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Medicines Safety Update

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In this issue

Candesartan, fetal malformations and use in pregnancy

Health professionals are reminded that candesartan and other angiotensin II receptor antagonists, as well as ACE inhibitors, are contraindicated in pregnancy. Exposure to these drugs in pregnancy can cause fetotoxicity. Patients who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

Reported cases

The TGA has received four reports of fetal abnormalities following candesartan use in pregnancy, including three reports in 2011. In one case, candesartan was started before conception and continued to 30 weeks gestation. The fetus was diagnosed with renal failure, nephrocalcinosis and congenital genitourinary system abnormalities. In another case, anhydramnios and possible renal dysplasia was diagnosed. Fetal death occurred at 34 weeks, seven weeks after ceasing candesartan. A third case reported renal failure and kidney malformation.

The TGA has also received reports of fetal abnormalities following the use of irbesartan, enalapril, lisinopril, perindopril and captopril during pregnancy.

Risk of fetal malformations

Angiotensin II receptor antagonists and ACE inhibitors are classified as Australian pregnancy category D. Their use is contraindicated in pregnancy.

Antihypertensives acting on the renin-angiotensin system have been associated with decreased renal function, oligohydramnios and retardation of skull ossification in the fetus. Their use in pregnancy has been associated with neonatal problems such as renal failure, hypotension and hypokalaemia.[1] The risk of fetal abnormalities is considered greatest with second and third trimester exposure.[2]

Advice for health professionals

Health professionals should review the use of angiotensin II receptor antagonists and ACE inhibitors in women of child-bearing age. These women should be advised of the risks to the fetus and counselled on the use of appropriate contraception to avoid inadvertent fetal exposure. Patients taking an angiotensin II receptor antagonist or ACE inhibitor should be advised to speak to their doctor if they may be pregnant, or planning a pregnancy. Women who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent. Information on the use of antihypertensive drugs in pregnancy can be found in the April 2012 issue of *Australian Prescriber*.[3]

REFERENCES

1. Atacand Product Information. Astra Zeneca Pty Ltd. 2011 Jul.
2. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. Early Hum Dev 2006;82:23-8.
3. Donovan P. Hypertensive disorders of pregnancy. Aust Prescr 2012;35:47-50.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

Zolpidem: continued reporting of abnormal sleep-related events and amnesia

The TGA continues to receive reports of potentially dangerous, complex sleep-related behaviours, amnesia and hallucinations associated with zolpidem use. Patients should be reminded of the risks associated with the use of hypnotics. Health professionals are encouraged to report cases to the TGA, including suspected cases.

Zolpidem, a non-benzodiazepine gamma-aminobutyric acid (GABA) receptor agonist, is indicated for the short-term treatment of insomnia in adults. It has been marketed in Australia since 2000 under various trade names, including Stilnox. The TGA has previously alerted prescribers to the spectrum of spontaneously reported adverse events and the risk of parasomnias associated with its use.[1,2]

In 2007, the Australian media drew attention to reports of parasomnias, amnesias, hallucinations and suicidality with zolpidem use. Subsequently, the following boxed warning was added to the zolpidem Product Information (PI):

> Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

Reported cases

A study of reports received by the TGA between 2001 and 2008 concluded that there was 'an association between zolpidem exposure and parasomnias, amnesia and hallucination both before and after the cluster of media publicity beginning in early 2007'.[3] Despite the publicity, reporting of these adverse events has persisted at high levels (see Table).

A recent study which found that hypnotics (e.g. temazepam, zolpidem) are associated with a substantially elevated hazard of dying has revived the debate about the risks of hypnotic use.[4]

The use of zolpidem may unmask pre-existing depression and suicidal tendencies; the current PI for zolpidem has a precaution regarding depression, psychosis and schizophrenia. More than half of the deaths reported to the TGA in patients taking zolpidem have occurred in conjunction with either alcohol use (which is contraindicated) or concomitant use of antidepressants or antipsychotics, which suggests a pre-existing psychiatric diagnosis.

Information for health professionals

Five years after increased media attention there continues to be reporting of potentially dangerous complex sleep-related behaviours, amnesia and hallucinations. When considering the use of zolpidem in the management of insomnia, prescribers should advise patients of the contraindications and precautions listed in the PI, and of the spectrum of adverse effects associated with zolpidem use.

REFERENCES

1. ADRAC. Seeing things with zolpidem. Aust Adv Drug React Bull 2002;21:1.
2. ADRAC. Zolpidem and bizarre sleep related effects. Aust Adv Drug React Bull 2007;26:1.
3. Ben-Hamou M, Marshall NS, Grunstein RR, Saini B, Fois RA. Spontaneous adverse event reports associated with zolpidem in Australia 2001–2008. J Sleep Res 2011;20:559-68.
4. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012;2:e00085.

Table
Commonly reported adverse events for zolpidem Jan 2009 – Apr 2012

Adverse event	All medicines (Zolpidem)
Somnambulism	54 (29)
Abnormal sleep-related event	36 (28)
Amnesia*	201 (27)
Hallucination	536 (12)
Drug dependence	96 (7)
Abnormal behaviour	190 (7)
Road traffic accident	40 (6)

* Includes the following terms: amnesia, anterograde amnesia, dissociative amnesia, paramnesia, retrograde amnesia, transient global amnesia

MEDICINES SAFETY UPDATE

Renal function assessment in prescribing

The Cockcroft-Gault (CG) formula to calculate creatinine clearance (CrCl) should be used to estimate renal function in patients being prescribed drugs which are preferentially renally excreted.

