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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 on the TGA website and sign up for free Medicines Safety Update email alerts at www.tga.gov.au/newsroom/subscribe-msu.htm

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Cramps, quinine and thrombocytopenia

Summary

The TGA continues to receive reports of thrombocytopenia in people taking quinine to treat muscle cramps. Health professionals are reminded that quinine is not approved for the treatment of nocturnal cramps because of its low efficacy and the risk of thrombocytopenia. Non-pharmacological interventions, such as stretching, should be considered for preventing cramps.

In 2004, the Product Information (PI) for quinine tablets was amended and the indication for nocturnal cramps removed. Quinine tablets (Quinbisul, Quinate and Quinsul) are now only approved for treatment of malaria due to strains of *Plasmodium falciparum* resistant to chloroquine and the related 4-aminoquinolines.

Thrombocytopenia continues to be reported

Up to 2004, the TGA had received 228 reports of thrombocytopenia in people taking quinine, six of which were fatal.[1] Since 2004, the TGA has received a further 21 reports of thrombocytopenia in people taking quinine, including several in the past few years (see table). In most cases, patients were prescribed quinine to treat leg cramps.

In 2010, a case reported to the TGA involved a 73-year-old woman who had been taking one quinine tablet every two days for muscle cramps for one year. She presented with a history of three days of bleeding gums, nose bleeding and multiple bruises and was found to have a platelet count of 4 x 10^9/L. Quinine was ceased and her platelet count recovered to normal.

Utilisation data show that although Pharmaceutical Benefits Scheme (PBS) prescribing of quinine has reduced substantially since removal of the indication and PBS listing for muscle cramps, private prescribing of quinine continues.[2] It is likely that 'off label' prescribing for muscle cramps occurs.

Quinine is not approved for treatment of muscle cramps

When a patient presents with leg cramps, consideration should be given to non-pharmacological interventions for cramps such as stretching. An NPS factsheet describes suitable stretches for people who experience nocturnal cramps.[3]

References

1. Quinine indications – cramps deleted. Aust Adv Drug React Bull 2004;23:5.
2. Department of Health and Ageing. PBS Statistics. Australian Statistics on Medicines. www.pbs.gov.au
3. Quinine: Poor efficacy in muscle cramps outweighed by risks of harm. Sydney: NPS; 2009 Dec 18. www.nps.org.au

Table

Reports to the TGA since 2005 of thrombocytopenia in patients taking quinine

Year	Number of reports in which quinine was suspected
2011*	1
2010	1
2009	0
2008	5
2007	2
2006	3
2005	9

*to 2 June 2011

Venlafaxine and stress cardiomyopathy

Summary

Published case reports have suggested that stress cardiomyopathy may be an adverse effect of venlafaxine. There is currently insufficient evidence to confirm an association, although a biologically plausible mechanism exists. Clinicians are reminded to report suspected adverse reactions of all types, even for drugs that have been available for many years.

Venlafaxine is a potent selective serotonin-noradrenaline reuptake inhibitor. It also exhibits rate-dependent sodium channel blocking activity. Venlafaxine is approved for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and panic disorder, including prevention of relapse.

Features of stress cardiomyopathy

Stress cardiomyopathy, or Taka-Tsubo cardiomyopathy, is characterised by an acute transient left ventricular dysfunction with akinesia of the left ventricular apex and a hypercontractile base, occurring predominantly in women in the context of emotional distress.[1] Accompanying transient electrocardiographic changes may mimic an acute coronary syndrome. It is thought the findings are due to catecholamine-mediated neurogenic myocardial stunning caused by emotional stress. Elevated plasma catecholamines are a typical finding.

Reported cases

Following a literature report[1] and routine pharmacovigilance activities, the TGA has undertaken a review of stress cardiomyopathy in association with venlafaxine use. To March 2011, the TGA had received three case reports of stress cardiomyopathy in patients taking venlafaxine: one in the context of overdose, and two in patients over the age of 70 with normal dosing. All three cases had the diagnosis confirmed with echocardiography and noradrenaline levels. For the same time period there were six other cases of cardiomyopathy and one case of cardiac failure reported in patients taking venlafaxine. These numbers are very small in the context of use of venlafaxine in Australia. Approximately 21 million PBS prescriptions for venlafaxine have been dispensed.

