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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

In this issue:

Cholinesterase inhibitors and syncope

Summary

Cholinesterase inhibitors have been associated with syncope and fall-related injuries, including hip fracture. Caution should be used when patients are started on a cholinesterase inhibitor, and patients should only be maintained on these medicines if there is evidence of continuing benefit.

The cholinesterase inhibitors, donepezil (Aricept), rivastigmine (Exelon) and galantamine (Galantyl, Reminyl) are available on the Pharmaceutical Benefits Scheme (PBS) as authority items for patients with mild to moderately severe Alzheimer's disease. More than 2.5 million PBS prescriptions for cholinesterase inhibitors have been dispensed since 2001.

A recent Canadian population-based cohort study found that cholinesterase inhibitor use was associated with increased rates of syncope, bradycardia, pacemaker insertion and hip fracture in older adults with dementia.[1] Hospital visits for syncope were more frequent in people receiving cholinesterase inhibitors than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted hazard ratio 1.76; 95% confidence interval 1.57 to 1.98). No comparison of event rates for individual cholinesterase inhibitors was conducted as it was assumed that donepezil, galantamine and rivastigmine have similar adverse-effect profiles. The authors noted that cholinesterase inhibitors generally augment vagal influences on the heart and promote bradycardia, which may result in neurocardiogenic syncope.

To June 2010, the TGA had received a total of 623 reports of suspected adverse reactions to cholinesterase inhibitors. Eighty-four (14%) of these reports describe syncope, syncope-related events or bradycardia.

While syncope and bradycardia are listed in the product information for each cholinesterase inhibitor as 'common' to 'very rare' adverse effects, the TGA reminds prescribers to use caution when starting patients on cholinesterase inhibitors, and that patients should only be maintained on these medicines if there is evidence of continuing benefit.

Reference

1. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SL, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 2009;169:867-73.

Statins, macrolides and rhabdomyolysis

Summary

The combination of a macrolide antibiotic and a statin can increase the risk of myopathy and rhabdomyolysis. If a patient taking a statin is to be prescribed a macrolide, consider temporarily stopping the statin or choosing a different antibiotic.

Combining clarithromycin or erythromycin with simvastatin or atorvastatin increases the risk of statin-induced myopathy and rhabdomyolysis. The TGA receives several reports of rhabdomyolysis in patients taking an HMG-CoA reductase inhibitor (statin) and a macrolide antibiotic almost every year. We remind health professionals to use caution with this combination.

If a patient taking a statin is to be prescribed a macrolide

antibiotic, consider temporarily stopping the statin or choosing a different antibiotic, if appropriate. Use particular caution in patients who are on higher statin doses, have comorbidities, are older, or are taking other medicines, because they are at higher risk of rhabdomyolysis (see box). Ask patients taking statins to promptly report muscle aches, pain or weakness, particularly if accompanied by malaise, fever or brown urine.

To July 2010, TGA had received 25 reports of rhabdomyolysis in patients prescribed a macrolide antibiotic and a statin. In 80% of cases, patients had at least one other risk factor for statin-induced myopathy before they were prescribed clarithromycin or erythromycin. In almost 50% of cases, patients had two or more other risk factors. The most common risk factors were older age; high statin dose; concomitant diltiazem, cyclosporin or gemfibrozil; and hypothyroidism or diabetes. This is consistent with an earlier analysis of reports to the TGA.[1]

Either simvastatin or atorvastatin was involved in each case reported to the TGA. Both of these statins are metabolised by cytochrome P450 3A4, which is inhibited by clarithromycin and erythromycin. Interactions with other statins or other macrolides are less likely: CYP3A4 has little or no involvement in the metabolism of pravastatin, fluvastatin and rosuvastatin, and the macrolides azithromycin and roxithromycin are not inhibitors of CYP3A4.[2]

Box

Factors that may increase the risk of rhabdomyolysis with statins [2,3]

Concomitant medicines*

Amiodarone	Grapefruit juice
Azole antifungals	Imatinib
Cyclosporin	Macrolide antibiotics
Diltiazem	Nicotinic acid
Delavirdine	Protease inhibitors
Efavirenz	Tacrolimus
Fibrates	Verapamil

Comorbidity

Diabetes	Severe intercurrent illness (infection, trauma, metabolic disorder)
Hepatic impairment	
Hypothyroidism	Surgery
Renal impairment	

Age

> 70 years

Statin dose

Higher doses, e.g. ≥ simvastatin 40 mg/day

* Interaction potential may differ between different statins and members of other drug classes. Refer to the product information or to texts such as the Australian Medicines Handbook for advice about interactions with specific drugs.

References

1. Risk factors for myopathy and rhabdomyolysis with the statins. Aust Adv Drug React Bull 2002;23:2.
2. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2010.
3. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003;289:1681-90.

Uterine perforation with levonorgestrel-releasing intrauterine system (Mirena)

Summary

Uterine perforation is a known but rare complication associated with the levonorgestrel-releasing intrauterine system (Mirena). Observing correct insertion technique is important to minimise the risk of perforation.

Mirena is an intrauterine delivery system that releases levonorgestrel 20 microgram/day. It is approved for use as a contraceptive for up to five years, for the treatment of idiopathic menorrhagia, and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. As with copper intrauterine devices, Mirena is associated with uterine perforation at an incidence of less than 0.1%.[1]

In June 2010 in Canada, a reminder was issued to health professionals about the possibility of uterine perforation with Mirena, after it was noted that the number of perforations reported was rising alongside increased use of Mirena.[2]

In Australia, a total of 161 adverse reactions to Mirena had been reported to the TGA to June 2010. Of these, 22 were reports of uterine perforation. In at least seven cases, patients had known risk factors for uterine perforation. Perforation was reported to have occurred during insertion in three cases.

