



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/adr/msu.htm

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Drug-induced hyponatraemia

Summary

Drugs are a common contributor to hyponatraemia. Diuretics, antidepressants, antiepileptics and antihypertensives appear commonly as suspected causes in reports to the TGA.

Hyponatraemia, defined as serum sodium less than 135 mmol/L, is often caused by drugs, with diuretics, antidepressants and antiepileptics some of the most commonly implicated medicines.¹ We present a summary of recent cases of hyponatraemia reported to the TGA. Management of severe hyponatraemia is discussed in this issue of *Australian Prescriber*.²

Between January 2009 and 2011, the TGA received 136 reports of hyponatraemia. Drugs well known to be associated with hyponatraemia appear in many reports (Table). Similar to reports of hyponatraemia received between May 2005 and Oct 2008,³ drug combinations are suspected in many reports, with the combination of a diuretic with an ACE inhibitor or angiotensin receptor blocker appearing in 41 reports.

Just over half of the reports (76; 56%) described patients aged 70 or over and 64% (49) of these involved females. Older age is acknowledged to be a risk factor for hyponatraemia.

Commonly reported symptoms with hyponatraemia were confusion, dizziness, dehydration, nausea and vomiting, although a number of reports describe asymptomatic hyponatraemia detected on routine laboratory tests. One example is the case of a 91-year-old woman admitted to an emergency department for lower leg pain. Her serum sodium was found to be 124 mmol/L. One month earlier, when she started taking escitalopram, her serum sodium was 139 mmol/L. The reporting health professional considered escitalopram to have contributed to the hyponatraemia. Escitalopram was

ceased and the woman was treated with fluid restriction and sodium replacement.

Other cases describe more severe, symptomatic hyponatraemia. Severe hyponatraemia is usually defined as serum sodium less than 120 mmol/L. In one case, a 71-year-old woman taking carbamazepine and indapamide experienced mental deterioration and was found to have serum sodium of 114 mmol/L. Both drugs were ceased and her symptoms resolved.

References

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2. Shannon G. Severe hyponatraemia. *Aust Prescr* 2011;34:42-5.
3. Drug-induced hyponatraemia. *Aust Adv Drug React Bull* 2008;27:19.

Drugs implicated in reports of hyponatraemia to the TGA, January 2009–January 2011

Class / drug	Number of reports
Thiazide diuretics	47
Antihypertensives	
angiotensin receptor blocker	28
ACE inhibitor	23
Antidepressants	
selective serotonin reuptake inhibitor	22
serotonin–noradrenaline reuptake inhibitor	20
mirtazapine	7
Carbamazepine	13

Rotavirus vaccination and risk of intussusception: investigation of a possible safety signal

Summary

The TGA has released an analysis of rotavirus vaccine and the risk of intussusception. A detailed report of the analysis, and links to fact sheets for parents and immunisation providers, are available from the TGA website (www.tga.gov.au).

The TGA, in collaboration with state health authorities, has undertaken an investigation of a possible association between the rotavirus vaccines Rotarix (GSK) and RotaTeq (Merck/CSL) and the occurrence of a rare form of bowel obstruction known as intussusception. Intussusception is a condition caused by the telescoping of one segment of the bowel into another. It is estimated to occur each year in around 80 per 100 000 children under 12 months of age, which represents approximately 200 cases per year in Australia. The peak incidence is in infants 5–10 months of age, with 80% of cases occurring before 24 months of age. It is much more common in males than females.

Intussusception was found to be an adverse effect of the first generation rotavirus vaccine (RotaShield, Wyeth) that was available in the US in 1998–99. RotaShield was estimated to cause intussusception in 10–20 of every 100 000 doses given to infants, and was voluntarily withdrawn in October 1999.^{1,2} RotaShield was not used outside the US; however, as the historical incidence of intussusception is 2.5 to 3 times higher in infants in Australia than in the US, this would have translated to 25–60 cases of intussusception for every 100 000 doses of RotaShield if the vaccine had been used here.

