

# Graylands Hospital Drug Bulletin

## What's new in Antipsychotics

North Metropolitan Area Health Service - Mental Health March 2011 Vol 18 No.1 ISSN 1323-1251

This edition of the Graylands Hospital Drug Bulletin looks at sertindole, ziprasidone mesilate and paliperidone palmitate, all of which have recently been registered for use in Australia for the treatment of schizophrenia. These medications are approved by the Therapeutic Goods Administration, but at the time of printing this bulletin are not listed on the Pharmaceutical Benefits Scheme or the Western Australian Hospital Formulary.

## Sertindole

Sertindole (Serdolect®) is an atypical antipsychotic recently approved in Australia for the treatment of schizophrenia.<sup>1</sup>

Sertindole was originally approved for use in the United Kingdom and several European countries in 1996<sup>2, 3</sup>, however in December 1998 the manufacturer voluntarily withdrew sertindole due to concerns regarding the prolongation of the QTc interval and associated increased risk of serious arrhythmias.<sup>3, 4</sup>

Extensive preclinical and epidemiological data has since shown that sertindole is not associated with a higher rate of cardiovascular mortality compared to other atypical antipsychotics,<sup>5</sup> but it does have a black box warning advising that "ECG monitoring is required before and during treatment with sertindole" as sertindole can prolong the QTc interval to a greater extent than some other antipsychotics.

Sertindole is indicated in Australia for the treatment of schizophrenia. However, due to cardiovascular safety concerns, it should only be used for people who are not responsive to, or intolerant of at least one other antipsychotic medication.<sup>1</sup>

### Mode of action

Sertindole's antipsychotic action is due to its inhibitory effects on dopamine D<sub>2</sub> and serotonin 5HT<sub>2</sub> receptors as well as α<sub>1</sub>-adrenergic receptors.<sup>1</sup> It is highly selective for dopaminergic neurones in the mesolimbic system, rather than the nigrostriatum. As dopamine receptors in the nigrostriatum are responsible for extra pyramidal side effects (EPSE), the incidence of EPSE with sertindole is similar to placebo.<sup>5</sup> Sertindole also has low affinity for histamine H<sub>1</sub> and muscarinic receptors, hence it has very low potential to cause sedation and cognitive impairment.<sup>5</sup>

### Efficacy

Several randomised, double-blind, controlled studies of 6-12 weeks duration have demonstrated efficacy of sertindole in patients with schizophrenia.<sup>5</sup> Doses of 12-24mg/day were more effective than placebo in the reduction of Positive and Negative Syndrome Scale (PANSS) total score.<sup>5</sup> Dose dependent changes in PANSS score occurred in doses 12-20mg/day. There was little benefit observed with doses above 24mg/day, and the efficacy of an 8mg/day dose was suboptimal.<sup>5</sup>

Two 8-week trials have shown sertindole to be at least as effective as haloperidol in reducing PANSS total score.<sup>5</sup>

A 12-week, double-blind study compared the efficacy of sertindole and risperidone in patients with schizophrenia. Sertindole was withdrawn from the market before the full complement of 400 patients was enrolled, meaning statistical significance could not be reached.<sup>5</sup> Sertindole has not been compared to other second-generation antipsychotics.

### Cardiovascular adverse effects

Sertindole prolongs the QTc interval to a greater extent than some other antipsychotics, and for this reason several safety measures should be undertaken prior to and during sertindole treatment<sup>1</sup> (see figure 1). Its effect on QTc is dose-related.<sup>5</sup>

Prolongation of the QTc interval is associated with an increased risk of torsades de pointes-type arrhythmias, which can result in sudden death.<sup>1</sup> Evidence suggests a QTc interval over 500msec is associated with an increased risk of arrhythmia.<sup>6</sup>

### Other adverse events

The most common adverse effects experienced by patients taking sertindole include headache, insomnia, rhinitis, and in men, abnormal ejaculation.<sup>5</sup> Sertindole can cause a small amount of weight gain, and produces small increases in plasma levels of

