



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

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Proton pump inhibitors and acute interstitial nephritis

Summary

The incidence of acute interstitial nephritis caused by proton pump inhibitors (PPIs) is unknown. Given the widespread and growing use of PPIs and the consequences of acute interstitial nephritis, the potential for this adverse reaction should not be forgotten.

PPIs are a leading cause of drug-induced acute interstitial nephritis (AIN), which may cause acute kidney injury and sometimes long-term damage.¹ The association between PPIs and interstitial nephritis was reported by the TGA in the Australian Adverse Drug Reactions Bulletin in 1995 and 2003.^{2,3}

Reports continue to be received of interstitial nephritis with PPI use. The table below shows reports to the TGA and the World Health Organization's (WHO) Program for International Drug Monitoring* to July 2011 of suspected cases of interstitial nephritis in which a PPI was suspected. These data should not be taken to reflect incidence rates.

The total number of PBS/RPBS prescriptions dispensed since 1992 for each PPI have been: omeprazole 50.1 million; lansoprazole 10.2 million; pantoprazole 29.6 million; rabeprazole 15.3 million; and esomeprazole 38.2 million. PPIs are also available for direct purchase by consumers.

Product Information documents for PPIs mention interstitial nephritis as a very rarely or rarely reported event in the postmarketing experience with these drugs. Fever and skin rash are also sometimes mentioned but patients with PPI-induced AIN rarely present with the classic hypersensitivity syndrome

* Adverse drug reaction information from this Program is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and the information does not represent the opinion of the World Health Organization

of fever, skin rash and eosinophilia in the context of renal impairment.⁴ Non-specific symptoms such as fever, anorexia, weight loss, fatigue, lethargy, nausea, vomiting and malaise predominate. Laboratory findings include pyuria, proteinuria and/or haematuria.¹

While AIN is considered a class effect of PPIs, the TGA has received no reports of interstitial nephritis with lansoprazole. The lack of reports may reflect the lower use of lansoprazole compared with other PPIs, but could possibly reflect variation in the incidence of rare adverse reactions within a class. Prescribers should be aware of the possibility of AIN with this class of medicine. If cases are suspected, please report them to the TGA – see 'What to report' on page 193.

References

1. Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. *Clin Gastroenterol Hepatol* 2006;4:597-604.
2. Omeprazole and interstitial nephritis. *Aust Adv Drug React Bull* 1995;14:4.
3. Interstitial nephritis with the proton pump inhibitors. *Aust Adv Drug React Bull* 2003;22:2.
4. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol* 2010;6:461-70.

Reports to the TGA and WHO to July 2011 of interstitial nephritis in patients taking a PPI

	TGA	WHO
omeprazole	54 (from 1990)	293 (from 1993)
lansoprazole	0 (from 1994)	23 (from 1996)
pantoprazole	21 (from 1995)	84 (from 1998)
rabeprazole	28 (from 2001)	54 (from 2000)
esomeprazole	28 (from 2002)	44 (from 2002)

Dabigatran (Pradaxa) and the risk of bleeding

Summary

Dabigatran (Pradaxa) is a potent short-acting anticoagulant for which there is no antidote or reversal agent. As with warfarin, bleeding events can occur. Clinicians are urged to give careful consideration to the suitability of their patients for dabigatran particularly with regard to recognised risks of bleeding.

Dabigatran (Pradaxa) is a potent oral anticoagulant. It is a direct thrombin inhibitor that inhibits free and clot-bound thrombin. It has a mean half-life of 12–17 hours. It is renally excreted and the rate of elimination is related to renal function. There is a close correlation between plasma dabigatran levels and anticoagulant effect.

Dabigatran may be considered an alternative to warfarin and it carries similar risks of bleeding. In clinical trials the risk of bleeding per year of treatment with dabigatran was 16.6% (1 in 6 patients) when taking 150 mg twice daily, and 14.7% (1 in 6.8 patients) taking 110 mg twice daily compared with 18.4% (1 in 5.4 patients) for warfarin.

Bleeding adverse events with dabigatran

In April 2011 the TGA approved dabigatran for use for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor for stroke. Since then, the TGA has received an increase in the number of bleeding-related adverse events reports for dabigatran (see table).

The analysis of these reports shows that some of the bleeding adverse events occurred during the transition from warfarin to dabigatran; many of the adverse events are occurring in patients on the reduced dosage regimen; and the most common site

of serious bleeding for dabigatran is the gastrointestinal tract, whereas for warfarin it is intracranial.

Risk factors for bleeding

- Age \geq 75 years
- Moderate renal impairment (30–50 mL/min) – severe renal impairment is a contraindication
- Concomitant use of aspirin (approximately twice the risk), clopidogrel (approximately twice the risk), non-steroidal anti-inflammatory drugs including COX-2 inhibitors

Monitoring renal function

New recommendations for assessing renal function before starting dabigatran and during its use are now in place. See information on the TGA website at www.tga.gov.au/safety/alerts-current.htm

Coagulation testing

In bleeding patients Thrombin Time is the most readily available clotting test reflective of the relationship between dabigatran concentration and clotting time. Although there is not a direct linear relationship, activated Partial Thromboplastin Time (aPTT) >80 seconds is associated with a higher bleeding risk. Prothrombin time (INR) should not be used.