Subsequently two new rotavirus vaccines, Rotarix and RotaTeq, were developed. Both were tested in large studies designed to explore the risk of intussusception. In each of these placebo-controlled preregistration studies, approximately 35 000 infants were given rotavirus vaccine, with no increased risk of intussusception observed.^{3,4} However, as large preregistration safety studies may not always detect rare events, postmarketing studies have been undertaken in a number of countries.

In Australia, two postmarketing studies have been conducted to investigate whether the new rotavirus vaccines are associated with an increased risk of intussusception. The first study used two surveillance systems – the Paediatric Enhanced Disease Surveillance with active surveillance of intussusception cases in four tertiary centres, and the Australian Paediatric Surveillance Unit with national retrospective reporting of intussusception cases by paediatricians. This study, conducted in NSW, Victoria, WA and SA, found an apparent four-fold increased risk of intussusception in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalisations coded as intussusception, but no overall increase in overall rates of intussusception up to the age of 9 months. This is much lower than the risk found with the earlier RotaShield vaccine.

Following this, a large self-controlled case series study using data on all hospitalised cases coded as intussusception from NSW, Victoria and WA was commissioned by the TGA. This study found a statistically significant four-fold increase in the occurrence of intussusception in the first 1–7 days following the first dose of either Rotarix or RotaTeq compared with other time periods after vaccine receipt. This increase in risk translates to approximately two additional cases of intussusception occurring in every 100 000 first doses of vaccine, or six additional cases each year in children under 12 months of age in Australia. *These findings are preliminary, as the data are subject to confirmation.*

It is currently unclear whether this represents a true increase in overall risk of intussusception, or an early increase in risk in infants which is compensated for by a subsequent decrease in risk leading to a reduction in cases of intussusception in older children. Longer-term studies are required to clarify this.

Prior to the introduction of rotavirus vaccine, there were an estimated 10 000 hospitalisations annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq onto the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under-5-years age group have been reduced by over 70%.^{5,6} Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation have recommended the continued use of rotavirus vaccine for infants under the National Immunisation Program.

References

1. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999;48:1107.
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3. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11-22.
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Coversyl and Coumadin: new packaging to reduce potential for dispensing errors

Summary

Pharmacists are asked to be aware of the similar packaging for Coversyl and Coumadin and to take extra care to ensure that dispensing errors do not occur.

Coversyl (perindopril) and Coumadin (warfarin) 5 mg appear near each other in the pharmacy dispensary and both are packaged in white bottles with green caps and labels (see figure). The similarity arose when changes were made to the Coversyl packaging to comply with new requirements for a child-resistant closure.

In late November 2010, the TGA received two reports of dispensing errors associated with Coversyl and Coumadin. In one case a patient developed haematuria when Coumadin was dispensed instead of Coversyl. Despite several weeks of warfarin therapy, the patient's INR was 3. The patient made a full recovery and did not require warfarin reversal. In the other case a patient's INR dropped to 1.1 when Coversyl was dispensed in place of Coumadin. The patient did not experience any symptoms. Coversyl was ceased, anticoagulant therapy reintroduced and the patient made a full recovery.

The sponsor for Coversyl, Servier, has been working with the TGA to review and update the Coversyl packaging. New Coversyl packaging has been approved by the TGA and is expected to start appearing in pharmacies in April 2011. The updated packaging will include new labelling and white lids.

Packaging for Coversyl and Coumadin tablets

Coversyl packaging will soon change to reduce the similarity between the bottles



In the interim, Servier has worked with the Pharmacy Guild to publish an article advising pharmacists of the similarities between the Coversyl and Coumadin packaging. Alerts have also been issued by Pharmaceutical Defence Limited and the Australian Commission on Safety and Quality in Health Care. Pharmacists should take care when dispensing not only Coversyl and Coumadin, but all drugs with similar trade names or packaging, ensuring appropriate checking and use of barcode scanners.

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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 (www.tga.gov.au/adr/bluecard.pdf) and with the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website (go to www.tga.gov.au and click on 'report a problem' on the left)
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

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