

Magnesium and the anaesthetist

Veronica F Watson FRCA

Ralph S Vaughan FRCA

Key points

Magnesium is a physiological antagonist of calcium

Hypomagnesaemia may cause dysrhythmias, myoclonus, stridor, tetanus, psychiatric disturbances and convulsions

Hypomagnesaemia is associated with hypokalaemia and hypocalcaemia.

Magnesium potentiates the action of non-depolarising muscle relaxants

In humans, magnesium is the fourth most plentiful cation after sodium, potassium and calcium. Intracellularly, it is second following potassium.

Approximately half of total body magnesium is contained within the soft tissues including muscle, while the majority of the remainder is found in bone with some in the erythrocytes. Magnesium in the extracellular compartment is both ionised and unionised. It is the ionised fraction which is physiologically active.

Physiological role of magnesium

Magnesium has been described as the physiological antagonist of calcium. It is an obligatory co-factor in all cells containing ATP. The involvement of magnesium in the Na^+/K^+ -ATPase system makes it an essential requirement in maintaining transmembrane sodium and potassium gradients and a normal potassium concentration. Therefore, magnesium plays an important part in determining the electrical potential across cell membranes.

The generation of cAMP via adenyl cyclase is magnesium-dependent. This allows magnesium to control the release and actions of parathyroid hormone, thereby having an effect on calcium metabolism. Hypomagnesaemia is often associated with hypocalcaemia. Other enzyme systems which are also dependent on magnesium include oxidative phosphorylation, glucose utilisation and protein synthesis. Thus, magnesium affects many systems which are particularly important to the anaesthetists.

Magnesium has direct effects on the myocardium and vascular smooth muscle. High concentrations of circulating magnesium depress myocardial contractility directly and can block catecholamine receptors by direct

action. Furthermore, it inhibits the release of catecholamines from both the adrenal medulla and peripheral adrenergic terminals. Anti-arrhythmic properties have been extensively demonstrated and appear to be related to the calcium channel blocking effect, regulation of intracellular potassium and activation of ATP. Vascular tone is decreased resulting in reduced peripheral and pulmonary vascular resistances and coronary artery vasodilation. In addition, magnesium blunts the response of vascular tissue to vasoconstrictors, such as noradrenaline and angiotensin II. However, conversely, magnesium is required for the inotropic effects of adrenaline.

Magnesium antagonises calcium ions at the presynaptic junctions and can result in a decreased release of acetyl choline at the neuromuscular junction. It also has a direct action causing decreased excitability of nerves and muscles. It is also involved in contraction and relaxation of muscles and, if the ionised magnesium concentration is high enough to cause muscle weakness, respiratory failure may result. As magnesium also affects the action of calcium channel blockers, it may influence the degree of bronchodilatation.

Magnesium inhibits platelet activity and has been shown to increase the bleeding time when administered by intravenous infusion in healthy volunteers and in patients with pre-eclampsia. The mechanism has not yet been clarified. Magnesium deficiency and its association with platelet hyper-reactivity has been noted in a variety of conditions including myocardial infarction, pre-eclampsia and diabetes.

Magnesium has been shown to suppress epileptic foci and reversal of cerebral vasospasm has also been demonstrated. The exact mechanisms for these effects are not known. It is also required for the utilisation of thiamine.

Veronica F Watson FRCA

Consultant Anaesthetist,
Department of Anaesthetics,
Hairmyres Hospital, Eaglesham Rd,
East Kilbride G75 8TG, UK

Ralph S Vaughan FRCA

Consultant Anaesthetist,
Department of Anaesthetics &
Critical Care, University Hospital of
Wales, Heath Park,
Cardiff CF14 4XW, UK

Magnesium homeostasis

While magnesium may flow between body stores and the circulating extracellular pool, quantitative body stores are regulated by hormonal and metabolic effects on gastrointestinal absorption and renal excretion. Normal magnesium concentrations are 0.7–1.05 mmol⁻¹.

Absorbed magnesium is excreted primarily by the kidney. Approximately 1% of filtered magnesium appears in the urine, the majority being re-absorbed in the ascending limb of the loop of Henle. The kidney is capable of reducing magnesium loss to less than 5 mmol day⁻¹. Aldosterone increases renal excretion while parathyroid hormone (PTH) enhances gut absorption and reduces the renal excretion of magnesium.

