Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Risperidone and risk of cerebrovascular adverse events in dementia patients

Health professionals are advised that the Product Information for risperidone has been updated to limit the indication in dementia and restrict this use to short-term management.

Previously, risperidone was indicated more generally for the treatment of behavioural disturbances in dementia, but it is now limited to treatment (up to 12 weeks) of moderate to severe dementia only of the Alzheimer type.

Risperidone is an atypical antipsychotic drug belonging to the benzisoxazole-derivative class. It is a selective monoaminergic antagonist with high affinity for serotoninergic 5-hydroxytryptamine2, dopaminergic D2 and alpha1-adrenergic receptors.

The updated indications for risperidone are:

- treatment of schizophrenia and related psychoses
- short-term treatment of acute mania associated with bipolar 1 disorder
- treatment (up to 12 weeks) of psychotic symptoms, or persistent agitation or aggression unresponsive to non-pharmacological approaches in patients with moderate to severe dementia of the Alzheimer type
- treatment of conduct and other disruptive behaviour disorders in children (over five years of age), adolescents and adults with sub-average intellectual functioning or mental retardation in whom destructive behaviours (for example, aggression, impulsivity and self-injurious behaviours) are prominent
- treatment of behavioural disorders associated with autism in children and adolescents.

Clinical studies

Results from controlled clinical studies that were submitted to the TGA by the sponsor, Janssen-Cilag, found an increased risk of cerebrovascular adverse events for patients being treated with risperidone for vascular or mixed dementia, compared with those taking it for Alzheimer's dementia.

The odds ratio for any cerebrovascular adverse event in patients with vascular or mixed dementia taking risperidone was 5.26 (95% confidence interval [CI] 1.18-48.11). The comparative odds ratio for Alzheimer's dementia patients was 2.23 (95% CI 0.85-6.88).

Product Information changes

The risk of cerebrovascular adverse events is reflected in the Product Information (PI) for all atypical antipsychotics, but risperidone is the only such drug that includes an indication for use in patients with dementia.

To address this increased risk in patients with non-Alzheimer type dementia, Janssen-Cilag recently updated the risperidone PI to remove the implicit indication for use in patients with vascular or mixed dementia.

Furthermore, the PI update includes a stipulation that the duration of risperidone treatment for this indication should not exceed 12 weeks, and that it should be used to treat persistent agitation or aggression only if the symptoms are unresponsive to non-pharmacological approaches.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

Use of risperidone to treat patients with Alzheimer's dementia should be based on each patient's individual circumstances, with risks considered in relation to the benefits.

Adverse event reports

From 1993 to 18 May 2015, the TGA had received 17 reports of cerebrovascular adverse events in patients being treated with risperidone.

In nine of those cases, the indication was dementia or behavioural management related to dementia, while two others related to treatment of primary psychotic conditions. In the remaining six cases, the indication was not reported to the TGA.

Of the nine cases relating to treatment of dementia, one report stated the diagnosis as Alzheimer's disease, while another referred to fronto-temporal dementia. Otherwise, the type of dementia was not specified.

Infliximab and non-melanoma skin cancers, particularly in psoriasis patients

The Product Information for infliximab has been updated to provide further information about the risk of skin cancers, particularly in psoriasis patients who have undergone phototherapy.

Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα).

It is marketed in Australia under the brand name Remicade and is indicated for treatment of rheumatoid arthritis in adults, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, refractory fistulising Crohn's disease and ulcerative colitis.

When used for treating rheumatoid arthritis in adults, infliximab is used in combination with methotrexate.

Product Information update

Following a TGA review of Australian and international adverse event data for non-melanoma skin cancers (NMSCs) in patients prescribed infliximab, the Product Information (PI) for infliximab was updated in September 2014.

The changes included updating the 'Precautions' section to include the statement 'Psoriasis patients should be monitored for NMSCs, particularly those patients who have had prior prolonged phototherapy treatment.'

In addition, basal cell carcinoma and squamous cell carcinoma were added to the 'Adverse events' section with the frequency listed as unknown.

Before being updated, the PI contained references to the risks of melanoma (frequency 'rare') and Merkel cell carcinoma (frequency 'very rare'), but not NMSCs.

TNFα inhibitors are a known risk for melanoma and NMSCs when used for the treatment of psoriasis in patients who have undergone previous phototherapy.

Information for health professionals

Skin cancers can be associated with both morbidity and mortality.

Australia has among the highest incidence rates of skin cancers in the world.

Many patients treated with infliximab have been exposed to other immunosuppressive agents.

Immunosuppressive treatments have the potential to impair the immune system, thus leading to an increased risk of skin cancer.[1]

Prescribers are reminded to monitor patients who have been prescribed infliximab for any new or changed skin lesions and ensure patients with any suspicious lesions undergo further investigation.

REFERENCE

1. Khan I, Rahman L, McKenna DB (2009). Primary cutaneous melanoma: a complication of infliximab treatment? Clinical and Experimental Dermatology 34: 524–526.

Medicines shortages information

The Medicine Shortages Information Initiative provides information about a temporary or permanent disruption to the supply of a prescription medicine. Health professionals and consumers are invited to subscribe to the Medicine Shortages email list to receive an alert when there is new or updated medicine shortage information reported to the TGA.

Tramadol oral drops – not for children under the age of 12 years

Health professionals are reminded that tramadol oral drops are not approved for use in children under the age of 12 years and no dosing instructions are provided for this age group in the Product Information.

Safety and efficacy in children have not been established.

The TGA has reviewed this issue following the death of a two-year-old Australian child as a result of tramadol toxicity following treatment with tramadol oral drops.

Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects.

There are 82 tramadol products registered on the Australian Register of Therapeutic Goods, but only one of these – Tramal – has an oral drop presentation.

Information for health professionals

Tramadol oral drops are safe and appropriate for use in adult and adolescent patients for whom the medicine is approved. However, given the concentration of the drops (100 mg/mL), there is a potential risk of overdose in children.

The dosing recommendations in the Product Information for tramadol oral drops are only valid for adults and adolescents over the age of 12 years.

Use of tramadol oral drops in children under the age of 12 years is off-label.

This medicine should only be prescribed for patients in the approved age group.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to 02 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Pharmacovigilance and Special Product Access Branch on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Pharmacovigilance and Special Product Access Branch at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Pharmacovigilance and Special Product Access Branch

Editor:
Dr Katherine Gray

Deputy Editor:
Mr Michael Pittman

Acting TGA Principal Medical Adviser:
Dr Tony Gill

Contributors include:
Dr Claire Behm
Dr Pam Whalan
Dr Margaret Wilson