An Unusual Cause of Hypocalcaemia: Magnesium Induced Inhibition of Parathyroid Hormone Secretion in a Patient with Subarachnoid Haemorrhage

C. BRADFORD, A. McELDUFF
Department of Intensive Care and Department of Endocrinology, Royal North Shore Hospital, St Leonards, NEW SOUTH WALES

ABSTRACT

We describe a case of a woman with subarachnoid haemorrhage who developed hypocalcaemia and decreased serum parathyroid hormone levels due to hypermagnesemia. The patient had been receiving bisphosphonate therapy prior to admission and this may have contributed to the severity of the problem.
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Key words: Subarachnoid haemorrhage, vasospasm, magnesium, hypocalcaemia, parathyroid hormone, intensive care

Subarachnoid haemorrhage (SAH) occurs in 8.1 per 100 000 Australians annually.[1] Approximately 70% of patients with subarachnoid haemorrhage will develop vasospasm.[2] The peak incidence of vasospasm occurs 5 to 10 days following SAH. Patients at greatest risk are young, female and smokers. Vasospasm contributes to the morbidity and mortality of patients with SAH due to cerebral ischemia and infarction. Vasospasm may cause cerebral infarction in as many as 25 - 35% of patients with SAH.[3, 4]

The prevention of delayed ischaemic deficits arising as a consequence of cerebral vasospasm is of extreme importance. Preventing vasospasm has the potential to significantly improve the outcome of patients suffering aneurysmal SAH.

Management of vasospasm may be divided into preventative measures and treatment. Preventative methods include avoidance of hypotension and the use of nimodipine.[3] Treatment of vasospasm focuses on optimising cerebral nutrient delivery.

Basic science and clinical audit data suggest a benefit in prevention of vasospasm with the administration of magnesium sulfate.[5] Clinical data also suggests that magnesium is safe to administer and may reduce the incidence and severity of cerebral vasospasm.[5-7]

A recently published randomised controlled trial assessed the use of magnesium in reducing the incidence of delayed cerebral ischemia (DCI).[8] A total of 283 patients were randomised with magnesium reducing the risk of DCI by 34% (hazard ratio 0.66, 95% CI 0.38 to 1.14) and of a poor outcome by 23% (RR 0.77; 95% CI 0.54 to 1.09). These results are non-definitive and further research is required.

CASE REPORT

A 60-year-old woman was admitted to the emergency department, following an acute onset of headache. The pain radiated down her neck and was associated with vomiting. There were no sensorimotor symptoms and no visual disturbance. On examination, she was afebrile and had marked nuchal rigidity. A computed tomography (CT) scan of the head demonstrated subarachnoid haemorrhage in the prepontine cisterns and in the fourth ventricle. She was transferred to the

Correspondence to: Dr C. Bradford, Intensive Care, Level 6, Main Block, Royal North Shore Hospital, St Leonards, New South Wales, 2065 (email: cbradfor@nsccahs.health.nsw.gov.au)

nearest tertiary referral neurosurgical unit. Her past medical history included hypertension, hypercholesterolemia, type I diabetes, gastro-oesophageal reflux disease and osteoporosis. Her medications on hospital admission were Ramipril, Pravastatin, Gemfibrozil, Actrapid insulin, Protophane insulin and Alendronate. She was a non-smoker.

On admission to the intensive care unit (ICU), she was haemodynamically stable (on no inotropic support), breathing spontaneously, on no supplemental oxygen and had a Glasgow coma score (GCS) of 15, with no focal neurological signs. Baseline serum biochemistry demonstrated normal calcium and magnesium concentrations (calcium 2.11 mmol/L, ionised calcium 1.14 mmol/L and magnesium 0.79 mmol/L). Her renal function and serum sodium and potassium were normal. She was commenced on an infusion of magnesium sulfate with the aim of achieving serum concentrations of 1.6 - 2.5 mmol/L. Nimodipine was also commenced. Twelve hours after commencing the magnesium infusion she complained of weakness and headache. Her magnesium level was 2.42 mmol/L and the infusion was reduced. At this time her corrected serum calcium was 1.76 mmol/L and ionised calcium was 0.85 mmol/L. The next measurement of serum magnesium did not occur for 16 hours at which time the level was 2.72 mmol/L. She remained weak, developed some circumoral paraesthesia and muscle cramping. There was no tetany and Trousseau's and Chvostek's signs were negative. She remained haemodynamically stable. The magnesium infusion was stopped. At this time her corrected serum calcium was 1.37 mmol/L and ionised calcium was 0.8 mmol/L. She was given 6.8 mmol of calcium chloride and her symptoms resolved over the next hour

