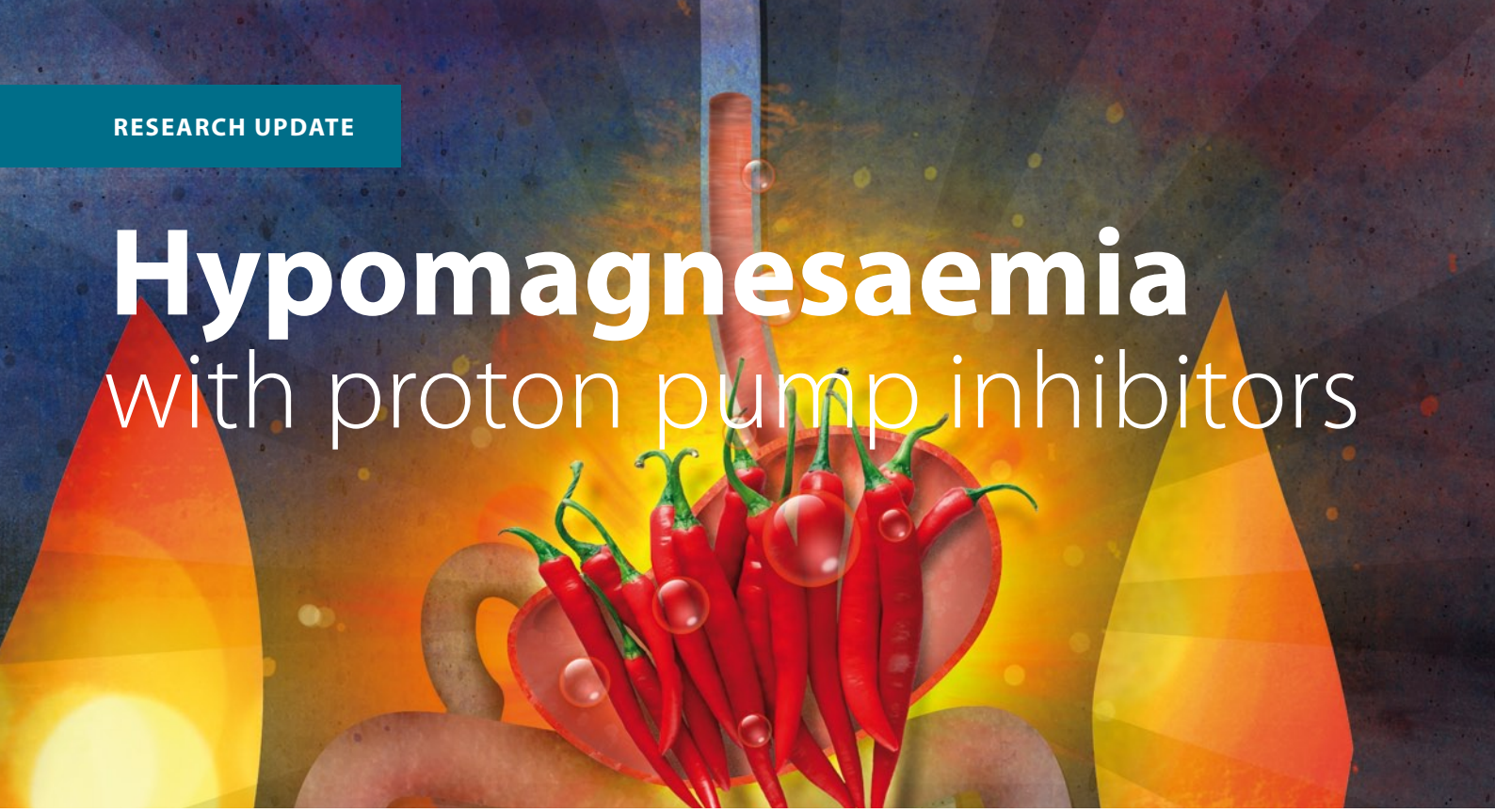
RESEARCH UPDATE

Hypomagnesaemia with proton pump inhibitors



IN DECEMBER, 2012 MEDSAFE published a warning on the risk of hypomagnesaemia for people taking any proton pump inhibitor (PPI).[1] This follows a previous Medsafe warning in 2010 about hypomagnesaemia associated with omeprazole,[2] the most commonly prescribed PPI in New Zealand.

Despite two decades of clinical use of omeprazole without concern about electrolyte changes, a "safety signal" was detected in 2008 after spontaneous reports to the Centre for Adverse Reactions Monitoring (CARM) of hypomagnesaemia in association with omeprazole. At this time, there was not enough evidence locally, or internationally, to confirm an adverse medicine reaction. More intensive monitoring of PPIs was encouraged in New Zealand by listing them on the Medsafe monitoring scheme: "M²" (see below). Further reports to CARM of hypomagnesaemia with a PPI, and similar international evidence,[3] has confirmed an association between PPIs (omeprazole, pantoprazole, lansoprazole) and hypomagnesaemia. In 2012 Medsafe recommended that hypomagnesaemia (and the possibility of hypocalcaemia) be added to New Zealand datasheets as a possible adverse effect of PPIs.[2] A suggested mechanism for the effect is interference with magnesium absorption by the PPI, however, this has not been determined by research.