Hypomagnesaemia

Hypomagnesaemia is defined as a plasma concentration of less than 0.7 mmol⁻¹. Since the plasma magnesium amounts to less than 1% of total body magnesium, an overall deficiency may exist in the presence of normal plasma concentrations. However, a low serum magnesium is generally indicative of a low total body magnesium. Exceptions to this occur in patients who are haemodiluted following massive crystalloid infusion or in those with severe hypo-albuminaemia.

It has been suggested that hypomagnesaemia may be the most underdiagnosed electrolyte deficiency in current medical practice. Some studies have shown it to be a relatively common disorder, *e.g.* 65% of an intensive care unit population and 11% of a general in-patient population.

Causes

Hypomagnesaemia can be caused by decreased intake, excessive renal losses, extra-renal losses and redistribution (Table 1). Deficiency in diet is seen more commonly in elderly people and chronic alcoholics. Decreased absorption may occur in pancreatic insufficiency, short bowel syndrome or, rarely, with inherited primary malabsorption of magnesium in infancy. Hypomagnesaemia may follow the intravenous administration of solutions or with total parental nutrition with insufficient or no magnesium added.

Excessive renal loss can be caused by drugs, including digoxin, gentamycin, loop diuretics, ethanol, cyclosporin, cisplatin, amphotericin and pentamidine. Bartters syndrome is another cause and is associated with juxtaglomerular hyperplasia and decreased sensitivity to angiotensin with a tendency to hypotension. Intrinsic renal dysfunction, including interstitial nephritis and the diuretic phase

of acute tubular necrosis, and excessive diuresis may cause renal loss of magnesium. Hyperaldosteronism is generally associated with hypertension and hypokalaemia with retention of sodium. Other electrolyte disturbances, including hypokalaemia, hypophosphataemia and hypercalcaemia, may be associated with hypomagnesaemia.

Extra-renal losses are primarily through the gastrointestinal tract and may occur either in prolonged diarrhoea or long-term nasogastric suction/drainage. Magnesium may be redistributed intracellularly in primary hyperparathyroidism, treatment of diabetic ketoacidosis with insulin, and massive transfusion with citrated blood.

Clinical manifestations

Clinical manifestations are summarised in Table 2.

Cardiovascular

Hypertension is common and can be associated with angina as coronary artery spasm can occur. Increased myocardial uptake of digoxin and loss of intracellular potassium may cause digoxin toxicity. Consequently, there is a tendency for rhythm disturbances which can include torsades de pointes, re-entry arrhythmias, ventricular tachycardia and fibrillation. ECG changes can include increased PR & QT intervals and T wave changes.

Neuromuscular hyperactivity

There is an increased incidence of myoclonus, cramps, stridor and dysphagia. Chvostek's and Trousseau's signs can be elicited.

Table 1 Causes of hypomagnesaemia

Decreased intake	Deficiency in diet Malabsorption Inappropriate i.v. infusions
Excessive renal loss	Drug induced Bartters syndrome Intrinsic renal dysfunction Hyperaldosteronism Other electrolyte disturbances
Extra renal loss	GI tract
Redistribution	Primary hyperparathyroidism Insulin administration Massive citrated blood transfusion

Table 2 Clinical manifestations of hypomagnesaemia

CVS	Hypertension Angina Dysrhythmias Digoxin toxicity
Myoclonus, stridor, dysphagia, tetanus	
CNS	Psychiatric disturbance Convulsions Coma
Other electrolyte abnormalities	Hypokalaemia Hypocalcaemia

ed and tetanus can occur, though they are more commonly associated with hypocalcaemia. Severe deficiencies may lead to convulsions and coma.

Electrolyte abnormalities

Hypomagnesaemia is associated with both hypokalaemia and hypocalcaemia.

Psychiatric disturbances

A low serum magnesium concentration can lead to anxiety, depression, confusion and psychosis, including Wernicke's encephalopathy.

