FEATURE

Medicinal mishap

Proton pump inhibitor-associated hypomagnesaemia and hypocalcaemia

Case

An 81-year-old man presented with light-headedness and paraesthesiae in his arms and legs. Past medical history included ischaemic heart disease, gastro-oesophageal reflux disease, chronic kidney disease, hypertension and loose stools, for many years. There was no previous history of peptic ulcer disease and a recent endoscopy was normal. He was taking aspirin 100 mg daily, perindopril 10 mg daily, amlodipine 10 mg daily, rosuvastatin 20 mg daily, omeprazole 20 mg daily and furosemide (frusemide) 40 mg daily. Examination was unremarkable, except for an unsteady gait.

Investigations revealed a normal full blood count, creatinine 142 micromol/L (normal range 64–108), estimated glomerular filtration rate 40 mL/minute (>60), potassium 3.5 mmol/L (3.5–5.2), sodium 142 mmol/L (135–145) and corrected calcium 1.10 (2.10–2.60). The presence of profound hypocalcaemia prompted the measurement of magnesium and parathyroid hormone. The results were magnesium 0.19 mmol/L (0.70–1.10), phosphate 1.87 mmol/L (0.75–1.50) and parathyroid hormone 3.7 pmol/L (1.0–7.0).

The proton pump inhibitor was considered to be the primary cause of the hypomagnesaemia, but the long history of loose stools, concomitant furosemide and chronic kidney disease could have contributed.

Omeprazole was therefore ceased and electrolytes successfully replaced, but due to ongoing reflux symptoms he was prescribed ranitidine. All other drugs were continued. One week later serum magnesium and calcium were normal.

The patient was readmitted nine days after discharge with a large bleeding duodenal ulcer requiring urgent endoscopy and subsequent embolisation. A proton pump inhibitor (pantoprazole) was restarted but the patient's magnesium dropped again. Magnesium concentrations were maintained initially with intravenous supplementation, but dropped to 0.51 mmol/L when this supplementation was ceased, despite oral magnesium sulfate 1 g three times a day. They subsequently stayed around this level with oral supplementation.

Comment

Hypomagnesaemia is a rare, potentially serious, adverse class effect of proton pump inhibitors, which is likely to be under recognised. The hypomagnesaemia is typically accompanied by hypocalcaemia, hypokalaemia and functional hypoparathyroidism. Recovery on stopping the proton pump inhibitor and recurrence on rechallenge, strengthen a causal association in this case.

There are increasing numbers of case reports, case series and retrospective reviews of hypomagnesaemia associated with long-term use of proton pump inhibitors. In a 2015 review, there were reports of the association in 64 individuals.[1] Life-threatening ventricular arrhythmias (torsades de pointes) have occurred in some cases. A search of the Australian Therapeutic Goods Administration Database of Adverse Event Notifications in August 2016 revealed 22 Australian reports of hypomagnesaemia. All proton pump inhibitors were implicated. Most reports described concomitant hypocalcaemia. In a cohort study of 366 patients hospitalised with hypomagnesaemia, current use of a proton pump inhibitor was associated with a 43% increased risk of hypomagnesaemia (adjusted odds ratio, 1.43; 95% confidence interval 1.06–1.93). The risk was increased in those on concomitant diuretics. There was no association with H_2 antagonists.[2]

Hypomagnesaemia is typically seen in patients over 50 years old on prolonged treatment (more than one year). It is more frequent when there are other factors that may lower magnesium, such as concomitant thiazides or loop diuretics, alcohol abuse and poor renal function. Symptoms can include lethargy, muscle weakness, cramping, carpopedal spasm, convulsions and arrhythmias. Hypomagnesaemia appears to be a class effect.

Low magnesium causes hypocalcaemia. This is likely to be due to interference with calcium-sensing receptor transduction, inhibition of parathyroid hormone release and end-organ resistance to parathyroid hormone. Parathyroid hormone concentrations are low or low-normal, in

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keeping with functional hypoparathyroidism. Both hypomagnesaemia and hypocalcaemia are associated with very low urinary magnesium and calcium excretion. Hypomagnesaemia-induced kaliuresis is the cause of the hypokalaemia.[3]

The suggested mechanism for proton pump inhibitor-induced hypomagnesaemia is impaired active and passive absorption of magnesium.[4]

Conclusion

Patients with suggestive symptoms, hypocalcaemia or 'idiopathic' hypoparathyroidism should be asked about their drug history. Consider measuring magnesium in those on proton pump inhibitors particularly if there are other predisposing factors for reduced magnesium concentrations.

Conflict of interest: none declared

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FURTHER READING

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