Guidelines for managing bleeding patients

Australian experts are currently developing Australian guidelines for the management of bleeding in patients taking dabigatran. In the meantime clinicians are referred to the New Zealand guidelines.¹

It is strongly recommended that clinicians read the Product Information **before** prescribing dabigatran. The Product Information is available from the TGA website.² For more detailed information regarding the considerations of the TGA in approving dabigatran please see the Australian Public Assessment Report (AusPAR).³

Reporting adverse events

Health professionals are requested to report adverse events associated with dabigatran to the TGA via the TGA website.

References

1. Guidelines for management of bleeding with dabigatran. New Zealand: PHARMAC; 2011 Aug. www.pharmac.govt.nz/2011/06/13/Dabigatran%20bleeding%20management.pdf [cited 2011 Nov 8]
2. Pradaxa Product Information. Boehringer Ingelheim Pty Limited. 2011 Aug.
3. Dabigatran etexilate mesilate – AusPAR. Therapeutic Goods Administration. 2011 May 24.

Adverse events reported to the TGA for dabigatran June 2009 – Oct 2011

Type of adverse event	Number
Total adverse events	297
Serious adverse events	196
Serious bleeding adverse events	70
Serious gastrointestinal bleeding	48
Serious intracranial bleeding	6
Events in patients aged 75 years or older	
Total adverse events	166
Serious adverse events	108

Risk of myopathy and rhabdomyolysis with simvastatin – new dosage recommendations and contraindications

Summary

To reduce the risk of myopathy and rhabdomyolysis, health professionals are advised of new recommendations to limit the use of high dose simvastatin (80 mg/day) and of new contraindications for the use of simvastatin with potent CYP3A4 inhibitors, gemfibrozil, cyclosporin or danazol (see box). They are also reminded of the need for lower doses when simvastatin is used concomitantly with drugs that interact with simvastatin and increase its absorption.

Simvastatin, like other inhibitors of HMG-CoA reductase, is known to cause myopathy and more rarely rhabdomyolysis. The risk of myopathy is dose related and is more likely to occur in the first year of treatment. Other risk factors include age ≥ 65 years, female gender, uncontrolled hypothyroidism and renal impairment. Myopathy can be the result of interactions with other drugs. Many cases may be associated with a genetic variant which results in reduced uptake of simvastatin by the liver.

A recent re-analysis by the US Food and Drug Administration of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial has confirmed the increased risk of myopathy and rhabdomyolysis with

Key safety related updates for simvastatin *

Risk of myopathy/rhabdomyolysis

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C lowering efficacy

New dose recommendation

The 80 mg/day dose of simvastatin should only be used in patients at high risk of cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks

New contraindications

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone). If treatment with these medicines is unavoidable, simvastatin should be suspended during the course of treatment.

Concomitant administration of gemfibrozil, cyclosporin or danazol

Precautions – interactions with other medicines

Amiodarone: the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone

Calcium channel blockers:

– **Verapamil or diltiazem:** the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem

– **Amlodipine:** the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine

Moderate inhibitors of CYP3A4: patients taking other medicines labelled as having a moderate inhibitor effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy

Other fibrates: concomitant use of gemfibrozil is contraindicated. The concomitant use of simvastatin and other fibrates should be avoided.

Niacin (≥ 1 g/day): the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1 g/day

Colchicine: there have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of patients taking this combination is advised.

* These updates provide information on changes to the recommendations for simvastatin. For full prescribing information, see the Zocor Product Information available on the TGA website.

increasing doses of simvastatin.¹ In the trial the incidence of myopathy increased from 0.02% among patients taking 20 mg of simvastatin daily to 0.9% among those taking 80 mg daily. The trial also found only a limited increase in benefit from the 80 mg dose compared with lower doses.

Following a review of these findings, the TGA is recommending limitations to the use of high dose simvastatin (80 mg/day) and changes to the contraindications. The TGA is working with the sponsors of simvastatin and simvastatin-containing medications to update the Product Information to provide increased warnings regarding the risk of myopathy associated with high doses of simvastatin, and to detail the new dosage recommendations and contraindications.

Important information for health professionals

The 80 mg/day dose of simvastatin should only be used in patients at high risk of cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks.

Concomitant administration of simvastatin with potent CYP3A4 inhibitors, gemfibrozil, cyclosporin, or danazol is now contraindicated (see box for details).

Simvastatin is contraindicated in patients who have previously experienced myopathy secondary to other lipid lowering agents. In patients taking simvastatin for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin with less potential for drug-drug interactions should be used.

Health professionals should advise patients who are commencing simvastatin therapy or whose dose is being increased, of the risk of myopathy and remind patients to report any unexplained muscle pain, tenderness or weakness to a health professional promptly.

Simvastatin therapy should be discontinued immediately if myopathy is suspected.

Health professionals are asked to report any suspected cases of myopathy to the TGA.

Reference

1. Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. US Food and Drug Administration. 8 June 2011. www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Simvastatin_Dose_Limitations [cited 2011 Nov 8]

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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
- 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** 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.

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