Magnesium: the forgotten electrolyte

Joyce Wu, Registrar, and Andrew Carter, Director, Department of Chemical Pathology, Queensland Health Pathology Service, Brisbane

Summary

Magnesium is important for the proper functioning of various metabolic pathways and ion channels so disturbances in magnesium concentration can cause clinical problems. Hypomagnesaemia has many renal and extra-renal causes whereas hypermagnesaemia is usually due to renal insufficiency. Magnesium should be monitored in conditions such as arrythmia and when other electrolytes are abnormal.

Key words: hypermagnesaemia, hypomagnesaemia.

(Aust Prescr 2007;30:102–5)

Introduction

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation after potassium. Dietary sources of magnesium include whole grain cereals, green leafy vegetables, legumes, soybeans, nuts, dried fruit, animal protein and seafood.[1,2,3] The minimum recommended daily intake of magnesium for adults is 0.25 mmol (6 mg)/kg body weight.[4]

The total body magnesium of an adult male is approximately 1 mol (24 g).[1] Approximately 66% is distributed in bone, 33% in muscle and soft tissues, and less than 1% in blood. In blood 55% of the magnesium is free (ionised) and physiologically active, 30% is bound to proteins (primarily albumin), and 15% is complexed to anions.[5]

Magnesium homeostasis

Under normal conditions the body maintains constant circulating concentrations of magnesium in the blood. Homeostasis depends on the balance between intestinal absorption and renal excretion, with kidney tubules having primary control.[4]

The main site of absorption is the small intestine with smaller amounts absorbed in the colon.[4] Absorption can range from 24% of ingested magnesium in magnesium replete states to 76% in deficient states. Approximately 1 mmol is lost in gastrointestinal secretions daily.[1]

The kidney's handling of magnesium is more complicated. There is a circadian excretory rhythm with more magnesium excretion occurring at night.[3,6] Ionised and complexed magnesium are freely filtered at the glomerulus (70% of circulating magnesium). To maintain homeostasis, the nephrons normally reabsorb more than 96% of the filtered magnesium.[1,4] The amount reabsorbed can vary, however, from nearly zero to 99.5% depending on the individual's magnesium balance.[1]

Most reabsorption occurs in the thick ascending limb of the loop of Henle where 65–75% of filtered magnesium is reabsorbed passively down an electrochemical gradient which is actively maintained.[1,4] The amount reabsorbed is inversely related to tubular flow. Situations that abolish the positive luminal charge (for example loop diuretics, hypercalcaemia) will reduce the reabsorption of magnesium. The reabsorption of magnesium and calcium parallel each other in this segment, but the hormonal regulation of magnesium homeostasis is incompletely understood.[1]

Function

Magnesium is involved in over 300 enzymatic reactions. It is needed in energy metabolism, glucose utilisation, protein synthesis, fatty acid synthesis and breakdown, muscle contraction, all ATPase functions, for almost all hormonal reactions, and in the maintenance of cellular ionic balance.[2]

Magnesium is needed for the proper functioning of the Na^+/K^+–ATPase pump, so a deficiency causes an increase in intracellular sodium and allows potassium to leak out of cells.[2] Loss of intracellular potassium also occurs in the renal tubules.[1] This can lead to a hypokalaemia which only responds to magnesium replacement.[2]

Magnesium also affects calcium homeostasis through two mechanisms. Firstly, many calcium channels are dependent on magnesium. When the intracellular magnesium concentration is high, calcium transport into the cell and from the sarcoplasmic reticulum is inhibited. In magnesium deficiency the inverse occurs and consequently the intracellular concentration of calcium rises.[2] Secondly, magnesium is needed for the release and action of parathyroid hormone.[2] Magnesium's relationship with calcium means that patients with hypomagnesaemia may have a low plasma calcium that remains refractory to calcium supplementation until the magnesium deficiency is corrected.[2]

Laboratory tests

Most laboratories measure total magnesium; measurement of ionised magnesium is not standard practice. The normal range for total magnesium is 0.7–1.0 mmol/L. Caution should be taken in interpreting results from patients who have low total magnesium and low albumin, as they may have normal concentrations of ionised magnesium. Blood levels may not reflect total body stores.[5] One reason for this is that in acidosis magnesium shifts from the intracellular to the extracellular space, whereas in alkalosis the reverse occurs.[2] This can cause a dilemma particularly in determining the presence or absence of hypomagnesaemia.

