Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

Volume 5, Number 3, June 2014

In this issue

Bexsero meningococcal B vaccine – enhanced monitoring

The TGA has been undertaking enhanced monitoring of the recently launched meningococcal B vaccine, Bexsero.

Bexsero is the first vaccine in Australia intended to prevent invasive meningococcal disease caused by strains of *Neisseria meningitidis* serogroup B (meningococcal B).

Bexsero is indicated for immunisation of patients aged two months and older. For infants aged under six months, three primary doses of Bexsero, plus a booster at 12 months of age, are recommended. Fewer doses are required for older age groups.

According to the National Notifiable Diseases Surveillance System, the majority of invasive meningococcal disease in Australia is caused by group B (84% in 2011–12). The highest incidence of group B disease occurs in children aged under five years, particularly infants aged under 12 months. A lower, secondary peak in incidence has been observed in late adolescence and early adulthood.

As with many other vaccines, patients may experience a rise in temperature following vaccination with Bexsero.

Pre-market evaluation

During pre-market evaluation of Bexsero, the TGA identified that use of the vaccine commonly induced fever in infants and children, including high fever, which is a risk factor for inducing a seizure.

When fever occurred, it generally followed a predictable pattern starting within six hours after vaccination. In the majority of cases, the fever had ceased by the next day.

Information for health professionals

The Australian Technical Advisory Group on Immunisation has recommended the prophylactic use of paracetamol for children aged under two years to reduce the probability and severity of fever.

It is recommended that the first dose of paracetamol (15 mg/kg per dose) be given within the 30-minute period before vaccination or as soon as practicable afterwards. This can be followed by two more doses given six hours apart.

Control of fever alone may not necessarily prevent the development of a seizure.

If you haven't done so already, read the Product Information for Bexsero. Further information is also available in the Australian Technical Advisory Group on Immunisation statement, which is available on the Department of Health's Immunise Australia Program website.

To help the TGA monitor the ongoing safety and risk profile for Bexsero, you are encouraged to report any seizures with a suspected link to the administration of this vaccine, including:

- both febrile and afebrile seizures
- whether Bexsero was administered singly or in combination with other vaccines
- whether an accompanying anti-fever medicine, such as paracetamol, was used or not.

The TGA is regularly reviewing all adverse event reports associated with Bexsero, as well as all other relevant safety information.

For clinical advice about the use of Bexsero, visit the Immunise Australia website.

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TGA Health Safety Regula

MEDICINES SAFETY UPDATE

Strontium ranelate and cardiovascular and venous thromboembolic risks

The Product Information for strontium ranelate has been updated following the completion of a TGA review into the medicine's benefit–risk profile.

Strontium ranelate is used to treat severe osteoporosis in postmenopausal women who are at high risk of fracture and men who are at increased risk of fracture. It is marketed in Australia under the brand name Protos.

The Product Information (PI) changes include an update to the indications requiring that strontium ranelate only be used if all other treatments are deemed unsuitable, either due to contraindications or intolerance. Other changes emphasise the contraindications, reinforce precautions, highlight the need for regular monitoring and update data relating to the risk of adverse events.

A black box warning has also been added to the PI, which summarises the changes.

Black box warning in strontium ranelate Product Information

Protos should only be used when other medications for the treatment for osteoporosis are considered unsuitable. Protos is contraindicated and must not be used in patients with established, current or past history of: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism, pulmonary embolism. It should also not be used in patients who are temporarily or permanently immobilised. Protos should be used with caution in patients with risk factors for cardiovascular events or venous thrombosis: hypertension, diabetes, smoking, hyperlipidaemia. All patients prescribed Protos should be fully informed of the risk of cardiovascular events and venous thrombosis. Patients should be regularly monitored, every six months.

Safety data

Data from randomised controlled trials show that strontium ranelate is associated with an increased risk of myocardial infarction and venous thromboembolism.

In pooled randomised placebo-controlled studies of postmenopausal osteoporotic patients, a significant increase of myocardial infarction was observed in patients treated with strontium ranelate as compared to placebo (5.7 per 1000 patient-years vs 3.6 per 1000 patient-years), with a relative risk of 1.6 (95% CI 1.07–2.38).

In phase III studies, venous thromboembolism occurred in 2.7% of patients in the strontium ranelate group and 1.9% of those in the placebo group, with a relative risk of 1.4 (95% CI 1.0–2.0).

Information for health professionals

Health professionals are encouraged to read the updated PI and advise patients of the potential cardiovascular and venous thromboembolic adverse events associated with strontium ranelate.

In particular, note that strontium ranelate should only be used if all alternative treatments are considered unsuitable.

Strontium ranelate is contraindicated in patients who have:

- history of ischaemic heart disease, peripheral arterial disease or cerebrovascular disease
- systolic blood pressure greater than or equal to 160 mmHg, or diastolic blood pressure greater than or equal to 90 mmHg
- current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism
- temporary or permanent immobilisation (for example, post-surgical recovery or prolonged bed rest)
- severe renal impairment
- known hypersensitivity to strontium ranelate or to any of the excipients.

