Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 6, Issue 1, August 2012

Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

NHS Evidence accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

For full details on our accreditation visit **NHS Evidence**

http://www.evidence.nhs.uk/Accreditation

In this issue: there is an increased risk of cancer with long-term use of **calcitonin**. Because of this risk, calcitonin should no longer be used in the treatment of osteoporosis. All intra-nasal calcitonin sprays, which are the only formulation of calcitonin licensed for osteoporosis, will be withdrawn from the European market (see article A1).

Also this month: the maximum dose of **intravenous ondansetron** for the management of chemotherapy-induced nausea and vomiting in adults is now restricted to 16 mg (infused over at least 15 minutes). This is to minimise the known associated risk of QTc prolongation (see article A2)

The recommended dose of **doripenem** to treat nosocomial pneumonia in patients with augmented renal function and/or infections with pathogens with possible decreased susceptibility has been increased to 1 g every 8 hours given as a 4-hour infusion (see article A3).

And finally: there are updated contraindications and dose recommendations for **simvastatin** when used with a number of other medicines. These changes have been driven by concerns over the risks of myopathy and/or rhabdomyolysis at higher plasma concentrations of simvastatin. An updated list of all interactions with simvastatin is provided in article S1.

Priya Venkatesan, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Calcitonin (Miacalcic): increased risk of cancer with long-term use – all intra-nasal formulations for osteoporosis to be withdrawn

There is an increased risk of cancer associated with the long-term use of calcitonin. Because of this risk, calcitonin-containing medicines should no longer be used in the treatment of osteoporosis.

All intra-nasal calcitonin sprays, which are the only formulation of calcitonin licensed for osteoporosis, will be withdrawn from the European market.

Calcitonin is a drug used to treat disorders of bone metabolism, such as osteoporosis, Paget's disease, acute bone loss due to sudden immobilisation and hypercalcaemia of malignancy. Calcitonin, which is not widely used in the UK, is currently available in intra-nasal and injectable formulations.

All available data on the risks and benefits of calcitonin have been reviewed, including data from randomised clinical trials with intra-nasal and unlicensed oral calcitonin formulations. In these trials, different types of malignancies were observed more frequently in patients treated with calcitonin, compared with placebo. The absolute increased risk of cancer varied between 0.7% and 2.4%. The review concluded that because of the increased risk of cancer associated with long-term use of calcitonin, the benefits of calcitonin no longer outweigh its risks in the treatment of osteoporosis.

Press release from the European Medicines Agency on the withdrawal of intranasal calcitonin [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001573.jsp&mid=WC0b01ac058004d5c1]

As the intra-nasal spray of calcitonin is only licensed in the indication of osteoporosis the European Committee on Medicinal Products for Human Use (CHMP) has recommended that this formulation should be withdrawn from the European market.

Calcitonin will still be available as a solution for injection and infusion for the short-term treatment of:

- Paget's disease – now restricted to patients who do not respond to, or cannot tolerate, alternative treatments (ie, patients with renal impairment). Duration of calcitonin should be limited to up to 3 months, but may be extended to 6 months under exceptional circumstances (eg, patients with impending pathologic fractures)
- acute bone loss prevention due to sudden immobilisation, for up to 4 weeks only (no change in use)
- hypercalcaemia of malignancy (no change in use)

In all remaining indications, treatment with calcitonin should be limited to the shortest possible time, using the minimum effective dose.

NICE guidance on the treatment of osteoporosis [http://publications.nice.org.uk/alendronate-etidronate-risedronate-raloxifene-and-strontium-ranelate-for-the-primary-prevention-ta160]

Advice for healthcare professionals:

- Healthcare professionals should no longer prescribe calcitonin-containing medicines for the treatment of osteoporosis
- Patients who are currently being treated with intra-nasal calcitonin for osteoporosis should be reviewed and changed to another suitable treatment in line with NICE recommendations
- While a change in treatment could happen at the next routine appointment, prescribers may wish to see patients sooner

Further information:

BNF section 6.6 Drugs affecting bone metabolism [http://www.medicinescomplete.com/mc/bnf/current/100042.htm]

Article citation: Drug Safety Update Aug 2012 vol 6, issue 1: A1.

Drug safety advice

A2 Ondansetron (Zofran): risk of QTc prolongation – important new intravenous dose restriction

The new maximum single intravenous dose of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in adults is now 16 mg (infused over at least 15 minutes).

This restriction follows a review of new study data, which showed that there is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for CINV.

Ondansetron is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

In a study in healthy adults, ondansetron 32 mg given intravenously (IV) over 15 minutes caused a maximum mean QTc prolongation of 19.57 (upper 90% confidence interval 21.49) milliseconds. This dose may therefore result in a clinically significant degree of QT prolongation in certain individuals.

Ondansetron 8 mg IV over 15 minutes caused a QTc prolongation of 5.84 (upper 90% CI 7.76) milliseconds – this level of prolongation is not usually associated with increased risk of cardiac arrhythmias.

Extrapolating from these results it was predicted that ondansetron 16 mg IV over 15 minutes would cause a QTC prolongation of 9.1 (upper 95% CI 11.2) milliseconds, an extent that is not usually associated with increased risk of cardiac arrhythmias.

