NEW DRUGS

Safinamide

Aust Prescr 2019;42:78–9
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Approved indication: Parkinson's disease

Xadago (Seqirus)
50 mg and 100 mg tablets
Australian Medicines Handbook section 16.2.3, Monoamine oxidase type B inhibitors

In idiopathic Parkinson's disease there is a deficiency of dopamine. Treatment therefore involves taking levodopa, a dopamine agonist or both. Usually levodopa is formulated with a dopa decarboxylase inhibitor to reduce peripheral dopaminergic adverse effects. As the disease progresses, long-term use of levodopa is associated with its effect wearing off between doses. To manage the resultant motor fluctuations, additional therapy may be considered. The options include inhibitors of monoamine oxidase type B. Inhibiting this enzyme reduces dopamine metabolism and so increases dopamine concentrations in the brain.

Safinamide is a selective, reversible monoamine oxidase type B inhibitor. It also inhibits the release of glutamate, a substance which may have a role in the motor fluctuations. The drug is well absorbed and has a half-life of 20–30 hours. It is suitable for once-daily dosing with or without food. Most of the dose is metabolised with the metabolites being mainly excreted in the urine. Lower doses are recommended for patients with moderate liver impairment, but safinamide is contraindicated in severe impairment.

The main clinical trials of safinamide have studied patients who were having motor fluctuations despite treatment with levodopa. One trial randomised 549 patients to add safinamide (target dose 100 mg daily) or a placebo to their treatment. The primary outcome was the change in the duration of the relief from motor symptoms ('on time') without troublesome dyskinesia. At the start of the study the daily on time was 9.3 hours in the safinamide group and 9.06 hours in the placebo group. After 24 weeks the on time increased by 1.42 hours with safinamide and 0.57 hours with placebo. Based on a clinical global impression, 57.7% of the patients taking safinamide improved compared with 41.8% of those taking a placebo.[1]

Another placebo-controlled trial randomised 669 patients to take safinamide 50 mg or 100 mg daily for 24 weeks. From a baseline of approximately 9.4 hours, the on time, without troublesome dyskinesia, increased by 1.37 hours with safinamide 50 mg and by 1.36 hours with 100 mg. The increase in the placebo group was 0.97 hours. The respective proportions of patients judged to have a clinical global improvement were 66.4%, 64.3% and 55.4%.[2] Patients who completed this trial could continue in an extension study.

There were 544 patients in the extension study. They continued in their original randomised groups for up to two years. The primary outcome was the change in the Dyskinesia Rating Scale from baseline to 24 months. This improved by 31% in patients taking safinamide 50 mg and by 27% in those taking 100 mg. There was only a 3% change in the placebo group. At the end of the study the on time without dyskinesia had increased by 1.01 hours with 50 mg, 1.18 hours with 100 mg and by 0.34 hours with placebo.[3]

Drugs that increase concentrations of dopamine can be expected to have adverse effects such as insomnia and altered blood pressure. In the clinical trials of safinamide the most frequent adverse events were dyskinesia, falls, nausea and insomnia. In the two-year study 6.7% of the patients stopped taking 100 mg safinamide because of adverse events. The withdrawal rate with 50 mg was similar to that of placebo (5.3 vs 5.7%).[3]

Although safinamide is selective for monoamine oxidase type B and dietary tyramine restrictions are not required, these are potentially serious drug interactions. Co-administration with pethidine is contraindicated and there is a risk of serotonin syndrome with other opioids and antidepressants. If the patient has been taking a serotonergic drug, a washout of at least five times the half-life is recommended before starting safinamide. To avoid potential interactions, doses of drugs such as ciprofloxacin, diclofenac and pravastatin should be separated from doses of safinamide by at least five hours.

Retinal degeneration was reported in some animal studies. Safinamide is therefore contraindicated in patients with conditions such as uveitis and retinopathy.

Safinamide adds another monoamine oxidase B inhibitor for managing fluctuating idiopathic Parkinson's disease. It increases on time more than a placebo does. Whether it has any advantage over other monoamine oxidase type B inhibitors is unknown. The longer-term effectiveness of safinamide also requires further scrutiny. During the two-year study the reduction in dyskinesia was greater than with placebo but was not statistically significant.[3] In a 12–month extension of a trial studying safinamide in early-stage Parkinson's disease, there was no difference from placebo in delaying the need to intensify treatment.[4] Whether these observations reflect declining efficacy or the progression of the disease is unclear.

T T manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True 2 False

Correction

The hot patient: acute drug-induced hyperthermia [Correction]

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A formatting error in the article by Nazila Jamshidi and Andrew Dawson has been corrected. View corrected article.

The diaphoresis row in Table 3 (Clinical features of neuroleptic malignant syndrome, serotonin toxicity, anticholinergic syndrome and sympathomimetic syndrome) was incorrect. Diaphoresis in serotonin toxicity is moderate (not severe), it is not a feature of anticholinergic toxicity (not moderate), and it is moderate (not severe) in sympathomimetic syndrome.

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