Treatment should be stopped if the patient develops any of these conditions after being prescribed this drug.

If the patient becomes immobilised, treatment can be resumed if the event or illness causing the immobilisation is resolved and mobility returns.

Patients should be evaluated for relevant risk factors, including hypertension, diabetes, smoking, hyperlipidaemia, before being treated with strontium ranelate. Patients receiving ongoing treatment with strontium ranelate should be monitored every six months.

You are encouraged to report to the TGA any suspected adverse events associated with strontium ranelate. This will assist the TGA to monitor the safety of this drug.

MEDICINES SAFETY UPDATE

Complex regional pain syndrome and vaccines

A small number of cases of complex regional pain syndrome following vaccination have been reported to the TGA. Health professionals are advised to be mindful of the potential for this adverse event when administering vaccinations and are encouraged to report any suspected cases to the TGA.

Complex regional pain syndrome (CRPS) is characterised by continuing pain that is disproportionate to any potential inciting event, when accompanied by sensory, motor, vasomotor and sweating/oedema signs and symptoms.[1]

There are two forms of CRPS, type 1 (CRPS-I) and type 2 (CRPS-II). CRPS-I is more common and describes a situation in which the patient does not have demonstrable nerve injury. CRPS-II tends to be more serious and describes a situation in which the patient has confirmed nerve injury.

While the cause of CRPS is unknown, it has been diagnosed after trauma, infection, surgery, cervical radiculopathy and myocardial infarction, as well as following vaccination.

The TGA has received five adverse event reports following vaccinations that are consistent with CRPS. Three of those cases involved a human papillomavirus vaccine. Of the other two reports, one involved an influenza vaccine and the other related to diphtheria-tetanus-acellular pertussis vaccination. Some other reports that listed CRPS as an adverse event did not meet the diagnostic criteria.

As part of a recent review of CRPS following vaccination, the TGA referred the issue to its Advisory Committee on the Safety of Vaccines for consideration.

The Committee noted that cases of CRPS were hard to capture, as there was a large variation in causes, but advised that CRPS following vaccination would have been triggered by the pain caused by the process of immunisation, rather than the contents of the vaccine itself.

Three cases of CRPS involving human papillomavirus vaccine in Australia were examined in an article in 2012, which found that:

> intramuscular immunisation is sufficient painful stimulus to trigger the development of CRPS-I, and that it is the process of a needle penetrating the skin that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related.[2]

Given that all vaccines had the ability to cause some degree of trauma, the Advisory Committee on the Safety of Vaccines deemed CRPS following vaccination was under-reported in Australia.

Following consideration of Australian and international data, the TGA review has concluded that CRPS following vaccination with any vaccine is a very rare event. However, there may be under-diagnosis and/or under-reporting of this adverse event in Australia.

The TGA will continue to monitor this issue.

Information for health professionals

Health professionals should be aware of the potential for CRPS following vaccination with any vaccine.

While the TGA concluded that this issue is very rare, you are encouraged to report any suspected cases of CRPS following vaccination. This will assist the TGA in monitoring the safety of vaccines.

REFERENCES

1. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326-31.
2. Richards S, Chalkiadis G, Lakshman R, Buttery JP, Crawford NW. Complex regional pain syndrome following immunisation. Arch Dis Child 2012;97:913-5.

MEDICINES SAFETY UPDATE

Azathioprine and cytomegalovirus reactivation

Information about the risk of cytomegalovirus reactivation in patients with inflammatory bowel disease has been added to the Product Information for azathioprine.

Azathioprine is used as an immunosuppressant antimetabolite. It can be used alone or in combination with corticosteroids and/or other immunosuppressive drugs and procedures.

Cytomegalovirus (CMV) is a common viral infection that normally remains dormant until reactivated when T-lymphocyte mediated immunity is compromised. CMV viraemia can lead to secondary haemophagocytic syndrome.

The Product Information (PI) update is the result of a TGA review of two cases of CMV reactivation associated with oral use of azathioprine.[1] The precautions section of the PI now advises that CMV viraemia resulting in severe pneumonitis and haemophagocytic syndrome in patients with inflammatory bowel disease has been reported in the literature. It recommends that caution be exercised and specialist literature consulted when assessing the risk of CMV reactivation and inflammatory bowel disease deterioration.

Four cases of CMV reactivation and/or haemophagocytic syndrome associated with azathioprine have been reported to the TGA since 1992.

REFERENCE

1. Van Langenberg DR, Morrison G, Foley A, Buttigieg RJ, Gibson PR. Cytomegalovirus disease, haemophagocytic syndrome, immunosuppression in patients with IBD: 'a cocktail best avoided, not stirred'. J Crohns Colitis 2011;5:469-72.

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 and with the October issue of *Australian Prescriber*
- **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 Office of Product Review on 1800 044 114.

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