The presentation of uterine perforation may be subtle. Patients should regularly check for the threads attached to Mirena to ensure that the device has remained in the uterus. Health professionals should instruct women on how to check for the threads, and inform them of the efficacy, risks and side effects of Mirena.

Minimising the risk of uterine perforation

Correct insertion technique is important for reducing the risk of perforation (see box). Women who are postpartum, lactating or have atypical uterine anatomy (such as a fixed retroverted uterus) are at greatest risk of perforation.

Training in inserting intrauterine devices and Mirena is available through the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and state and territory sexual health and family planning organisations. An education DVD is available from Bayer (ph 1800 673 270) and a leaflet explaining insertion is included in the packaging.

Box

Steps to minimise the risk of uterine perforation [1]

- Only health professionals who are experienced or have had sufficient training should undertake Mirena insertion
- Perform a physical examination including pelvic examination and a cervical smear to rule out pregnancy, uterine anomalies, sexually transmitted disease and genital infections
- Review insertion instructions included in every Mirena package. It is important not to force the inserter and to dilate the cervical canal if necessary.
- Review the training DVD which shows a Mirena device being fitted
- When insertion is difficult and/or exceptional pain or bleeding occurs during insertion, consider physical examination and performing an ultrasound or X-ray imaging immediately to exclude uterine perforation
- Re-examine the patient 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated
- Instruct the patient to consult her doctor if she develops pain and abnormal bleeding and/or if she is unable to locate the threads

References

1. Bayer Schering. Mirena Product Information. 23 September 2009.
2. Bayer Healthcare. Mirena (levonorgestrel-releasing intrauterine system) – potential risk of uterine perforation – for health professionals. Ottawa: Health Canada; 2010 Jun 15. www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/mirena_hpc-cps-eng.php [cited 2010 Sep 1]

Rivaroxaban (Xarelto) – an overview of adverse event reports

Summary

Most adverse event reports involving rivaroxaban received by the TGA describe thrombotic or haemorrhagic events, consistent with international experience and the known safety profile of rivaroxaban. The TGA will continue to routinely monitor reports of adverse reactions to rivaroxaban. We encourage health professionals to report suspected adverse reactions promptly.

Rivaroxaban is an oral anticoagulant that acts through direct inhibition of coagulation factor Xa. It was first registered in Australia in November 2008 and is approved for prevention of venous thromboembolism following elective total hip replacement or total knee replacement. Approximately 6800 PBS prescriptions have been dispensed since the drug was listed in August 2009.

At 15 July 2010, the TGA had received 44 adverse event reports involving rivaroxaban. Of these, 22 (50%) described thrombotic events and 17 (39%) haemorrhagic events (see Table). This is consistent with the known adverse effects of rivaroxaban (the Product Information lists haemorrhage, anaemia and deep vein thrombosis as adverse events[1]). It is also similar to reports submitted to the World Health Organization's Programme for International Drug Monitoring,* to which more than 90 countries contribute spontaneous adverse drug reaction reports.[2,3]

Table

Adverse events involving rivaroxaban reported to the TGA to 15 July 2010

Adverse event	Number of reported cases
Deep vein thrombosis	10
Pulmonary embolus	12
Gastrointestinal haemorrhage	3
Haematuria	3
Haemarthrosis	6
Other haemorrhagic	5
Other	5

* The information in adverse event reports in the WHO database is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. The information in this article does not represent the opinion of the WHO.

Reports received by the TGA do not indicate any new safety signals for rivaroxaban, but report numbers to date are small. Routine monitoring of adverse events with rivaroxaban will continue and as with all new drugs, health professionals are encouraged to report adverse events to the TGA (see *What to report* below).

There were several reports to the TGA in which rivaroxaban was apparently not used according to the dosing and administration instructions. These involved use of rivaroxaban sequentially with postoperative enoxaparin (3 cases: one haemarthrosis, two thrombotic events); double dosing with rivaroxaban for 3 days (one case: haemarthrosis); and starting rivaroxaban therapy one day after surgery (one case: thrombotic event). A causal link between these administration errors and the adverse events reported has not been established. Nevertheless, note that rivaroxaban should be started 6–10 hours after surgery, providing that haemostasis has been established, and a single 10 mg tablet taken daily for up to 14 days (knee replacement) or 35 days (hip replacement).[1]

In two cases, haemorrhagic events were associated with concomitant use of meloxicam or clopidogrel. Rivaroxaban should be used with caution in patients taking clopidogrel or non-steroidal anti-inflammatory drugs because of an increased risk of bleeding.[1]

References

1. Bayer Australia Limited. Xarelto Product Information. 26 March 2009.
2. WHO Collaborating Centre for International Drug Monitoring. Rivaroxaban – a new anticoagulant drug. Signal: analyses of reports in the WHO global ICSR Database – VigiBase. Uppsala: Uppsala Monitoring Centre; 2010 Apr.
3. FAQ – Vigibase Services. Uppsala: Uppsala Monitoring Centre. www.umc-products.com/DynPage.aspx?id=73565&mn1=1107&mn2=1132&mn3=6051 [cited 2010 Sep 1]

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

Suspected reactions causing

- death
- admission to hospital or prolongation of hospitalisation
- increased investigations or treatment
- birth defects

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and in 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

For further information, please contact the TGA's Office of Product Review on 1800 044 114.