Graylands Hospital

DRUG BULLETIN

Pharmacy Department 56 Mooro Drive Mount Claremont WA 6010
Telephone (08) 9347 6681 Email GHPharmacy@health.wa.gov.au Fax (08) 9384 4586

Profile of Amisulpride

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Amisulpride (Solian®) will become the latest addition to the range of atypical antipsychotics available in Australia, though it has been available in parts of Europe since the late 1980s. It belongs to the benzamide class and will be available on the PBS for the treatment of schizophrenia from 1st August 2002.

Pharmacology

Although it shares clinical properties that characterise other atypical agents eg. decreased incidence of extrapyramidal symptoms (EPS), amisulpride is unusual in that it lacks the combined antagonism of $5HT_2/D_2$ receptors which usually defines "atypicality".

At **low doses**, amisulpride enhances dopaminergic neurotransmission by preferentially blocking *pre*-synaptic D_2/D_3 dopamine receptors. This may explain its efficacy in the treatment of negative symptoms in schizophrenia.

At **higher doses**, amisulpride antagonises *post*-synaptic D_2/D_3 dopamine receptors, reducing dopaminergic transmission, which may explain its efficacy against the positive symptoms of schizophrenia.

Amisulpride has little affinity for other dopamine receptor subtypes or other neurotransmitter receptors such as serotonin, α-adrenergic, histamine and muscarinic. It is selective for dopamine receptors in the limbic system rather than the striatum, which should reduce its tendency to produce EPS.

Pharmacokinetics

Absorption

Amisulpride is absorbed rapidly, within 3-4 hours of oral administration.

Metabolism

Amisulpride undergoes minimal metabolism to form two metabolites (both inactive). Hepatic metabolism plays a limited role in healthy patients.

Excretion

Excretion is primarily via urine (mainly as unchanged drug). The elimination half-life is approximately 12 hours. Plasma protein binding is low, therefore drug interactions due to displacement are unlikely.

Efficacy

Recent reviews have concluded that amisulpride (400 to 1200mg/day) was as effective as haloperidol (5 to 40mg/day), flupenthixol (25mg/day) and risperidone (8mg/day) in patients with acute exacerbations of schizophrenia with predominantly positive symptoms [1,2]. Amisulpride was found to be more effective than haloperidol but equally as effective as risperidone in controlling negative symptoms.

In patients with predominantly persistent negative symptoms, low dosages of amisulpride (50 to 300mg/day) significantly reduced negative symptoms compared to placebo.

Amisulpride has been shown to be efficacious in long-term studies where it has been used as maintenance therapy in patients with chronic schizophrenia with

mixed symptoms. Long-term use was also associated with improvements in measures of quality of life and social functioning.

Contraindications
These include prolactin-dependant tumours, phaeochromocytoma and use in combination with medications that may induce torsade de pointes – see drug interactions.

Precautions
Amisulpride shares similar warnings with other atypical antipsychotics regarding the rare events of neuroleptic malignant syndrome, seizures and the need for caution in the elderly and Parkinson's disease.
In renal impairment, use a decreased dose and consider intermittent treatment in severe cases.
Use with caution in patients with moderate or severe hepatic impairment – limited data.

Pregnancy and Lactation
Pregnancy Category B3 – Contraindicated.

Adverse effects
Similarly to risperidone, amisulpride appears to be linked with dose-related EPS and hyperprolactinemia. Unlike other atypicals however, sedation and hypotension do not prominently feature in its side-effect profile.

Other commonly reported adverse events in clinical trials included insomnia, anxiety, agitation and weight gain. Cases of QT prolongation have been reported (dose dependant) and very rarely (<0.01%) torsade de pointes.

No reference is made in the product information to possible disturbances in glucose metabolism. During the period January 1997 to January 2002, the manufacturers received only 3 reports of this nature worldwide (Personal communication, Sanofi-Synthelabo).

Dosage and administration
The recommended dose varies according to which symptoms predominate.

Acute positive symptoms: 400-800mg/day (two divided doses). May be increased to 1200mg/day in individual cases (no superior efficacy proven).

Predominantly negative symptoms: 50-300mg/day given once daily.

Mixed positive and negative symptoms: adjust dose to obtain optimal control of positive symptoms.

