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

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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.

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Prolonged use of proton pump inhibitors (PPIs) has been associated with case reports of hypomagnesaemia, some serious. Healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (eg, diuretics; see article A1)

In addition, recent epidemiological studies have highlighted an association between long-term PPIs and an increased risk of fracture. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium (see article A2).

Tolvaptan (Samsca▼) is a selective vasopressin V2-receptor antagonist for treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH). Treatment can result in over-rapid correction of hyponatraemia, which can lead to serious neurological events. Careful monitoring of serum sodium is therefore important and co-administration of other drugs that may increase serum sodium is not recommended.

Tolvaptan may also reduce the effect of vasopressin analogues used to control or prevent bleeding. See article A3 for further information.

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Drug safety advice

A1 Proton pump inhibitors in long term use: reports of hypomagnesaemia

Prolonged use of proton pump inhibitors (PPIs) has been associated with hypomagnesaemia. Healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (eg, diuretics).

Proton pump inhibitors (PPIs) are a class of drugs for the treatment of duodenal and gastric ulcers, and are used in combination with antibacterials for the eradication of *Helicobacter pylori*. They are also used to treat gastroesophageal reflux disease, dyspepsia, and Zollinger-Ellison syndrome and for prevention and treatment of ulcers associated with the use of non-steroidal anti-inflammatory drugs. The class of PPIs includes esomeprazole (Nexium), lansoprazole (Zoton), omeprazole (Losec), pantoprazole (Protium), and rabeprazole (Pariet). Multiconstituent products containing PPIs are also available (Vimovo, Axorid).

Case reports of hypomagnesaemia

Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs, although the exact incidence is unknown. A review of case reports described in the literature or reported to regulatory authorities in Europe suggests that PPIs may cause hypomagnesaemia. Some cases occurred after 3 months of PPI therapy, but most occurred after 1 year of treatment. Serious manifestations of hypomagnesaemia—fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia—can occur, but they may begin insidiously and be overlooked. In most case reports, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment, and especially for those who take PPIs with digoxin or drugs that may cause hypomagnesaemia (eg, diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during treatment.

PPIs obtained over the counter

The observed increase in risk of hypomagnesaemia has been associated with prolonged use of PPIs (>1 year). PPIs obtained without prescription over-the-counter should not be used for more than 4 weeks without consulting a doctor. If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should consult a doctor. Provided that PPIs obtained over the counter are taken short-term and according to the recommended posology, their use is not expected to significantly increase the risk of hypomagnesaemia.

Further information

BNF section 1.3.5 Proton pump inhibitors (http://www.medicinescomplete.com/mc/bnf/current/2137.htm

Advice for healthcare professionals:

- Consider measurement of magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (eg, diuretics)
- Take into account any use of PPIs obtained over-the-counter

Advice for patients:

- If you are currently taking non-prescription PPIs, do not use them for more than 4 weeks without consulting a doctor
- See your doctor if you experience symptoms of hypomagnesaemia (eg, muscle twitches, tremors, vomiting, tiredness, loss of appetite) while taking PPIs

Article citation: Drug Safety Update April 2012 vol 5, issue 9: A1.

A2 Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of bone fracture

There is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium

Observational studies on a risk of fracture associated with PPIs suggest there may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses and over long durations (>1 year). The increased risk was observed mainly in elderly patients, and it is possible that other risk factors contribute to the increase in risk.

Two meta-analyses[1,2] of published pharmacoepidemiology studies suggest the risk of fracture is increased by 10–40% above baseline. The primary studies in these analyses have varied in the extent to which they have adjusted for other potential risk factors for fracture, and use of calcium or vitamin D.

Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.

PPIs obtained over the counter

The observed increase in risk of fracture has been associated with prolonged use of PPIs (>1 year). PPIs obtained without prescription over-the-counter should not be used for more than 4 weeks without consulting a doctor. If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should consult a doctor. Provided that PPIs obtained over the counter are taken short-term and according to the recommended posology, their use is not expected to significantly increase the risk of fracture.

1 Eom CS, et al. Ann Fam Med 2011; 9: 257–67.

2 Kwok CS, et al. Bone 2011; 48: 768–76.

Further information

BNF section 1.3.5 Proton pump inhibitors (http://www.medicinescomplete.com/mc/bnf/current/2137.htm

Advice for healthcare professionals:

- Treat patients at risk of osteoporosis according to current clinical guidelines and ensure they have an adequate intake of vitamin D and calcium
- Take into account any use of PPIs obtained over-the-counter

Advice for patients:

- If you are currently taking non-prescription PPIs, do not use them for more than 4 weeks without consulting a doctor
- Consult your doctor to make sure you are taking enough vitamin D and calcium

Article citation: Drug Safety Update April 2012 vol 5, issue 9: A2.