What is a "Safety Signal"?

A safety signal can be described as information that arises from one or more sources (including observations, research and spontaneous reporting by health care providers, health authorities and lawyers) that suggests a potentially causal association between an intervention, e.g. a prescribed medicine, and an adverse event. A safety signal may be a new association, or a new aspect of a known association that helps define subgroups of patients who are at increased risk.

In New Zealand, CARM is responsible for assessing safety reports and determining the likelihood of an association. CARM may recommend that a safety warning be issued by Medsafe about a specific medicine, or class of medicines, with recommendations about a change in prescribing or monitoring practice. Alternatively a medicine maybe listed on Medsafe's Medicines Monitoring scheme "M²", to gather more information about the safety signal.

The purpose of M² is to highlight potential safety issues from reports of suspected adverse medicine reactions, and to stimulate further case reports from practitioners. Placing a medicine on M² does not mean that a change in prescribing practice is recommended at that time.

For further information see "M² Medicines Monitoring", available from: **www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp**

Who is at risk? What should I do?

All general practices will have a significant number of patients who are being treated with a PPI. Although hypomagnesaemia is classed as a rare adverse effect of PPIs, given their frequency of use, practitioners will need to be alert to the possibility of hypomagnesaemia occurring, and minimise the risk for certain patients.

Most reports of hypomagnesaemia with PPIs have occurred at doses of omeprazole 20 – 40 mg daily, and after 12 months or more of use; however, some cases of hypomagnesaemia were detected after three months of PPI treatment.[1, 2]

Symptoms of hypomagnesaemia are non-specific and include muscle cramps, weakness, fatigue, irritability and confusion. More serious symptoms include delirium, convulsions, tetany and arrhythmias. Some symptoms may occur gradually and therefore be easily overlooked.

People taking PPIs who are most at risk of hypomagnesaemia are:

- Those taking other medicines associated with hypomagnesaemia, e.g. diuretics, ciclosporin, aminoglycosides
- Those whose condition puts them at risk of deterioration should hypomagnesaemia occur, e.g. taking digoxin, with cardiac conduction concerns

Patients should be informed of the possibility of hypomagnesaemia when prescribed a PPI, particularly if treatment is anticipated to be long-term. Patients who are concerned can be advised to increase dietary magnesium intake with milk, wholegrain cereals, wholemeal bread, green leafy vegetables (spinach, parsley, cabbage), lean meat, nuts, seeds, bananas and peas.

If a patient who has been taking a PPI long-term, especially those at increased risk, presents with unexplained symptoms that may be suggestive of hypomagnesaemia, consider requesting a magnesium level.

If hypomagnesaemia is present, increased dietary intake of magnesium rich foods or magnesium supplementation may be sufficient to improve serum magnesium levels while continuing the PPI. For some patients the PPI will need to be stopped; if the indication for using the PPI is strong, a re-challenge while monitoring magnesium can be undertaken. It is reported that hypomagnesaemia can occur more rapidly in a person who has already experienced hypomagnesaemia while taking a PPI.[1]

Omeprazole is a "Pharmacy only" medicine

Be aware that your patients could be taking a PPI without a prescription. Omeprazole 10 mg and 20 mg tablets can be purchased in pharmacies for the short-term relief of reflux-like symptoms in people aged 18 years or older. If there is no improvement in symptoms after two weeks of treatment, patients are advised to consult a doctor (or pharmacist

There are no magnesium-only supplements subsidised on prescription; these can be purchased over-the-counter. N.B magnesium supplements can cause diarrhoea. The only product that could be prescribed for magnesium supplementation that has a prescription subsidy (partial only) is Mylanta P liquid, although it is approved for use in indigestion, heartburn, upset stomach and as an anti-flatulent. Mylanta P contains approximately 340 mg of Mg^{2+} per 20 mL dose, which is approximately the recommended daily magnesium intake for an adult; the dose for indigestion and as an anti-flatulant is 10 – 20 mL up to four times daily. Mylanta P also contains aluminium and simethicone, and can interfere with the absorption of other medicines, and therefore should not be taken within two hours of other medicines.

What about calcium?

Low magnesium is often associated with low calcium levels, which causes similar symptoms to hypomagnesaemia. If measuring magnesium levels in a symptomatic patient taking a PPI, consider measuring calcium also.

References

1. Medsafe. Hypomagnesaemia – a risk associated with all proton pump inhibitors. Prescriber Update 2012;33(4): 32. Available from: www.medsafe.govt.nz (Accessed April, 2013).
2. Medsafe. Omeprazole and risk of hypomagnesaemia. Prescriber Update 2010;31(2):13-4. Available from: www.medsafe.govt.nz (Accessed April, 2013).
3. United States Food and Drug Administration (FDA). Drug Safety Communication: Low magnesium levels can be associated with Long-term use of proton pump inhibitor drugs (PPIs). FDA; 2011. Available from: www.fda.gov/drugs/drugsafety/ucm245011.htm (Accessed April, 2013).