Amisulpride has been available in France to treat schizophrenia since 1986, where a group of clinicians have produced a dosage algorithm [3] (see Figure 1 below). This suggests management strategies according to symptoms and treatment setting.

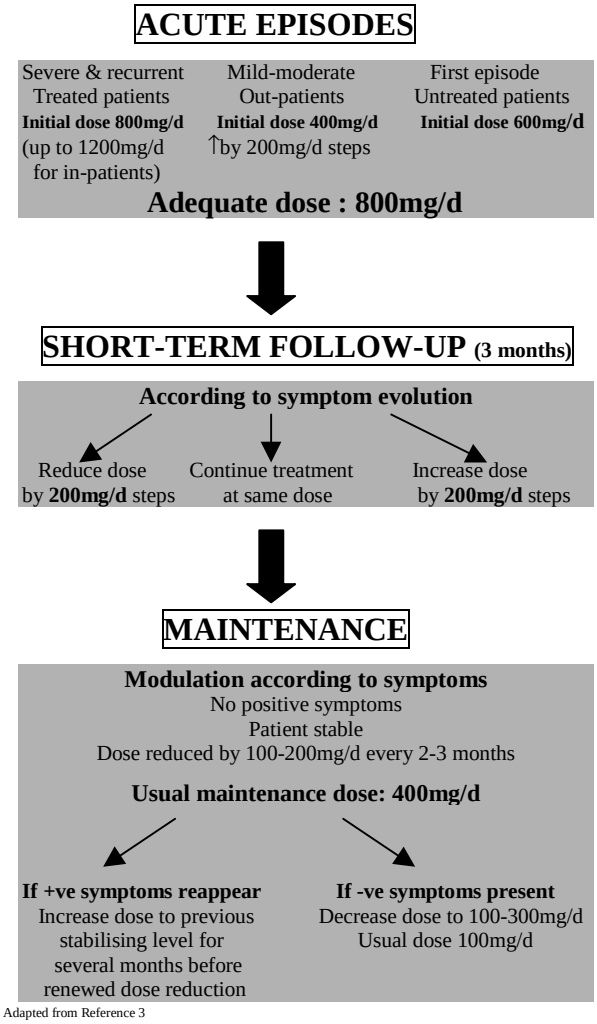
Due to its lack of sedative properties, it may be appropriate in the initial stages to use a benzodiazepine or sedative antipsychotic to help control the symptoms of a very disturbed or aggressive patient.

No specific titration is required for initiation of therapy; adjust dosage to individual response. Where the dose is above or equal to 400mg, administer twice daily. Preferably give the dose before meals.

Renal impairment Dosage reduction will be required in this patient group.

Hepatic impairment Dosage reduction should not be necessary as the drug is weakly metabolised.

Figure 1: Amisulpride dosage algorithm (based on extensive use in France).



Adapted from Reference 3

Switching to amisulpride
Taper down existing antipsychotic and during this period, begin amisulpride at the therapeutic dose required; no titration is necessary. Overlapping periods of 1-4 weeks have been described depending on the patient's clinical state.

Drug Interactions
Interactions via the CYP450 system are unlikely as amisulpride is not significantly metabolised by the liver.

The potential for increased risk of ventricular arrhythmias must be borne in mind. Use with Class IA and III antiarrhythmic agents eg. flecainide and amiodarone respectively, is **contraindicated**. Caution is required in the concomitant use of drugs that may induce bradycardia or hypokalemia or other drugs known to prolong the QT interval, such as thioridazine and droperidol.

Caution is advised when used with other renally cleared drugs eg. lithium, which may interfere with clearance of amisulpride. However, a study of the concomitant use of lithium carbonate (500mg twice daily) with low dose amisulpride (100mg twice daily) in healthy young males, showed no effect of amisulpride on the pharmacokinetics of lithium.

The effects of CNS depressants eg. benzodiazepines, narcotics and alcohol may be enhanced by amisulpride. Concomitant use with levodopa is not recommended due to reciprocal antagonism of effects.

Conclusion – place in therapy
Amisulpride appears to offer no significant benefit over the existing atypical agents. It may be associated with the least weight gain of the atypicals [(4)] and has less potential for interaction with other drugs, due to its lack of hepatic metabolism.