Treatment

To ensure normal homeostasis of magnesium, approximately 10–20 mmol day⁻¹ intake is usually sufficient. If there has been chronic loss, 35–70 mmol of magnesium in 5% dextrose can be given intravenously over 12–15 h. A further dose of approximately 25 mmol day⁻¹ may be required.

In the more acute situation, correction is faster with 8 mmol (200 mg) of magnesium sulphate diluted in dextrose and administered intravenously over 15 min and repeated if required, particularly for the treatment of malignant tachyarrhythmias.

Hypermagnesaemia

There are relatively few causes of hypermagnesaemia, most are iatrogenic. The most frequent of these is overdose in the treatment of pre-eclampsia or eclampsia.

Hypermagnesaemia also occurs in patients with end-stage renal disease and in those undergoing haemodialysis (reduced renal clearance). Symptomatic concentrations are usually only reached following abnormally high intake of magnesium in antacids or purgatives.

Adverse effects may be exacerbated by hypocalcaemia and reduced by hypercalcaemia. Chronic hypermagnesaemia may also affect bone and impair blood coagulation.

Clinical signs

These primarily affect the cardiovascular and neurological systems. The signs and symptoms increase as serum magnesium concentration increases. They range from nausea and vomiting to respiratory and cardiac arrest. Concentrations can increase suddenly, usually associated with rapid intravenous injection of magnesium salts. However, the usual pattern is that of increasing concentration due to the failure of regulatory systems.

Treatment

In the presence of severe systemic effects, the actions of magnesium are readily antagonised with intravenous calcium, *e.g.* calcium gluconate given intravenously in bolus doses of 2.5–5 mmol. Magnesium excretion may be also enhanced by fluid loading and drug-enhanced diuresis. Other measures may include the administration of glucose and insulin to promote magnesium entry into the cells. In life-threatening complications or in patients with renal failure, dialysis with magnesium-free dialysate may be needed.

Pregnancy-induced hypertension and eclampsia

World-wide, pregnancy-induced hypertension (PIH) is a major cause of maternal mortality and fetal loss. The aetiology is uncertain, but appears to be related to uteroplacental ischaemia. It is a multisystem disorder which can affect cardiovascular, renal, respiratory, hepatic, haemostatic and central nervous systems. The treatment of PIH is aimed at controlling the blood pressure and abnormal haemodynamic state, preventing convulsions and ensuring safe delivery.

The use of magnesium sulphate in obstetrics has aroused controversy over many years. Currently, magnesium sulphate is the most widely used anticonvulsant in North America for the management of either PIH or eclampsia. Until relatively recently, use in the UK was limited, with only 2% of obstetricians using magnesium for the management of these conditions. However, the Collaborative Eclampsia Trial has established the superiority of magnesium sulphate over both diazepam and phenytoin in the prevention of recurrent convulsions in women with eclampsia. Other studies have also indicated a reduction in the incidence of eclamptic convulsions in women with PIH.

The mechanism and sites of action of magnesium sulphate are still unknown. There is some debate with regard to the cerebrovascular and central nervous systems as to whether the main action is central or peripheral. The cause of convulsions in PIH has no definite aetiology, but it is known that in both PIH and eclampsia there is intense cerebral vasospasm with increased sensitivity to pressor agents. It has been proposed that convulsions are a consequence of a reduction in cerebral blood flow. It has been shown that women with PIH who are given magnesium sulphate have a reduction in intracerebral vascular spasm when measured by a Doppler examination of the middle cerebral artery. Further Doppler studies show evidence of decreased cerebrovascular

resistance in the internal carotid and middle cerebral arteries in severe pre-PIH and eclampsics.

Administration of magnesium

Magnesium sulphate is usually administered intravenously. A loading dose of 4 g is given (some centres advocate 5 g) followed by an intravenous infusion starting at 1 g h^{-1} . Modifications may be required to obtain acceptable serum concentrations. In some centres, higher infusion rates are used. The infusion is continued for 24 h after the last convulsion. If a further convulsion occurs, another 2–4 g are given over 5 min. Although there is no single accepted therapeutic concentration of magnesium, a plasma concentration of 2–4 mmol l^{-1} is usually acceptable. Intramuscular regimens also exist, though this route is painful and plasma concentrations are less predictable.

