Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update Volume 2, Number 3, June 2011

Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/hp/msu.htm

In this issue:

Risk of hypomagnesaemia with proton pump inhibitors

Summary

A recent international safety advisory has warned of a potential association between prolonged use of proton pump inhibitors (PPIs) and serious hypomagnesaemia-related adverse events such as tetany, seizures, delirium and cardiac arrhythmias. While this occurs rarely, prescribers should be vigilant to PPI-associated hypomagnesaemia. Patients presenting with hypomagnesaemia may require PPI discontinuation.

Proton pump inhibitors (PPIs) are among the most widely used classes of drugs in Australia, with more than 130 million Pharmaceutical Benefits Scheme prescriptions dispensed since 1992.

Suspected PPI-induced hypomagnesaemic hypoparathyroidism was first reported in the literature in 2006, based on two cases identified in Australia.[1] To March 2011, the TGA had received 2545 reports of suspected adverse reactions to PPIs, six (0.2%) of which were reports of hypomagnesaemia. In five cases, the PPI was the only suspected medication and serum magnesium levels returned to normal after the PPI was discontinued. In two of these cases a subsequent fall in serum magnesium levels was reported after an alternative PPI was prescribed. The underlying mechanism is unclear; however, extrarenal magnesium wasting by impaired intestinal magnesium transport or intestinal loss has been proposed.[2]

The presentation of patients with mild-to-moderate hypomagnesaemia may be asymptomatic or non-specific. Patients with severe hypomagnesaemia often have coexistent hypokalaemia and hypocalcaemia, which can contribute to potentially life-threatening sequelae such as tetany, seizures and cardiac arrhythmias, and may not be easily corrected without magnesium supplementation. For several of the cases reported in the literature, magnesium supplementation was only partially effective at correcting the hypomagnesaemia while PPIs were continued.[3] For further information on magnesium homeostasis and abnormalities, see the overview in *Australian Prescriber*.[4]

While most of the TGA reports and those analysed recently by the US Food and Drug Administration occurred in patients who had been taking a PPI for longer than one year,[5] there is no way to reliably predict those who may be at higher risk. Other medications (e.g. loop and thiazide diuretics) may cause or worsen hypomagnesaemia. Prescribers should be vigilant to the potential risk of hypomagnesaemia in patients requiring long-term PPI treatment. Patients developing hypomagnesaemia may require PPI discontinuation.

References

1. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med 2006;355:1834-6.
2. Cundy T, Mackay J. Proton pump inhibitors and severe hypomagnesaemia. Curr Opin Gastroenterol 2011;27:180-5.
3. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. Q J Med 2010;103:387-95.
4. Wu J, Carter A. Abnormal laboratory results. Magnesium: the forgotten electrolyte. Aust Prescr 2007;30:102-5.
5. United States Food and Drug Administration. FDA drug safety communication: low magnesium levels can be associated with long-term use of proton pump inhibitor drugs. Silver Spring, MD: FDA; 2011 Mar 2. www.fda.gov/Drugs/DrugSafety/ucm245011.htm [cited 2011 May 4]

Use of 2011 seasonal influenza vaccines in children

Summary

The 2011 seasonal influenza vaccines vary in their approved indications and recommendations for use in children. These variations relate to the availability of Australian safety information for the vaccines and the ability of sponsors to meet requirements for active surveillance of children. The TGA requests that consumers and healthcare professionals report all adverse events associated with influenza vaccination in patients of any age and any instances of inadvertent administration to a child of a vaccine not currently recommended for use in children, regardless of whether the child has a reaction.

During the 2010 influenza season an excess number of cases of febrile reactions and febrile convulsions was observed in paediatric populations following immunisation with one of the registered seasonal trivalent influenza vaccines.[1] Consequently, the TGA imposed a condition on the registration of all 2011 seasonal influenza vaccines with a paediatric indication which were not supplied in Australia in 2010. Sponsors were required to undertake active surveillance of children from six months to nine years of age, to ensure effective monitoring of paediatric populations in Australia previously unexposed to these vaccines.

Two sponsors were unable to meet this condition of registration. Although the safety of Agrippal and Fluarix has been demonstrated in the Northern Hemisphere 2010–11 influenza season, the TGA does not have any safety data on the use of these vaccines in Australian children. Hence, the TGA recommends that these vaccines are not used in any child under the age of nine years.

For children under the age of nine years it is recommended that they be vaccinated with either Influvac or Vaxigrip. These two vaccines were not associated with increased rates of fever or febrile reactions in 2010.