Investigations of the parathyroid hormone (PTH) concentration revealed an interesting relationship between magnesium, calcium and parathyroid hormone levels. The initial PTH was slightly elevated (88 ng/L) with normal serum calcium and magnesium. When she developed hypermagnesaemia, PTH level was low (33 ng/L) despite the hypocalcaemia. When the serum calcium level fell further to 1.37 mmol/L, the PTH rose to 148 ng/L (figure 1). As the serum magnesium returned to normal so did the serum calcium and the PTH returned to its previous mildly elevated level and her symptoms disappeared (figure 1).

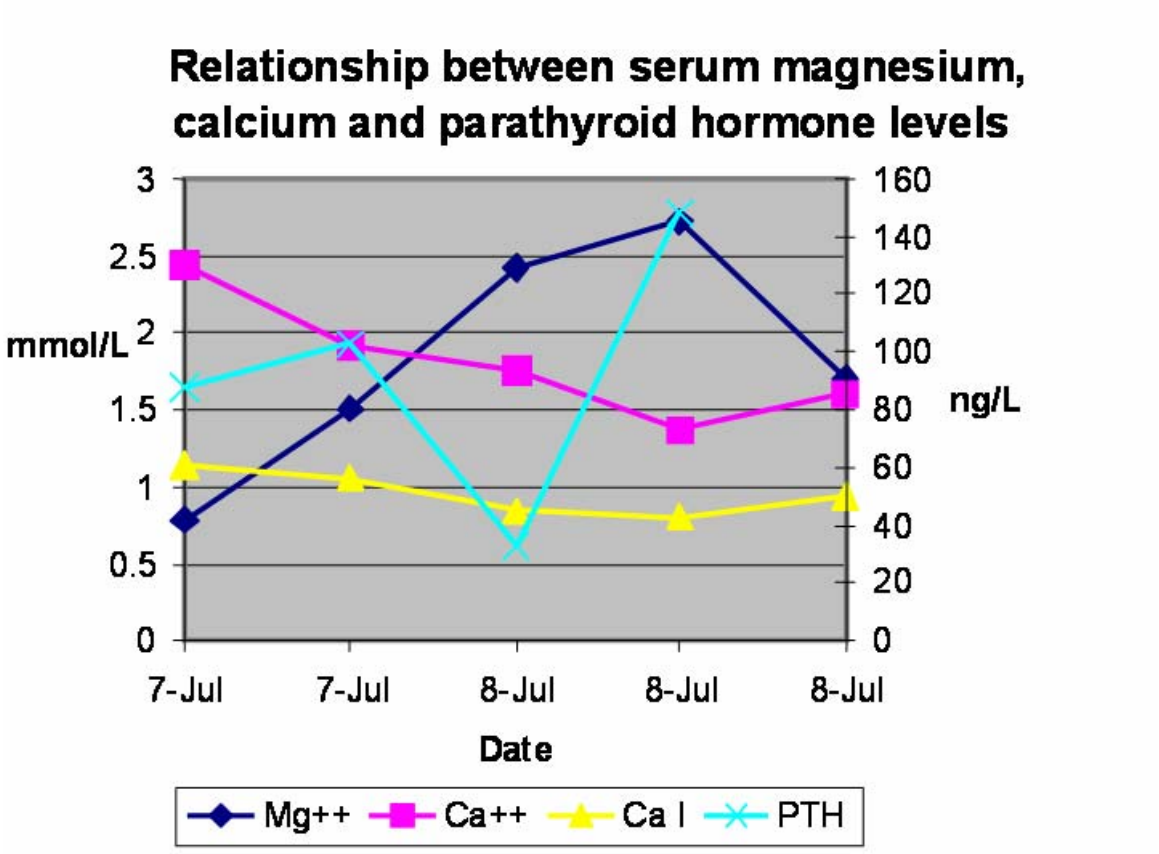

Figure1. As magnesium levels increased, parathyroid hormone levels fell causing a decrease in calcium concentration. At a crucial level of hypocalcaemia, this stimulus overrode the stimulus of hypermagnesaemia and parathyroid hormone levels increased.