Prolongation of the QTc can lead to Torsade de Pointes (TdP), a potentially life-threatening cardiac arrhythmia. Although no cases of TdP were observed in the study, TdP has been reported in association with the use of ondansetron in clinical practice.

Advice for healthcare professionals:

- A single dose of intravenous ondansetron given for the management of chemotherapy-induced nausea and vomiting in adults must not exceed 16 mg (infused over at least 15 minutes)
- Ondansetron should be avoided in patients with congenital long QT syndrome.
- Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities; use of other medicines that prolong the QT interval (including cytotoxic drugs) or may lead to electrolyte abnormalities; congestive heart failure; bradyarrhythmias; and use of medicines which lower the heart rate
- Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration

The maximum recommended intravenous dose of ondansetron for the prevention and treatment of post-operative nausea and vomiting in adult patients is a single dose of 4 mg and this has not changed. In addition there are no changes in the recommended intravenous dosing for any indication in paediatric patients.

Further information:

Letter sent to healthcare professionals sent in August 2012 [https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101815]

Revised wording for ondansetron product information [http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con178193.pdf]

BNF section 4.6: Drugs used in nausea and vertigo [http://www.medicinescomplete.com/mc/bnf/current/129637.htm]

There are no changes to the recommended dosing for oral or rectal ondansetron formulations in adult or paediatric patients in any indication.

Article citation: Drug Safety Update Aug 2012 vol 6, issue 1: A2.

Drug safety advice

A3 Doripenem (Doribax▼): current dosing regimen is insufficient in some patients – updated dosing recommendations

The recommended dose of doripenem to treat nosocomial pneumonia in patients with augmented renal function and/or infections with pathogens with possible decreased susceptibility has been increased to 1 g every 8 hours given as a 4-hour infusion. Previous dosing regimens for doripenem in such patients were found to be insufficient.

Doripenem (Doribax) is a carbapenem antibacterial agent indicated for nosocomial pneumonia (including ventilator–associated pneumonia), complicated intra-abdominal infections and complicated urinary tract infections.

A recent review of study data on nosocomial pneumonia (including ventilator–associated pneumonia) indicates that the currently approved dose of doripenem is insufficient in patients with augmented renal function (particularly those with creatinine clearance (CrCl ≥ 150 mL/min) and/or infections with pathogens with possible decreased susceptibility and should be increased.

The new recommendations will be available in the updated product information [http://www.medicines.org.uk/EMC/medicine/21208/SPC/Doribax+500mg+powder+for+solution+for+infusion/].

Information on the appropriate use of antibiotics and prevalence of resistance can be found in NICE guidance [http://www.nice.org.uk/#panel3].

Advice for healthcare professionals:

- For patients with augmented renal function and/or infections with pathogens with possible decreased susceptibility, the recommended dose of doripenem to treat nosocomial pneumonia is now 1 g every 8 hours given as a 4-hour infusion
- Treatment duration of 10-14 days is usually required for patients with such infections and is often closer to 14 days for patients infected with pathogens such as *Pseudomonas* spp. and *Acinetobacter* spp.

Further information:

Letter to healthcare professionals sent in July 2012 [link to: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con175479.pdf]

BNF section 5.1: Antibacterial drugs [link to: http://www.medicinescomplete.com/mc/bnf/current/201584.htm]

No changes to the recommended doripenem doses for treating nosocomial pneumonia (including ventilator-associated pneumonia) due to susceptible pathogens in patients with non-augmented renal clearance, or for treating complicated intra-abdominal infections and complicated urinary tract infections, are required.

Article citation: Drug Safety Update Aug 2012 vol 6, issue 1: A3.

S1 Simvastatin: updated advice on drug interactions - updated contraindications

Drug Safety Update May 2010 [http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085169]

We have previously communicated on the increased risk of myopathy associated with use of high-dose simvastatin (80 mg daily) – see Drug Safety Update May 2010.

Considering the risk of myopathy associated with simvastatin, recent analysis of clinical trial data, spontaneously reported cases and drug- drug interaction studies has resulted in further changes to the simvastatin prescribing information. The changes include contraindications to concomitant use with certain medicines and maximum dose recommendations when simvastatin is taken with a number of other medicines, as these interactions may increase plasma concentrations of simvastatin which is associated with an increased risk of myopathy and/or rhabdomyolysis. Key points to note are that:

- Simvastatin is now contraindicated with ciclosporine, danazol and gemfibrozil
- The maximum recommended dose for simvastatin in conjunction with amlodipine or diltiazem is now 20 mg/day

Further information:

BNF section 2.12: Lipid-regulating drugs [http://www.medicinescomplete.com/mc/bnf/current/128041.htm?q=simvastain&t=search&ss=text&p=1#_128041]

A full updated listing of all the interactions is provided in the table below.

Drug interactions associated with increased risk of myopathy/rhabdomyolysis	
Interacting agents	Prescribing recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (eg, nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20 mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Article citation: Drug Safety Update Aug 2012 vol 6, issue 1: S1.