CSL's vaccine Fluvax is not approved for use in children under the age of five years for the 2011 influenza season. Although CSL has an active surveillance system in place to actively monitor children aged 5–18 years, the Australian Technical Advisory Group on Immunisation (ATAGI) has advised that there is a strong preference for the use of either Vaxigrip or Influvac in children aged five years to less than 10 years. ATAGI advises that Fluvax may be used in children aged five years to less than 10 years when no timely alternative vaccine is available.[2]

The approved indication for each seasonal influenza vaccine and the recommendations for their use in children are found in the table below.

The TGA requests that consumers and healthcare professionals report all adverse events associated with influenza vaccination in patients of any age. Healthcare professionals are also requested to report any inadvertent administration to a child of a vaccine not currently recommended for use in children regardless of whether the child has a reaction. See 'What to report' on page 84 for further information – inadvertent administration can be reported in the same way as adverse reactions.

References

1. Therapeutic Goods Administration. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Status report as at 2 July 2010, updated 2010 Sep 24. Canberra: TGA; 2010. www.tga.gov.au/safety/alerts-medicine-seasonal-flu-100702.htm [cited 2011 May 4]
2. Australian Technical Advisory Group on Immunisation. Clinical advice for immunisation providers regarding the administration of 2011 trivalent seasonal influenza vaccines. Canberra: ATAGI; 2011. www.immunise.health.gov.au/internet/immunise/Publishing.nsf/content/immunise-atagi-vaccine-advice [cited 2011 May 4]

Vaccine	Sponsor	Approved indication	Recommendations for use in children
Fluvax	CSL	5 years +	Not approved for use in children under 5 years There is a strong preference that Vaxigrip or Influvax be used in children under the age of 10 years*
Influvac	Abbott	6 months +	Use in children aged 6 months and above
Vaxigrip	Sanofi Pasteur	6 months +	Use in children aged 6 months and above
Intanza	Sanofi Pasteur	18–59 years	Do not use (approved for adults aged 18–59 years only)
Fluarix	GSK	6 months +	Not recommended in children under the age of 9 years
Agrippal	Novartis	6 months +	Not recommended in children under the age of 9 years

* CSL has an active surveillance system in place to actively monitor children aged 5–18, however ATAGI has advised that there is a strong preference that Influvac or Vaxigrip be used in children under the age of 10 years

Investigation of Prevenar and deaths in children in Japan: what does it mean for Australia?

Summary

In response to the suspension of Prevenar and ActHIB in March 2011 in Japan due to a potential link with childhood deaths, the TGA conducted an investigation finding no safety signal for an association between Prevenar and death in Australia. As a result, the registration and recommendations for use of Prevenar are unchanged. This article describes the process used by the TGA to investigate this potential safety concern.

On 7 March 2011, Japan's Health Ministry suspended the use of two paediatric vaccines, Prevenar and ActHIB, following reports of the death of four children who had recently been immunised with these vaccines. Both Prevenar and ActHIB are registered in Australia, although ActHIB has not been supplied in this country. Prevenar, a pneumococcal conjugate vaccine (7vPCV), has been supplied under the National Immunisation Program since 2005 for children at ages 2, 4 and 6 months.

A search of the TGA's Adverse Drug Reactions Database using the terms 'Prevenar' (medicine tradename) and 'death' or 'death maybe drug' (outcome) identified five cases. For these five reports, the age at death ranged from 2 to 4 months, the dates of death from 2002 to 2010, and concomitant vaccine was administered in all cases (Infanrix and/or rotavirus vaccine).

Further information, including hospital records (discharge summary) and coroners' reports, was collected for each of these cases by contacting the initial reporter of the event. A causal association between Prevenar and the adverse event of death was determined to be unlikely for four of the five cases. These assessments were based on the length of time between vaccination and event, the detailed description of the circumstances surrounding the event, coroners' report and past medical history. For the remaining case, the initial description suggested that causality was unlikely, and we are continuing our follow-up to obtain verifying information.

Approximately 4 million doses of Prevenar (an average of 800 000 per year over five years, based on data from Medicare Australia and the Australian Childhood Immunisation Register) were given in Australia between 1 January 2005, when Prevenar was included on the National Immunisation Program for all children under two years of age, and March 2011.