Figure 1: Required safety measures for prescribing of sertindole<sup>1</sup>

#### ECG Monitoring:

- ECG monitoring is mandatory prior to and during treatment with sertindole.
- Sertindole is contraindicated if a QTc interval of more than 450msec in males or 470msec in females is observed at baseline, i.e. before starting sertindole treatment.
- ECG monitoring should be conducted at baseline (before starting sertindole), upon reaching steady state after approximately 3 weeks or when reaching 16mg and again after 3 months of treatment.
- During maintenance treatment ECGs should be repeated at a minimum of 12 monthly intervals.
- During maintenance treatment, ECG measurements should take place prior to and 3 weeks after any increase in dose.
- An ECG is recommended after the addition of or increase in dosage of concomitant medication that may increase the sertindole concentration.
- If a QTc interval of more than 500msec is observed during treatment with sertindole, treatment should be discontinued.
- Should the QTc be prolonged by more than 60msec from baseline at any time during treatment, the ECG should be repeated. If QTc prolongation remains high ( $\geq 60$ msec) the dosage should be lowered and a search made for any explanatory factor that may contribute to the increase in QTc. If no explanatory factor is found and QTc prolongation remains  $\geq 60$ msec, the drug should be withdrawn.
- For patients with symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation, including an ECG.
- ECG monitoring is ideally conducted in the morning.

prolactin, cholesterol, triglycerides and glucose.<sup>5</sup>

Sertindole 8-24mg/day is associated with rates of EPSE similar to that of placebo and significantly lower than those of haloperidol.<sup>5</sup>

### Dosing

Sertindole is available in tablet strengths of 4mg, 12mg, 16mg and 20mg and is administered orally once a day with or without food.<sup>1</sup>

All patients should be started on 4mg/day.<sup>1</sup> The dose should be increased by 4mg every 4-5 days until the optimal maintenance dose is reached, which is usually within the range of 12-20mg/day.<sup>1</sup>

Sertindole has  $\alpha_1$ -blocking activity, meaning symptoms of postural hypotension may occur during the initial titration period.<sup>1</sup> A more rapid dose increase may result in significantly increased postural hypotension.<sup>1</sup> The patient's blood pressure should be monitored during the initial titration period and early in maintenance treatment.<sup>1</sup>

No dose reduction is required in renal impairment. Slower titration and lower maintenance doses are required in mild-moderate hepatic impairment.<sup>1</sup>

### Drug Interactions (Contraindications)

Coadministration of sertindole is contraindicated in patients taking potent inhibitors of cytochrome P450 3A4 inhibitors and drugs known to prolong QTc interval (due to increased risk of torsades de pointes)<sup>1</sup>.

### Conclusion

Studies have shown sertindole to be an effective antipsychotic for the treatment of schizophrenia.<sup>5</sup> It is

generally well tolerated,<sup>7</sup> with a reported low incidence of EPSE and sedation<sup>3</sup> and appears not to impair cognition.<sup>5</sup> It does however carry the potential to cause a prolonged QTc interval and stringent ECG monitoring is required during treatment.

## Ziprasidone mesilate (Zeldox IM)

Intramuscular (IM) ziprasidone mesilate is an atypical antipsychotic that was recently introduced into Australia indicated for acute and short-term management of agitation and disturbed behaviours in patients with schizophrenia and related psychoses when oral therapy is not appropriate.<sup>8</sup>

Clinical trials indicated that ziprasidone IM 20mg reduced agitation within 15-30 minutes of dosing.<sup>9</sup> Improvements continued to increase until 2 hours post-dose, and were maintained until at least 4 hours post-dose.<sup>9</sup>

IM ziprasidone can be given at the same time as an IM benzodiazepine if required.

### Mode of Action

The proposed mechanism of action of ziprasidone is through a combination of dopamine type 2 ( $D_2$ ) and serotonin type 2 ( $5-HT_2$ ) antagonism.<sup>8</sup> It also binds modestly to  $\alpha_1$ -adrenergic receptors and has moderate affinity for histamine H1-receptors.<sup>8</sup>

### Pharmacokinetics

The bioavailability of ziprasidone is 100% after IM administration. The mean terminal half-life of ziprasidone IM after a single dose ranges from 2-5

hours. Because ziprasidone is highly metabolised, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone.<sup>8</sup>