A3 **Tolvaptan (Samsca▼): over-rapid increase in serum sodium and risk of serious neurological events**

Treatment with tolvaptan (Samsca▼) can result in over-rapid correction of hyponatraemia, which can lead to serious neurological events. Careful monitoring of serum sodium is therefore important and co-administration of other drugs that may increase serum sodium is not recommended.

Tolvaptan may also reduce the effect of vasopressin analogues used to control or prevent bleeding.

Tolvaptan (Samsca▼) is a selective vasopressin V2-receptor antagonist. It has been licensed in the UK since 2009 for the treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH) at a dose of 15–60 mg once a day.

Risk of over-rapid increase in serum sodium

Tolvaptan achieves its therapeutic effect by increasing free water clearance without affecting sodium excretion, thereby raising serum sodium. However, there have been reports of serious neurological events (see below: advice for healthcare professionals) in patients treated with tolvaptan where the correction of serum sodium has exceeded the suggested rate. Further information on the rates at which serum sodium should increase is also set out in the advice for healthcare professionals.

Serum sodium should be closely monitored in patients receiving tolvaptan, especially those with very low serum sodium (<120 mmol/L) at baseline or where there is increased risk of demyelination syndromes (eg, hypoxia, alcoholism, or malnutrition).

Product information for tolvaptan has been updated to reflect the new advice.

Interaction with high sodium content medicines or other treatments for hyponatraemia

There is also a risk of a rapid rise in serum sodium when tolvaptan is given concomitantly with medicines with a high sodium content or with other treatments for hyponatraemia (for example normal or hypertonic saline). Treatment with such combinations is therefore not recommended.

Interaction with vasopressin analogues

In addition to its effect on the renal tubule, tolvaptan can block vasopressin V2-receptors involved in the release of coagulation factors (eg, von Willebrand factor). Therefore, tolvaptan may interact with vasopressin analogues such as desmopressin used to prevent or control bleeding, reducing their effect.

Further information

See also letter sent to healthcare professionals in March 2012 [http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con146921.pdf]

BNF section 6.5.2 Tolvaptan (http://www.medicinescomplete.com/mc/bnf/current/4426.htm)

Advice for healthcare professionals:

- Increases in serum sodium which are too rapid can be harmful and cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death
- Close monitoring of serum sodium during tolvaptan treatment is recommended, especially in patients with very low serum sodium (<120 mmol/L) at baseline or in those at high risk of demyelination syndromes—for example, those with hypoxia, alcoholism, or malnutrition
- Sodium correction that exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first 6–12 hours may be too rapid; in such patients close monitoring of serum sodium and administration of hypotonic fluid is recommended

- If the increase in serum sodium exceeds 12 mmol/L in 24 hours, or 18 mmol/L in 48 hours tolvaptan treatment should be interrupted or discontinued and followed by administration of hypotonic fluid
- Co-administration of tolvaptan with medicines with a high sodium content or with other treatments for hyponatraemia (for example normal or hypertonic saline) is not recommended
- The effect of vasopressin analogues such as desmopressin may be attenuated in patients using them to prevent or control bleeding when given with tolvaptan

Article citation: Drug Safety Update April 2012 vol 5, issue 9: A3.

Other information from the MHRA

O1 Learning about reducing medicines risk

Opioids

We have just launched a learning module on opioids[1] for clinical practitioners. This self-directed learning package outlines the key risks of this important class of medicines. For each adverse effect, the package outlines:

- The main features of the adverse effect
- Factors that increase the risk
- How the risk can be reduced
- Specific treatment for the adverse effect

Self-assessment questions, together with full feedback, complement the learning material. Interspersed in the content, clinicians will find 'activities' to help consolidate the learning.

A short evaluation form is included at the end of the module—we will use the information to shape our future learning modules.

The opioids learning module joins a similar module on selective serotonin reuptake inhibitors (SSRIs)[2] as well as one on pharmacovigilance[3]. The education[4] page on our website lists other learning materials and gives information on obtaining continuing professional development (CPD) credits.

New Centre for Postgraduate Pharmacy Education e-learning package

The Centre for Postgraduate Pharmacy Education has developed an e-learning package on adverse drug reactions, with MHRA input.

The package can form part of Continuing Professional Development for pharmacists.

Topics covered include:

- Introduction to adverse drug reactions
- Classification of adverse drug reactions
- Assessing the safety of medicines
- Reporting adverse drug reactions and the Yellow Card Scheme

1 http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Opioidslearningmodule/index.htm

2 http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/SSRIlearningmodule/index.htm

3 http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/pharmacovigilanceelearningmodule/index.htm

4 http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/index.htm

Access the module or gain further information here:
https://www.cppe.ac.uk/mycppe/ssl/login.asp

Article citation: Drug Safety Update April 2012 vol 5, issue 9: O1.