Hypomagnesaemia

Due to magnesium's wide-ranging functions, magnesium deficiency may be the cause of numerous serious pathologies.[1,2,3,7,8]

As total blood magnesium concentrations do not always reflect total body stores, a high index of suspicion is needed particularly in patients at high risk of magnesium deficiency (see Table 1). Magnesium is often not included in routine electrolyte testing, so it is important that clinicians remember to order and monitor it. Changes in magnesium concentrations for an individual might be significant, even if they remain within the normal range.[2] Occasionally the magnesium-loading test is required to confirm magnesium deficiency.[2,4]

Causes

The causes of hypomagnesaemia are extra-renal or renal (Table 1). A 24-hour urine collection can be used to determine the presence or absence of renal magnesium wasting. In the presence of hypomagnesaemia, a 24-hour urine total magnesium less than 0.5 mmol is evidence of an intact renal response to hypomagnesaemia. A value greater than 1.0 mmol indicates abnormal renal wasting. Alternatively, the fractional excretion of magnesium (FE_{Mg}) on a random urine specimen can be used. In the presence of hypomagnesaemia, FE_{Mg} less than 2% indicates appropriate response to hypomagnesaemia while FE_{Mg} greater than 2% indicates renal wasting.[1]

Extra-renal causes

Conditions that cause malabsorption may lead to decreased gastrointestinal absorption of magnesium. These conditions include inflammatory bowel disease, chronic pancreatitis and alcoholism. In alcoholics, increased urinary magnesium wasting may also contribute to hypomagnesaemia. As magnesium is present in gastric secretions, vomiting and nasogastric suction are recognised (rare) causes of hypomagnesaemia. Skin loss of magnesium can be significant in burns patients. 'Hungry bone' syndrome which can occur following parathyroidectomy can also drop blood calcium, magnesium and potassium concentrations.[1]

Renal causes

There are two classic congenital magnesium wasting syndromes – Bartter's syndrome and Gitelman's syndrome. Both groups of patients have hypomagnesaemia, hypokalaemia, metabolic alkalosis and normal blood pressure. The main difference between the two syndromes is that urinary calcium is elevated in Bartter's syndrome and decreased in Gitelman's syndrome.[1,4]

Table 1

Causes of hypomagnesaemia*

Extra-renal		**Renal losses**	
Gastrointestinal	diarrhoea steatorrhoea alcoholism inflammatory bowel disease vomiting short bowel syndrome sprue chronic pancreatitis enteral nutrition gastric suction intestinal bypass for obesity protein calorie malnutrition (rare)	Drugs	aminoglycoside toxicity pentamidine toxicity amphotericin B toxicity thiazide and loop diuretics calcineurin inhibitors e.g. cyclosporin, tacrolimus foscarnet cisplatin alcohol
		Loop of Henle	hypercalcaemia
		Increased tubular flow	osmotic diuresis diabetes mellitus type I and II hyperaldosteronism volume expansion diabetic ketoacidosis
Skin	burns toxic epidermal necrolysis		
Bone	'hungry bone' syndrome		
		Tubular dysfunction	recovery from acute tubular necrosis recovery from obstruction
		Congenital renal magnesium wasting	

* adapted from reference 1

Drugs can cause renal wasting of magnesium. They either cause tubular toxicity (for example amphotericin B, aminoglycosides) or block renal reabsorption (for example loop diuretics).[1]

Hypercalcaemia can block renal reabsorption of magnesium, resulting in hypomagnesaemia. However, when hypercalcaemia is due to hyperparathyroidism, patients are usually normomagnesaemic because parathyroid hormone stimulates magnesium reabsorption.[1]

Effects

Hypomagnesaemia can cause hypokalaemia and hypocalcaemia. It is also associated with hyponatraemia and hypophosphataemia.[1]

Magnesium's usual role in the sodium-potassium ATPase pump and calcium-blocking activity is impaired by hypomagnesaemia leading to membrane destabilisation and hyperexcitability.[7] Patients can develop Trousseau's and Chvostek's signs even in the presence of a normal ionised serum calcium concentration.[1] With severe hypomagnesaemia, patients can have tetany and seizures (Table 2).

The effect on the myocardium is an increase in atrial and ventricular arrhythmias. Some ventricular arrhythmias caused by hypomagnesaemia only respond to treatment with magnesium.[1]

Table 2

Clinical findings associated with altered magnesium concentrations *†

Total magnesium concentration (mmol/L)	Findings
<0.5	tetany seizures arrhythmias
0.5–0.7	neuromuscular irritability
0.7–1.0	normal range
1.0–2.1	typically asymptomatic
2.1–2.9	lethargy drowsiness flushing nausea and vomiting diminished deep tendon reflexes
2.9–5.0	somnolence loss of deep tendon reflexes hypotension ECG changes
>5.0	complete heart block cardiac arrest apnoea paralysis coma

* adapted from reference 1
† when magnesium concentrations are altered, also check calcium and potassium

Treatment

An attempt should be made to identify the underlying cause for the hypomagnesaemia. In asymptomatic hypomagnesaemic or magnesium-deficient patients, oral magnesium supplements are used. Recommended dosages vary. Commonly, magnesium aspartate (1.65 mmol magnesium ion per tablet) is prescribed at 2–4 tablets per day, given in divided doses.[9] As higher doses have a laxative effect, dosage will be limited by diarrhoea.[2,4]