Two additional cases of stress cardiomyopathy in patients taking venlafaxine, both in the context of overdose, are identified in the database of the World Health Organization's Programme for International Drug Monitoring. Thirty-nine patients were reported to have a cardiomyopathy, nine had congestive cardiomyopathy, and 58 patients had cardiac failure in association with venlafaxine use. The WHO database provides insufficient information about the diagnosis and features of the reported cases of cardiomyopathy to confirm an underlying causal relationship beyond a temporal association.*

By increasing plasma catecholamine levels, possibly by the inhibition of noradrenaline reuptake, a potential mechanism exists for venlafaxine to cause stress cardiomyopathy.

Cardiovascular precautions

The PI states that venlafaxine causes a dose-related increase in resting heart rate and is associated with hypertension and increased serum cholesterol, which are presumed to be additive to other cardiovascular risk factors, and that venlafaxine should be used with caution in patients with unstable heart disease.[2] In these patients, assessment of the cardiovascular system (e.g. ECG, serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150–200 mg daily.

The TGA continues to monitor the potential association between venlafaxine and stress cardiomyopathy. Clinicians are reminded to report all adverse events that are potentially medication-related.

References

1. Christoph M, Ebner B, Stolte D, Ibrahim K, Kolschmann S, Strasser RH, et al. Broken heart syndrome: TakoTsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor venlafaxine. Eur Neuropsychopharmacol 2010;20:594-7.
2. Pfizer Australia Pty Ltd. Efexor XR (venlafaxine) Product Information. 2011 May 19.

* 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.

In utero antipsychotic exposure and neonatal extrapyramidal and withdrawal adverse effects

Summary

Neonates exposed to antipsychotic medications during the third trimester of pregnancy may be at risk of experiencing extrapyramidal signs and/or withdrawal symptoms. Neonatal drug withdrawal symptoms may occur when drug exposure ceases at birth. All registered antipsychotics are now classified as Australian pregnancy category C.

The safety of antipsychotic use in pregnancy and lactation has not been thoroughly studied. The antenatal management of serious mental illnesses, such as schizophrenia and bipolar affective disorder, involves clinical decision-making about the continuation, commencement or discontinuation of psychotropic treatments. If the use of an antipsychotic in a pregnant woman is clinically indicated, avoid unnecessarily high doses and duration of treatment.[1] The decision about using antipsychotics should be made on a case-by-case basis, taking into account the woman's individual characteristics, her mental health history and tendency to relapse, the risk to the fetus or infant, and the risk – to both mother and fetus – of not treating the disorder.[2]

The potential risks to the fetus or infant from antipsychotic exposure include structural teratogenicity, pregnancy complications (e.g. inducing maternal diabetes), effects on fetal growth, neonatal toxicity/withdrawal and long-term adverse neurodevelopmental outcomes. There is growing evidence that psychiatric disorders themselves appear to independently elevate the risk of spontaneous abortion, pre-eclampsia, premature birth, low birth weight, smaller head circumference and long-term adverse neurodevelopment.[1,3]

Reported cases

When used in pregnancy, many typical antipsychotics are known to be associated with the development of reversible extrapyramidal signs (EPS), such as dyskinetic movements, in the neonate. Although the incidence of EPS tends to be lower in patients treated with some atypical antipsychotics, this may not necessarily translate to a lower risk to neonates exposed *in utero*. Fetal exposure is largely dependent on placental transfer which can vary depending on the placental permeability of different antipsychotics. Spontaneous adverse event reporting provides evidence of both EPS and withdrawal symptoms occurring in the neonate following chronic *in utero* exposure to atypical antipsychotics.

To May 2011, the TGA had received 19 reports of EPS or withdrawal symptoms in neonates. Of these, an atypical antipsychotic was suspected in 18 reports. Many reported cases were confounded by concomitant use of other psychotropic medication (e.g. antidepressants), obstetric complications (e.g. fetal distress) or tobacco and alcohol exposure. However an antipsychotic alone was suspected in four reports.

In the cases reported to the TGA, adverse events included jitteriness, agitation, tremor, feeding problems, somnolence, breathing difficulties, hypertonia, hypotonia, pronounced startle reflex and myoclonus. Although the term 'neonatal drug withdrawal' was specifically identified in 14 reports, it was not possible to definitively determine whether these were related directly to antipsychotic toxicity or to withdrawal. Reported time to onset ranged from birth to seven days. Where outcome was described, most neonates recovered within a few days although some required supportive therapy and prolonged hospitalisation. An analysis of adverse events reported in the United States described similar findings.[4]

Changes to PI for antipsychotics

PI documents for all antipsychotics are being updated with warnings about neonatal EPS and withdrawal symptoms. All registered antipsychotics are Australian pregnancy category C. Category C refers to: 'Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.'

