendelson S, Crimson ML. One-year rehospitalisation rates of patients discharged on atypical versus conventional antipsychotics. *Psychiatr Serv* 2002;53(7): 891-893.
9. Moore DB, Kelly DL, Sherr JD, Love RC, Conley RR. Rehospitalisation rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. *Am J Health-Syst Pharm* 1998;55(4):S17-19.
10. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002;346:16-22.
11. Conley RR, Love RC, Kelly DL, Bartko JJ. Rehospitalisation rates of patients recently discharged on a regimen of risperidone or clozapine. *Am J Psychiatry* 1999;156(6): 863-868.
12. Rabinowitz J, Lichtenberg P, Kaplan Z, Mark M, Nahon D, Davidson M. Rehospitalisation rates of chronically ill schizophrenic patients discharged on a regimen of risperidone, olanzapine, or conventional antipsychotics. *Am J Psychiatry* 2001;158(2):266-269.

### **Acknowledgement**

This article was prepared by Anouska Feszczur, and reviewed by members of the Pharmacy Department.

Comments are welcome at the e-mail address: Druginformation.Graylands@health.wa.gov.au