Medicines Safety Update

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In this issue

Olmesartan and sprue-like enteropathy

Health professionals are advised that the Product Information documents for olmesartan-containing products have been updated with a precaution for sprue-like enteropathy.

Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist, which is used to treat hypertension. It has been on the Australian Register of Therapeutic Goods since 2005 and is listed on the Pharmaceutical Benefits Scheme.

Case series

A TGA investigation was conducted after the publication of a case series involving 22 patients experiencing chronic diarrhoea and enteropathy while taking olmesartan.[1]

Each patient suffered chronic diarrhoea for more than four weeks and had no other identified cause for enteropathy, such as coeliac disease or tropical sprue.

All patients experienced weight loss, with an average loss of 18 kg, and intestinal biopsy revealed villous atrophy in each case. In some instances the adverse events experienced were severe, with 14 of the 22 patients hospitalised to manage severe dehydration. Four of the patients suffered acute renal failure and four required total parenteral nutrition.

Where information was available, the mean duration of olmesartan use prior to onset of diarrhoea was 3.1 years.

All of the patients demonstrated clinical improvement after stopping olmesartan treatment.

Product Information update

The Product Information (PI) for olmesartan-containing products had previously listed diarrhoea and gastroenteritis as potential adverse events, but not more severe forms of enteropathy.

The updated PI includes a precaution for sprue-like enteropathy and lists it in the adverse effects section, under 'Post-marketing experience'.

Adverse event reports

Between 2005 and 31 January 2014, the TGA received 10 reports of diarrhoea in patients being treated with olmesartan, including four which were serious. Two reports involved enterocolitis and acute renal failure, another described villous atrophy and dehydration, and the fourth included acute renal failure, villous atrophy and *Clostridium difficile* colitis. All four patients experiencing these serious adverse events recovered after discontinuing olmesartan treatment.

Information for health professionals

Advise patients who are being treated with olmesartan to contact you if they develop severe, chronic diarrhoea with weight loss, even if these symptoms arise months or years after they started taking the drug.

If a patient experiences severe, chronic diarrhoea with weight loss while taking olmesartan, exclude other potential causes. If no other aetiology is identified, consider discontinuation of olmesartan.

In many reported cases in Australia and overseas, stopping olmesartan treatment has resulted in clinical improvement of sprue-like enteropathy symptoms in patients.

REFERENCE

1. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Murray JA, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012;87:732-8.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Codeine use in children after tonsillectomy and/or adenoidectomy

Health professionals are advised of the risk of rare but very serious adverse events when using codeine to treat children after tonsillectomy and/or adenoidectomy.

Codeine is a widely used opioid analgesic and, in combination with paracetamol, can be prescribed for children after tonsillectomy and/or adenoidectomy.

Ultra-rapid metabolism of codeine

Patients may respond differently to codeine treatment due to genetic differences. Codeine is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6). Patients who are deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not experience adequate pain relief. Conversely, patients who metabolise codeine to morphine very rapidly ('ultra-rapid metabolisers') are at increased risk of morphine toxicity, even at low codeine doses.

Cases of respiratory depression and death following the use of codeine in children after tonsillectomy and/or adenoidectomy have been reported in the United States.[1,2] The US Food and Drug Administration (FDA) found that many of the cases of serious adverse events relating to such codeine use occurred in children with obstructive sleep apnoea. The affected children were also identified as being ultra-rapid metabolisers of codeine.

It is estimated that up to 10% of Caucasians may be ultra-rapid metabolisers. Estimated rates for other ethnic groups are generally lower, with the exception of North African and Middle Eastern people (10–29%).[3]

Reported cases in Australia

The TGA has received no reports of death in children after tonsillectomy and/or adenoidectomy in which codeine has been a suspected drug in Australia.

To January 2014, there have been seven adverse event reports in children and adolescents involving codeine that are suggestive of respiratory depression. All except one of them included co-administration of morphine, pethidine or midazolam.

The TGA further investigated this issue by checking the National Coronial Information System database for child deaths involving codeine and child deaths after tonsillectomy and/or adenoidectomy. No cases similar to the situation described by the FDA were found.

The TGA continues to monitor this issue.

Information for health professionals

Health professionals may wish to consider using an alternative analgesic for children after tonsillectomy and/or adenoidectomy. If codeine is used, it should be at the lowest effective dose for the shortest time possible.[4]

You are also encouraged to educate parents and caregivers about possible adverse events associated with the general use of codeine in children, including codeine-containing products purchased over the counter. You should advise parents and caregivers to stop using codeine and seek medical attention if symptoms of toxicity are observed in a child.

Symptoms of morphine toxicity or overdose may include:

- somnolence
- difficulty waking
- confusion
- shallow breathing
- nausea/vomiting
- constipation
- lack of appetite
- coma.

The effects of morphine toxicity or overdose can be reversed with the narcotic antagonist, naloxone.

REFERENCES

1. US Food and Drug Administration. Codeine use in certain children after tonsillectomy and/or adenoidectomy: drug safety communication - risk of rare, but life-threatening adverse events or death. 2012, updated 2013.
2. Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.
3. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics 2006;47:75-85.
4. NPS MedicineWise. Codeine in children – deaths prompt new safety warnings. 2013 Aug.

MEDICINES SAFETY UPDATE

Methoxyflurane and occupational exposure

Health professionals are reminded of the risks associated with extended or repeated occupational exposure to methoxyflurane.

Methoxyflurane is an anaesthetic that is only approved for short-term use as an analgesic in stable, conscious patients. It is a volatile liquid intended for vaporisation and administration by inhalation.

While still used as an analgesic in the emergency setting, methoxyflurane has been withdrawn from use as an anaesthetic due to its well-documented nephrotoxicity and hepatotoxicity risks.[1]

The potential risk of extended or repeated occupational exposure for health professionals administering methoxyflurane, particularly in closed or poorly ventilated environments, is well known. There is a precaution for occupational exposure in the Product Information that states that multiple use creates additional risk and recommends health professionals consider using an optional activated carbon scavenging unit, which is available with the inhaler.

Health facilities and ambulance services have workplace occupational health and safety guidelines that mitigate risks for employees. Health professionals who administer methoxyflurane are advised to familiarise themselves with and follow these guidelines.

NPS MedicineWise has also published advice for health professionals on its website regarding this issue.[2]

Despite widespread use of methoxyflurane in Australia, there has been a comparatively low number of adverse event reports. From 1985 to 31 January 2014, there have been 11 adverse event reports for methoxyflurane, none of which involved occupational exposure for health workers.

REFERENCES

1. US Food and Drug Administration. Determination that Penthrane (methoxyflurane) inhalation liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. 2005 Aug.
2. NPS MedicineWise. Methoxyflurane (Penthrox) for analgesia (doctor's bag listing). 2010 May, updated 2010 Nov.

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, and 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 October 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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