See page 111 for information about the TGA's new 'Prescribing medicines in pregnancy' database.

References

1. Psychotropic Expert Group. Therapeutic guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Limited; 2008.
2. Austin M-P, Highet N; Guidelines Expert Advisory Committee (2011). Clinical practice guidelines. Depression and related disorders – anxiety, bipolar disorder and puerperal psychosis – in the perinatal period. A guideline for primary care health professionals. Melbourne: beyondblue; 2011. www.beyondblue.org.au/index.aspx?link_id=6.1246&tmp=FileDownload&fid=1626 [cited 2011 Jul 4]
3. Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull 2010;36:518-44.
4. US Food and Drug Administration. FDA drug safety communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. 2011. www.fda.gov/Drugs/DrugSafety/ucm243903.htm [cited 2011 Jul 4]

Prescribing medicines in pregnancy – new TGA database

As part of the recent website upgrade, the TGA has developed a new, searchable database for use by health professionals prescribing medicines to pregnant women. The database can be found at www.tga.gov.au/hp/medicines-pregnancy.htm.

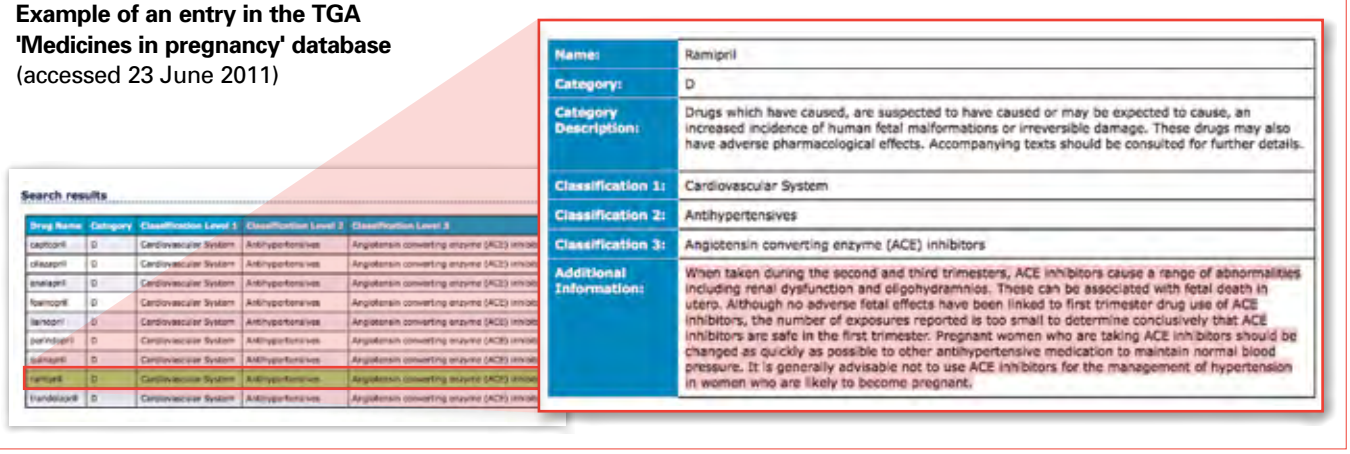
The 'Prescribing medicines in pregnancy' database replaces the booklet 'Prescribing medicines in pregnancy – an Australian categorisation of the risk of drug use in pregnancy'. The booklet was first published in 1989, with the latest edition published in 1999, and subsequent updates added as amendments on the TGA website. Unlike the booklet, the new database is searchable by generic name (or part of the generic name), and by classification using a drop-down list.

Once the user finds the relevant medicine, clicking on the medicine name will display the pregnancy category, an explanation of the category and, if available, a safety statement specific for the medicine or medicine group (see figure).

The database contains over 1200 individual entries, including all new medicines and any changes of pregnancy category for existing medicines. A separate page lists the therapeutic goods exempted from pregnancy classification.

Other pages on the TGA website with information relevant to prescribing medicines in pregnancy include the PI documents (www.ebs.tga.gov.au) and the Australian Public Assessment Reports (www.tga.gov.au/industry/pm-auspar.htm).

Example of an entry in the TGA 'Medicines in pregnancy' database
(accessed 23 June 2011)



Medicines Safety Update is written by staff from the Office of Product Review of the TGA. Editor: Ms Elspeth Kay. Principal Medical Advisor: Dr Megan Keaney. Contributors to this issue include Dr Kevin Dodd, Dr Kaye Robertson, Dr Jennifer Elijah, Dr Manuel Navarro-Gonzalez and Dr Jin Zhu. 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.