Symptomatic or severe (< 0.4 mmol/L) hypomagnesaemia should be treated with intravenous magnesium, as correcting magnesium deficiency takes six times longer with oral supplementation – six weeks versus seven days.[8] Intravenous magnesium sulfate is the formulation commonly used. One 5 mL ampoule of magnesium sulfate contains 10 mmol of magnesium ions. 10–20 mmol of magnesium ions can be given in 100 mL of 0.9% sodium chloride over 1–2 hours. Sulfate anions however may bind calcium and aggravate existing hypocalcaemia. Calcium should thus be administered as well.[9,10] Patients with renal insufficiency should have their doses decreased appropriately, be monitored closely for decreased deep tendon reflexes, and have their magnesium concentrations checked regularly.[1,7]

Hypermagnesaemia

Causes

The most common cause of hypermagnesaemia is decreased renal excretion of magnesium with increased intake being the second major cause (Table 3).

Table 3

Causes of hypermagnesaemia *

Renal insufficiency		
Excess magnesium intake	parenteral	dosing error treatment of specific conditions e.g. eclampsia, torsades de pointes
	oral	damage to the intestinal epithelium may increase magnesium absorption magnesium-containing antacids Epsom salts ($MgSO_4$) and other magnesium-containing cathartics magnesium-containing enemas aspiration
	other	theophylline toxicity familial hypocalciuric hypercalcaemia acute rhabdomyolysis[8] lithium ingestion[8]

* adapted from reference 1

Effects

Magnesium can block synaptic transmission of nerve impulses causing loss of deep tendon reflexes. More severe toxicity can cause flaccid paralysis and apnoea. The effect on smooth muscle results in ileus and urinary retention. Through its effect on calcium and potassium channels, hypermagnesaemia can cause bradycardia and hypotension (Table 2). Hypermagnesaemia can also cause hypocalcaemia, possibly by inhibiting the release of parathyroid hormone. Hyperkalaemia has also been associated with hypermagnesaemia.[1]

Treatment

Hypermagnesaemia can be prevented by not using magnesium containing antacids or cathartics in patients with renal insufficiency. Patients with normal renal function will usually recover after the infusion or oral intake of magnesium-containing compounds stops. Intravenous calcium can be used as an antidote for hypotension and respiratory depression. In patients with severe renal dysfunction, dialysis may be required.[1]

Conclusion

Disturbances in magnesium homeostasis can lead to serious conditions some of which are only amenable to treatment with magnesium. Doctors must remember to measure magnesium especially in patients who are at risk. Patients with hypocalcaemia and hypokalaemia who are magnesium deficient should be treated with magnesium. Hypermagnesaemia can be prevented by not using magnesium-containing compounds in patients with renal insufficiency.

References

1. Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. Rev Endoc Metab Disord 2003;4:195-206.
2. Gums JG. Magnesium in cardiovascular and other disorders. Am J Health-Syst Pharm 2004;61:1569-76.
3. Fox C, Ramsoomair D, Carter C. Magnesium: its proven and potential clinical significance. South Med J 2001;94:1195-201.
4. Schlingmann KP, Konrad M, Seyberth HW. Genetics of hereditary disorders of magnesium homeostasis. Pediatr Nephrol 2004;19:13-25.
5. Moe SM. Disorders of calcium, phosphorus, and magnesium. Am J Kidney Dis 2005;45:213-18.
6. Whang R, Hampton EM, Whang DD. Magnesium homeostasis and clinical disorders of magnesium deficiency. Ann Pharmacother 1994;28:220-6.
7. Tso EL, Barish RA. Magnesium: clinical considerations. J Emerg Med 1992;10:735-45.
8. Tietz NW, Burtis CA, Ashwood ER, Bruns DE, editors. Tietz textbook of clinical chemistry and molecular diagnostics. St Louis, MO: Elsevier Saunders; 2006.
9. Prescribing intravenous fluids and electrolytes. Version 2. Fluid and electrolyte safety team, Safe medication practice unit. Queensland Health; 2005. [Available on request from RBWH-SMPU@health.qld.gov.au]
10. Bringhurst FR, Demay MB, Krane SM, Kronenberg HM. Bone and mineral metabolism in health and disease. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2005. Chapter 331.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 111)

7. Hypermagnesaemia results in increased deep tendon reflexes.
8. Patients with hypomagnesaemia and a low albumin may have normal concentrations of ionised magnesium.

Book review

Disputes and Dilemmas in Health Law. Freckleton I, Petersen K, editors.

Sydney: The Federation Press; 2006. 698 pages. Price $125

Cate Howell, General Practitioner, Primary Care Mental Health Unit, Discipline of General Practice, Adelaide

Disputes and Dilemmas in Health Law is an Australian book which explains that health law is significant because it reflects on fundamental issues that impact on the beginning, end and quality of life. The book is divided into sections on health law and ethical dilemmas, human rights, public health, reproductive technologies, the end of life, litigation and liabilities, and privacy and confidentiality. The contributors include many eminent Australian legal and medical experts.