## Dosage and administration

Ziprasidone IM requires reconstitution with 1.2mL of the supplied sterile water for injection prior to administration, giving a concentration of 20mg/mL.<sup>8</sup> This produces a viscous solution, some of which will always remain in the vial after dosing.<sup>8</sup>

The recommended dose is 10-20mg administered as required up to a maximum dose of 40mg/day. Doses of 10mg may be administered every 2 hours, doses of 20mg may be administered every 4 hours up to a maximum of 40mg/day.<sup>8</sup>

If continued therapy is indicated, oral ziprasidone hydrochloride capsules up to 80mg twice daily, should replace the IM administration as soon as possible.<sup>8</sup> If oral and IM dosages are used concurrently, the combined daily dose should not exceed 160mg/day.<sup>8</sup>

## Contraindications

Contraindications for use of ziprasidone IM include recent acute myocardial infarction, uncompensated heart failure and conditions with a potential to increase QTc interval.<sup>8</sup>

## Adverse effects

The most common reactions are nausea, sedation, dizziness, injection site pain, headache and somnolence.<sup>8</sup> It can also cause mild to moderate prolongation of the QT interval.<sup>8</sup>

# Paliperidone Palmitate: paliperidone long-acting injection

Paliperidone (9-hydroxy risperidone) is an atypical antipsychotic indicated for the treatment of schizophrenia. The oral formulation is taken once-daily at doses ranging from 3-12mg daily.<sup>10</sup>

Paliperidone palmitate (Invega Sustenna®) is a long-acting injectable form of paliperidone that was registered in Australia in July 2010.<sup>11</sup> It is indicated for the acute and maintenance treatment of schizophrenia in adults.<sup>11</sup> Paliperidone palmitate is designed to be administered once-monthly<sup>12</sup> and does not require refrigeration or reconstitution<sup>13</sup>.

## Mode of action

Paliperidone is a centrally acting dopamine D<sub>2</sub> receptor and serotonin 5-HT<sub>2A</sub> receptor antagonist.<sup>14</sup> Paliperidone also has antagonistic activity at α<sub>1</sub>- and α<sub>2</sub>-adrenergic and H<sub>1</sub>-histaminergic receptors.

## Formulation

Paliperidone palmitate is an ester that dissolves slowly into the interstitial fluid after intramuscular administration due to its extremely low water solubility.<sup>11</sup> It is then hydrolysed by esterases to palmitic acid and the active compound paliperidone, which is absorbed into the systemic circulation.<sup>11</sup>

Paliperidone palmitate is an aqueous formulation available in a pre-filled syringe, meaning reconstitution is not required.<sup>11</sup>

Paliperidone palmitate is available in five different strengths: 25mg, 50mg, 75mg, 100mg, and 150mg.<sup>11</sup> The strength is expressed in milligrams of paliperidone.<sup>11</sup> These strengths are equivalent to 39mg, 78mg, 117mg, 156mg and 234mg, respectively, of paliperidone palmitate.<sup>14</sup>

## Efficacy

The efficacy of paliperidone palmitate has been established in four short-term placebo-controlled trials and one maintenance placebo-controlled trial.<sup>11</sup> A total of 2652 patients were included in these trials, 2142 of whom received paliperidone palmitate.<sup>11</sup>

Paliperidone palmitate has been compared to risperidone long-acting injection (LAI) in two active comparator, non-inferiority studies. Paliperidone was not found to be non-inferior in a 53-week study, but in a separate 13-week study results suggested it was non-inferior.<sup>15</sup>

## Administration

Paliperidone palmitate should be administered as a single, deep intramuscular injection.<sup>14</sup> The syringe must be shaken vigorously for a minimum of 10 seconds to ensure a homogenous solution prior to attaching the needle.<sup>14</sup> After the appropriate needle is attached, the entire contents of the syringe should be injected intramuscularly.<sup>14</sup>

Paliperidone palmitate can be given in either the deltoid or gluteal muscle. Trials indicate that following a single injection, deltoid muscle administration results in a 28% higher peak concentration,<sup>11</sup> though total absorption of paliperidone is similar from each injection site.<sup>16</sup>

The volume of paliperidone palmitate that is injected ranges from 0.25 to 1.5mL. This is less than risperidone LAI which is 2mL for all doses.<sup>17</sup>