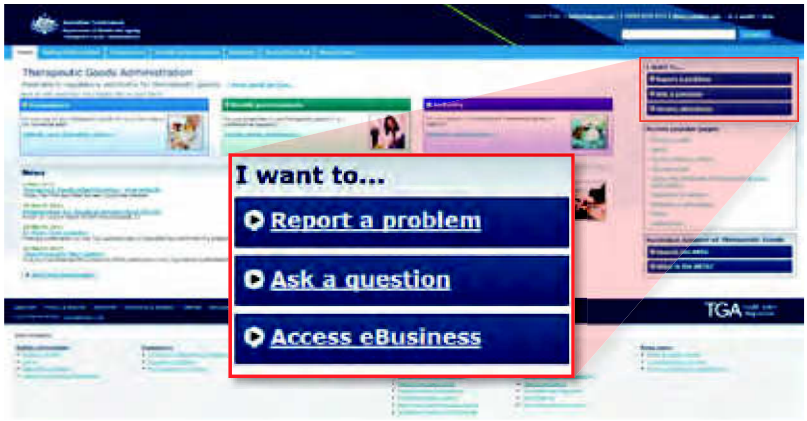
The TGA has concluded that there is no evidence of a causal association between Prevenar and deaths in children in Australia. The TGA's finding is consistent with that of a Japanese advisory panel, which also found no direct causal association between the deaths and the vaccines. The suspension of these vaccines is expected to be lifted in Japan.

This is an example of many similar investigations the TGA conducts using the Adverse Drug Reactions Database and other resources in response to safety concerns raised internationally and nationally, to determine the appropriate action required, if any, in Australia.

Finding information about adverse reaction reporting on the new TGA website

In early May, the TGA launched its new website at www.tga.gov.au. The website improves access to important information on the safety and regulation of medicine in Australia.

The new site makes it easier to find the 'blue card' adverse reaction reporting form and links to information about reporting online or to the Adverse Medicine Events Line for consumers. From the home page, click on 'Report a problem' on the right of the page (see figure) or choose 'Reporting problems' from the 'Safety Information' menu at the top of the page.



Medicine recalls in Australia

Summary

A medicine can be recalled when a deficiency is identified in its quality, safety or efficacy.

There are about 40 medicine recalls each year in Australia. Medicines are recalled when a deficiency is identified in their quality, safety or efficacy. This might include simple labelling or packaging errors, or a more serious increase in unexpected adverse effects.

Recalls in Australia are often initiated by sponsors when they become aware of a problem with a product. Companies wishing to recall their medicine in Australia contact the TGA to discuss their proposed recall strategy and communication plan. The Australian company has the prime responsibility for the conduct of the recall by contacting suppliers and recovering product. The TGA's role is to review reports on the recall supplied by the company. The TGA can take further action if the recall is not progressing satisfactorily.[1]

Most recalls can be traced back to a single incident within the product's manufacturing site. The majority of recalls are batch-specific and companies are readily able to supply replacement batches that are not defective.

In most cases, defective batches are recalled from wholesalers or pharmacies. If the risks posed by the product defect are unacceptable the company will attempt to recover product from consumers. Only 10% of medicine recalls in Australia are conducted at a consumer level. In such recalls companies normally place recall notices in national newspapers and provide information to pharmacists and doctors who may have sold or prescribed the medicine. For example, in 2010 batches of two medicines were recalled because of concerns that cartons may have included tablets of a different strength. In both cases, letters were sent to pharmacists and notices were placed in newspapers.

In December 2010, Pfizer Australia Pty Ltd initiated a recall of sitaxentan (Thelin), used for pulmonary hypertension, following a safety review that found that the benefits of sitaxentan no longer outweighed the risks. In the first stage of the recall, wholesalers were notified to cease distribution of the medicine to pharmacies, and the sponsor informed pharmacies and prescribers of the need to start switching patients to alternative therapies. In the second stage, a recall notice was issued to retail and hospital pharmacies requesting them to return the product. The two-staged approach allowed time for patients to switch safely to an alternative therapy.

Further information about recalls and notices for some consumer-level recalls in Australia are available from the TGA website (www.tga.gov.au).

Reference

1. Uniform Recall Procedure for Therapeutic Goods. Canberra: Therapeutic Goods Administration; 2004. www.tga.gov.au/pdf/recalls-urptg.pdf [cited 2011 May 10]

Medicines Safety Update is written by staff from the Office of Product Review. Editor: Ms Elspeth Kay. Principal Medical Advisor: Dr Megan Keaney. Contributors to this issue include Mr Trevor Byrne, Dr Kerryn Coleman, Dr Kevin Dodd and Dr Katherine Gray. For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114.

What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of all suspected reactions to new medicines, all suspected medicines interactions, and 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 April, August and December issues of *Australian Prescriber*
- **online** on the TGA website
- **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.