DISCUSSION

Magnesium is a cation primarily found intracellularly. It has an important role as a coenzyme in phosphate transfer reactions. Hypomagnesaemia is commonly seen in clinical practice, for example malabsorption syndromes, renal tubular acidosis and following diuretic therapy. Hypermagnesaemia is less common. In most circumstances, hypermagnesaemia is iatrogenic, due to administration of magnesium salts for conditions including pre-eclampsia, cardiac arrhythmias and subarachnoid haemorrhage.

Although calcium is considered the primary cation responsible for PTH secretion, magnesium can also regulate secretion. There are a number of animal and human studies that have examined the relationship between magnesium and PTH.[9-14] Cholst *et al*,[9] measured PTH and calcium levels in seven pregnant women who were receiving intravenous magnesium sulfate for the suppression of premature labour. It was noted that total and ionised calcium levels fell gradually in all subjects from a normal baseline (2.2 $\pm$ 0.1 and 1.1 $\pm$ 0.03 mmol/L to 1.9 $\pm$ 0.1 and 0.98 $\pm$ 0.03 mmol/L.) PTH levels also fell rapidly from 13.1 $\pm$ 2.5 to 7.8 $\pm$ 0.7 ng/L at 30 minutes (significantly below baseline). However, with more pronounced and prolonged hypocalcaemia (i.e. after three hours) parathyroid levels returned toward those at base line, although compared to the degree of hypocalcaemia they were inappropriately low.

Ferment *et al*,[13] studied the effect on PTH of a moderate dose of magnesium sulphate (7.08 mmol) in seven healthy men. In addition, for comparison, the effect of calcium (4.25 mmol) was studied. Both substances caused a statistically significant decrease in plasma PTH levels within 45 minutes of injection. The effect of the hypercalcemia was more sustained (2 hours) compared with the magnesium (45 minutes).

Magnesium is thought to directly inhibit the release of PTH from the parathyroid gland.[15] Magnesium is an agonist of the G-protein coupled calcium-sensing receptor (CaR). The CaR was discovered and cloned in 1993. It is found on various tissues and the effect of stimulation varies depending on the cell type. In the parathyroid gland, activation of the CaR triggers a cascade of intracellular events, leading to decrease in PTH secretion.[16] Compared to calcium, magnesium acts as a partial agonist, with less potent effects.[17] It is not clear if this is the only mechanism of inhibition of PTH secretion by hypermagnesaemia. In the kidney stimulation of the CaR enhances magnesium excretion in the renal tubules.[16]

In our case the bisphosphonate therapy may have contributed to the dramatic response seen in serum calcium and PTH levels. Alendronate is a bisphosphonate that, in animal studies, localises preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Therefore, mobilisation of calcium stores in response to decreased PTH concentrations may have been impaired.

The case is of interest as magnesium therapy is used frequently in critical illness and has potential serious adverse effects on calcium and parathyroid homeostasis. Patients who are susceptible to hypocalcaemia are particularly at risk of developing symptomatic hypocalcaemia, for example patients with pancreatitis, sepsis, renal failure, osteoporosis and those receiving bisphosphonate therapy. The approach to a patient with hypocalcaemia should be focused at stopping contributing agents, investigating for underlying causes and treatment with calcium supplements. In the short term, if the patient is symptomatic, intravenous calcium chloride can be given to provide relief.

CONCLUSION

When magnesium therapy is utilised, the effects on other serum electrolytes, particularly calcium, need to be appreciated. Magnesium for the prevention of vasospasm following subarachnoid haemorrhage is an experimental therapy which, to date, has not been shown to improve outcomes in this patient group.

Hypermagnesaemia has been shown *in vivo* and *in vitro* to reduce PTH secretion. Calcium/magnesium homeostasis may be further effected in susceptible patient groups, for example those receiving bisphosphonate therapy.

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