For DELTOID administration, the 1-inch 23 gauge needle is used if the patient is <90kg, and the 1½-inch 22 gauge needle if the patient is ≥90kg.<sup>11</sup>

For GLUTEAL administration, the 1½-inch needle must be used.<sup>11</sup>

## Dosing

### Test dose

For patients who have never taken risperidone or oral paliperidone, oral doses of either drug are recommended prior to initiating paliperidone palmitate to establish tolerability.<sup>11</sup> No oral supplementation is required once paliperidone palmitate is commenced.<sup>18</sup>

### Dose on Initiation

150mg on day 1 into the deltoid muscle  
100mg on day 8 into the deltoid muscle

The recommended dose of paliperidone palmitate on initiation is 150mg on day 1 and 100mg one week later (day 8), both administered into the deltoid muscle.<sup>11</sup> A subsequent monthly dose of 75mg (day 36) is then recommended, which can be increased or decreased in the range of 25-150mg monthly, based on tolerability and efficacy.<sup>11</sup>

This two-dose initiation regimen is used to achieve steady state concentrations at the start of treatment that are similar to those achieved from a monthly maintenance dose of paliperidone palmitate 75mg, or 6mg oral paliperidone.<sup>14</sup> It is to be used when initiating treatment for acutely symptomatic patients and those who are clinically stable, and avoids the need for oral supplementation.<sup>14</sup>

This need to achieve an adequate steady state concentration early in treatment is also the reason the first two doses are given in the deltoid muscle. Deltoid injection provides a peak concentration earlier in therapy compared to gluteal administration.<sup>14</sup>

### Maintenance dosing

25-150mg every 4 weeks into the deltoid or gluteal muscle

After treatment initiation, the recommended dose of paliperidone palmitate is 75mg (range 25-150mg) every four weeks, commencing on day 36. These injections can be given in the deltoid or gluteal muscle.<sup>14</sup>

The equivalent doses between paliperidone palmitate and oral paliperidone<sup>13</sup> are listed in Table 1.

### Switching to paliperidone palmitate

When switching from an oral antipsychotic, ensure the patient has had an oral test dose of risperidone or paliperidone before commencing. No oral antipsychotic supplementation is required once paliperidone palmitate is commenced.<sup>11, 14</sup>

If switching from another long-acting (depot) injection, administer paliperidone palmitate on the

next scheduled date of the previous injection and then every month thereafter.<sup>14</sup> There is no need for the initial dosing regimen in this case.<sup>14</sup>

Table 1: Equivalent paliperidone doses

Paliperidone palmitate dose	Oral daily paliperidone dose	Risperidone long-acting injection
50mg	3mg	25mg
75mg	6mg	37.5mg
100mg	9mg	50mg

### Missed doses

During the initiation phase, there is a flexible dosing window of  $\pm 2$  days for the timing of the second injection on day 8 (i.e. it can be administered on days 6-10).<sup>14</sup>

During the monthly maintenance period, the dose can be administered within 7 days of the scheduled injection without disrupting the treatment schedule.<sup>14</sup> This does not imply that a 3- or 5-week dosing interval can be used, rather there is a  $\pm 7$  day window for administration without significantly impacting on treatment outcome.<sup>14</sup>

## Adverse effects

Common adverse effects of paliperidone palmitate include insomnia, anxiety, headache, weight increase, and tachycardia.<sup>13, 14</sup>

## Conclusion

Current evidence indicates that paliperidone palmitate does not provide superior antipsychotic efficacy compared to other long-acting injectable antipsychotics, however the dosage form and administration do offer benefits.

The advantages of this formulation are that it is a once-monthly injections for all doses, requires no reconstitution or refrigeration, no oral antipsychotic supplementation, has some flexibility with missed doses and a smaller injection volume compared to other LAI antipsychotics.

Sertindole and Paliperidone were written by Katie Walker, Ziprasidone was written by Suret Nel.

This Drug Bulletin was reviewed by the Graylands Pharmacy Department and Dr Haroon Riaz

References available on request

Comments are welcome at the email address:  
DrugInformation.Graylands@health.wa.gov.au