Further trials are needed comparing it with the other atypical agents. Comparative data with olanzapine should be available later this year.

Presentation
Manufacturer: Sanofi-Synthelabo
Brand name: Solian
Available in following tablet strengths: 100mg, 200mg and 400mg (all breakable).

References
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Serotonin syndrome – recognising the signs

Serotonin syndrome (SS) is a condition caused by drug-induced serotonin hyperstimulation. It is difficult to diagnose, usually mild and as a result may go largely unreported. SS may occur with co-administration of drugs or lack of adequate washout period when switching drugs. This increases synaptic serotonin concentration causing hyperstimulation of mainly $5HT_{1A}$ receptors (other serotonin receptors may be involved). See Table 1 for examples of drugs that may contribute to the development of this syndrome.

Possible causes of serotonin syndrome
- inhibition of serotonin re-uptake eg. antidepressants (particularly the SSRIs), sumatriptan and related agents, tramadol, some MAOIs
- concomitant use of agents that promote the release of serotonin from presynaptic neurons eg. amphetamines
- pharmacokinetic interactions eg. CYP2D6 inhibition of tricyclic antidepressant (TCA) metabolism by agents such as paroxetine, bupropion, leading to increased TCA plasma levels
- inhibition of serotonin metabolism eg. cocaine
- stimulation of postsynaptic serotonin receptors eg. lithium

Less often, SS results from the use or overdose of a single serotonergic agent. Many patients can take two, possibly even more, serotonergic drugs together without problems while a very small number of cases can be severe and result in death. This suggests other factors not yet identified may play a role.

Table 1: Examples of drugs that may contribute to development of SS (i.e. serotonergic)

All antidepressants	Lithium
Amphetamines	Naratriptan
Buspirone	Pentazocine
Carbamazepine	Phentermine
Cocaine	Selegiline
Dextromethorphan (in OTC cough preps)	St John's Wort
Diethylpropion	Sumatriptan
Ergot derivatives (in migraine preps)	Tramadol
Fentanyl	Tryptophan
Illicit drugs (eg. MDMA, LSD)	Zolmitriptan

Clinical features of serotonin syndrome

The clinical features of SS fall into three main areas as follows; altered mental status, autonomic dysfunction and neuromuscular abnormalities. Typical symptoms are shown below.

Mental state changes eg. confusion
Hypomania
Agitation
Myoclonus
Hyperreflexia
Sweating
Shivering
Tremor
Diarrhoea
Lack of co-ordination
Fever

Sternbach's criteria are most commonly cited for diagnosis of SS. He suggested that at least **three** of the above symptoms must be experienced in order for the reaction to be classified as SS. In contrast to neuroleptic malignant syndrome (NMS), with which it shares many features, SS peaks and later resolves over a period of hours rather than days. Symptoms include myoclonus and hyperreflexia in contrast to "lead-pipe" rigidity seen in NMS.

Other potential causes, such as infection, substance abuse or concurrent antipsychotic dose changes prior to symptom onset, must be ruled out.

Onset of SS symptoms

Onset can occur as early as an hour after single or multiple drug overdose or the addition of another serotonergic agent to current therapy and as long as several days after increasing the dose of one or more agents. Effects may last from 6 to 48 hours, depending on severity.

Treatment

Drugs with serotonergic activity should be discontinued. Most cases are mild and resolve quickly with supportive symptom management.

Chlorpromazine and cyproheptadine have been used successfully to treat SS.

Summary

Antidepressant combinations are increasingly being used by clinicians to treat depression. This strategy is not recommended and should only be undertaken with extreme caution and when other treatment options have failed.

The most common drug combinations thought to be the cause of SS are MAOIs/SSRIs, MAOIs/TCAs and MAOIs/pethidine. Although the incidence of SS may be low, serotonergic drug combinations should be avoided where possible due to rare reports of fatalities and severe complications such as hyperthermia, rhabdomyolysis and kidney/liver failure.

Caution should be used when starting serotonergic agents following cessation of similar agents with long elimination half-lives, such as fluoxetine.

Swapping or cross-tapering of antidepressants should be undertaken with care. In general, antidepressants should not be used in combination with MAOIs or within two weeks of stopping phenelzine or tranylcypromine.

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