Australian Government
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Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Ondansetron and QTc interval prolongation – dosing change

To reduce the risk of QTc interval prolongation, health professionals are advised that the 32 mg once-daily intravenous dose of ondansetron is no longer recommended and should not be used.

Ondansetron is a potent, highly selective $5HT_3$ receptor antagonist. It is indicated for use in the prevention of chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting.

Study results

A recently completed study has shown that ondansetron at a single intravenous dose of 32 mg can cause QTc interval prolongation, which in turn could lead to torsade de pointes.[1] At the highest tested dose of 32 mg intravenously over 15 minutes, the maximum mean QTc interval prolongation was about 20 milliseconds and the upper bound remained greater than 10 milliseconds during the two hours after the infusion. This suggests that this dose could result in a clinically significant degree of QTc interval prolongation in some patients.

Information for health professionals

Health professionals are advised of the following information:

- Intravenous doses greater than 8 mg (up to a maximum of 16 mg) should be infused over at least 15 minutes
- No single intravenous dose of ondansetron should be greater than 16 mg
- There are no changes to the recommended dosing with oral or rectal ondansetron formulations. Dosing with all formulations should be as described in the approved Product Information (PI).[2]
- Patients should be assessed for QTc interval prolongation or cardiac arrhythmia before being prescribed ondansetron
- Avoid ondansetron in patients with congenital long QT syndrome
- Caution should be exercised when prescribing for patients who have or may develop QTc interval prolongation, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or who take other medicines that can lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected before using ondansetron.

The sponsor has updated the PI and written a Dear Healthcare Professional letter advising of the revised dosing recommendations.

Health professionals are encouraged to report any suspected adverse events to the TGA.

REFERENCES

1. GSK Clinical Trials Registry. A randomised, double-blind, four-period crossover study to investigate the effect of intravenous ondansetron, a 5-HT3 antagonist, on cardiac conduction as compared to placebo and moxifloxacin in healthy adult subjects. Clinical study ID: S3A115458.
2. Zofran Product Information. GlaxoSmithKline Australia Pty Ltd. 2011 Nov.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Domperidone (Motilium) – serious ventricular arrhythmias and sudden cardiac death

Health professionals are advised that domperidone should be initiated at the lowest possible dose in adults. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

Domperidone is a gastrointestinal motility modifier indicated for the short-term treatment of symptoms associated with idiopathic or diabetic gastroparesis in adults, and is also indicated for intractable nausea and vomiting from any cause.

Evidence of risk

The epidemiological studies showed that the risk of sudden cardiac death and/or serious ventricular arrhythmias was higher in patients using daily doses greater than 30 mg[1] and in patients older than 60 years of age[2].

Information for health professionals

Health professionals are advised:

- Domperidone should be initiated at the lowest effective dose
- The risk of serious ventricular arrhythmias or sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age
- Domperidone is contraindicated with ketaconazole, erythromycin or other potent CYP3A4 inhibitors which prolong QTc interval such as fluconazole, voriconazole, clarithromycin and amiodarone
- Domperidone should be used with caution and at the lowest effective dose in at-risk patients such as those:
  - with existing prolongation of cardiac conduction intervals (particularly the QT interval)
  - using potent CYP3A4 inhibitors which may increase plasma levels of domperidone such as itraconazole, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, diltiazem, verapamil and aprepitant
  - with significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia)
  - with underlying cardiac diseases such as congestive heart failure.

The dose of domperidone may be adjusted upward with caution to achieve the desired effect as needed. The expected benefit of an increased dose should outweigh the potential risks. The maximum dose of domperidone is 80 mg.

Domperidone should not be used in children.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

The PI for domperidone has been updated to include the new drug dosage and usage recommendations, as well as information about the risk of serious ventricular arrhythmias and sudden cardiac death.

REFERENCES

1. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf 2010;33:1003-14.
2. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol Drug Saf 2010;19:881-8.

MEDICINES SAFETY UPDATE

Cardiovascular safety risk with fingolimod (Gilenya) – updates to the Product Information

The TGA is advising health professionals of important cardiovascular safety related changes to the fingolimod (Gilenya) Product Information including new contraindications.

Fingolimod is a sphingosin 1-phosphate receptor modulator used in the treatment of relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis to delay the progression of physical disability and reduce the frequency of relapse.

Following a review of the cardiovascular safety of fingolimod, the PI has been updated with new contraindications and a new precaution regarding first-dose monitoring and QTc interval prolongation.

Following the death of a patient in the US within 24 hours of their first dose of fingolimod, the US Food and Drug Administration (FDA) undertook a re-evaluation of safety data related to the cardiovascular effects of fingolimod. The FDA could not definitively conclude that the administration of fingolimod was related to the patient's death but made a number of recommendations to improve the safe use of the drug.

Fingolimod is now contraindicated:

- in patients with specific cardiac conditions; and
- with concomitant treatment with Class Ia or Class III anti-arrhythmic drugs during fingolimod initiation.

The Precautions section has been updated to include first-dose monitoring, with emphasis on cardiac monitoring, namely pulse, blood pressure and electrocardiogram. Should a patient require pharmacological intervention during the first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring strategy should be repeated after the second dose of fingolimod.

More information

Health professionals are advised to consider this new cardiovascular safety information when prescribing fingolimod. For full prescribing details, health professionals should refer to the Gilenya PI, available from the TGA website.

Disposal of unwanted medicines

Health professionals may like to inform their patients that they can safely dispose of expired, unwanted, or unused medicines, at no cost, by taking them to their community pharmacist.

Medicines may become unwanted after they expire, if they remain unused, or after the TGA publishes a safety alert recommending their disposal. Disposal of any expired and unwanted medicines can also take place with the consent of the consumer if a need is identified after a Home Medicines Review, or by a health professional.

The Australian Government-funded Return Unwanted Medicines (RUM) Project facilitates the collection and disposal of expired, unwanted or unused medicines from the community. The RUM Project operates nationally with the cooperation of the pharmaceutical industry bodies in Australia.

The RUM Project uses the national community pharmacy network to collect unwanted medicines, which are then disposed of through high temperature incineration. This means of disposal reduces the risk of accidental use of medicines and prevents environmental damage from unsafe disposal, such as flushing medicines down the toilet, tipping them down the sink or putting them out with the garbage.

More information on the RUM Project for consumers and pharmacists is available at www.returnmed.com.au.

MEDICINES SAFETY UPDATE

Changes to over-the-counter cough and cold medicines for children

Health professionals are advised that the TGA has recently completed a review of the safety and efficacy of over-the-counter cough and cold medicines for use in children.

The TGA concluded that there are no immediate safety risks with these medicines. However, the review found there is evidence that they may cause harm to children, while the benefits of using them in children have not been proven.

As a result, these medicines:

- should not be given to children under 6 years of age
- should only be given to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner
- should be labelled with warnings and instructions to the above effect
- should only be available in child-resistant packaging.

Health professionals are advised that no changes have been made to the scheduling of these medicines and a prescription is not required. A recommendation for treatment with these medicines for a child under 6 years of age constitutes off-label use.

Existing stock with older labelling can still be sold for adults and children aged 12 years and over (or 6 to 11 years on the advice of a health professional) until stocks are exhausted.

For further details of the review, see the TGA website: www.tga.gov.au/industry/otc-notices-cough-cold-review-outcomes.htm.

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.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

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

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