True glomerular filtration rate (GFR) is most accurately assessed by radioisotopic measurement. However, as this test is time consuming, expensive and likely to delay appropriate clinical management, it has a limited role in the immediate management of most patients.

Measured CrCl has historically been used to estimate GFR, however it is also time and labour intensive, and can be unreliable; the gain in accuracy is minimal compared to using estimates of GFR.

Estimates of GFR

GFR can be estimated using either the Modification of Diet in Renal Disease formula (MDRD, used to calculate eGFR) or CG formula for CrCl.

In Australia, eGFR is routinely supplied with laboratory measurement of serum creatinine, providing a potentially convenient screening tool. However eGFR assumes a body surface area (BSA) of 1.73 m^2 and there is the potential to overestimate GFR at low BSA. In such circumstances, reliance on eGFR could result in an excessive dose being prescribed.

The CG formula for CrCl is an alternative estimate of GFR. This formula takes into account the patient's weight, age and gender. It can be ordered from pathology laboratories or alternatively can be calculated by the prescriber. CG is relatively simple to determine, is familiar to clinicians, and most clinical software is able to perform this calculation.

Limitations of formulae to estimate GFR

In certain situations, there is an important and clinically significant disparity between the CG formula for CrCl and eGFR, including in the following patient populations:

- age greater than 70 years
- ethnicity (e.g. Asian)
- low muscle mass (e.g. elderly, amputee, malnourished patients)
- low intake of dietary protein (e.g. vegan)
- obesity.

In these patient populations, the estimation of GFR by either method could lead to overestimation of GFR. If there is evidence of renal insufficiency in the patient populations listed above, use caution and thoughtful clinical judgement when deciding on appropriate drug dosing adjustments.

Advice for health professionals

Most guideline groups recommend using the CG formula for drug dosing until more clinical studies with the MDRD eGFR formula are conducted. There are, however, published statements indicating that for most drugs in primary care, and for most patients of average age and body size, dosage adjustments based on eGFR should be similar to those based on CrCl.[1,2]

eGFR should not replace CG for determining dosage adjustments for drugs that have a narrow therapeutic index until more studies of eGFR are conducted. Nevertheless, eGFR has a role in alerting treating clinicians to the possibility of reduced renal function and to prompt consideration of dosage adjustments.

Renal function should be assessed in circumstances where there is clinical suspicion of a deterioration in kidney function due to acute kidney injury (examples include hypovolaemia, septicaemia, causes of nephrotoxicity or any other major acute medical illness).

Chronic kidney disease classification

The stages of chronic kidney disease (CKD) as defined by Kidney Health Australia are as follows:

Stage 1
Kidney damage with normal or ↑ GFR ≥90 mL/min

Stage 2
Kidney damage with mild ↓ GFR 60–89 mL/min

Stage 3
Moderate ↓ GFR 30–59 mL/min

Stage 4
Severe ↓ GFR 15–29 mL/min

Stage 5
Kidney failure GFR <15 mL/min (or dialysis)

At the present time, information on dosage adjustments in patients with renal impairment may be presented in the Product Information in terms of CrCl, not CKD.

Acknowledgement: The TGA wishes to acknowledge advice from the Advisory Committee on the Safety of Medicines, used in the preparation of this article.

REFERENCES

1. Johnson DW, Jones GRD, Becker GJ, Mathew TH. Automated reporting of eGFR: a useful tool for identifying and managing kidney disease. Med J Aust 2009;190:200-3.
2. Automatic eGFR reporting – its role in screening for kidney disease and drug-dosing decisions. NPS RADAR. 2008 Aug.

MEDICINES SAFETY UPDATE

Anaphylaxis with chlorhexidine-impregnated central venous catheters

Clinicians are reminded that certain brands of central venous catheter (CVC) are impregnated with chlorhexidine to reduce the likelihood of CVC-associated bloodstream infections. A history of chlorhexidine hypersensitivity should be sought before choosing this type of CVC.

Chlorhexidine is known to cause IgE-mediated immune responses.

Chlorhexidine hypersensitivity is considered rare (estimated to occur at a rate of one case for every 385 000 catheter insertions),[1] but is probably under-reported. There are warnings on the packaging of CVCs regarding chlorhexidine hypersensitivity.

Antimicrobial surface-treated CVCs have been available since the 1990s. In 1998, the US Food and Drug Administration alerted clinicians to the possibility of hypersensitivity reactions to chlorhexidine-impregnated CVCs and other products containing chlorhexidine.[2] Over time sporadic case reports of anaphylaxis have appeared in the literature.[3]

The TGA has received three reports of anaphylaxis associated with the insertion of a chlorhexidine-impregnated CVC.

A high index of suspicion should be maintained by critical care clinicians faced with anaphylaxis temporally associated with the insertion of a chlorhexidine-impregnated CVC. Clinicians are encouraged to report all adverse events associated with chlorhexidine-impregnated CVCs to the TGA.

REFERENCES

1. Sponsor communication to the TGA. 2011 May.
2. FDA Public Health Notice: Potential hypersensitivity reactions to chlorhexidine-impregnated medical devices. US Food and Drug Administration. 1998.
3. Lee R, Nel L, Gnanakumaran G, Williams A, Eren E. Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg? Br J Anaesth 2009;103:614-5.

What to report? You don't 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 and with the August issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **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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