Anaesthesia

The actions of magnesium are complex and both hypo- and hypermagnesaemia can be very relevant in anaesthetic practice. Furthermore, manifestations of either may occur for the first time during anaesthesia.

In the normal clinical situation, hypomagnesaemia is the more likely. It may occur relatively commonly in the hospital in-patient population, particularly in patients presenting for surgery from critical care areas. Careful study of drug regimens are, therefore, important in identifying these at-risk patients.

Pre-operative assessment and premedication

The key factor is being aware of patients who may have abnormal plasma magnesium concentrations which are frequently accompanied by other electrolyte disturbances. Subsequent actions are determined by the urgency of the surgery. If it is not urgent, it would be prudent to postpone the procedure and bring ionised magnesium concentrations to within normal values. Anaesthetising hypomagnesaemic patients may exacerbate pre-existing cardiovascular disease and increase the risk of peri-operative dysrhythmias. Similarly, hypermagnesaemia should be considered in PIH and ITU patients being treated with magnesium, either enterally or parenterally. Magnesium sulphate therapy should be avoided in patients with A-V block and used with extreme caution, if at all, in either myasthenia gravis or muscular dystrophy. There are no contra-indications to standard drugs used for premedication.

Induction of anaesthesia

Induction of general anaesthesia in the hypomagnesaemic

patient may be associated with an increased chance of stridor provoked by airway stimulation. Hyperventilation, leading to respiratory alkalosis, should be avoided as this will cause magnesium to shift intracellularly thus depressing plasma magnesium concentrations still further. Vasodilatation resulting from butyrophenones, volatile anaesthetic agents and narcotics may be exacerbated by magnesium leading to hypotension.

Intubation

Magnesium sulphate has been used to suppress the responses to laryngoscopy, intubation and extubation. It is particularly relevant in the management of obstetric patients with PIH or eclampsia requiring general anaesthesia and intubation. The pressor responses to laryngoscopy and intubation may increase the risk of cerebrovascular accident, increase myocardial oxygen requirements, provoke cardiac dysrhythmias, induce pulmonary oedema and reduce uterine blood flow. Many different drugs have been used to suppress these responses with varying effect. Magnesium sulphate, given intravenously at a dose of 40 mg kg^{-1} , has been shown to be effective.

Neuromuscular blockade

Magnesium administration or hypermagnesaemia may have an effect on neuromuscular blockade. Magnesium is known to decrease the presynaptic release of acetylcholine and it reduces the sensitivity of the post-junctional membrane and excitability of muscle fibres. Both depolarising and non-depolarising relaxants are potentiated by magnesium.

Recent work has shown that the neuromuscular blockade produced by suxamethonium is not potentiated in those patients receiving magnesium therapy for eclampsia or for those undergoing elective surgery. Succinylcholine is rapidly hydrolysed by plasma cholinesterase and magnesium does not impair the activity of plasma cholinesterase: in fact, magnesium may even increase its activity. In practical terms, this means that a single dose of suxamethonium chloride may be used safely to facilitate tracheal intubation without the worry of either delayed onset of relaxation or a prolonged period of paralysis. These findings may not hold true when repeated doses of suxamethonium are used where there is the likelihood of development of a phase II block. This may be potentiated by magnesium.

Magnesium sulphate causes a dose-related depression of acetylcholine release by competition with calcium at the presynaptic membrane and in the sarcoplasm of muscle. There is a significant correlation between the ratio of calcium to magnesium ions and the effect produced. The result is a

reduction in indirect twitch responses that are synergistic with that produced by non-depolarising blockers. Unlike non-depolarising blockers, magnesium decreases twitch responses without the train of four fade.

Some long-acting muscle relaxants, *e.g.* pancuronium, are potentiated by magnesium sulphate as well as the intermediate acting muscle relaxants, such as vecuronium and rocuronium. Enhancement of the blockade produced by the shorter acting agent mivacurium has also been observed. In one case, the duration of rocuronium was prolonged by 4 times in a patient receiving a magnesium infusion for the treatment of pre-term labour. Therefore, it is important to remember that magnesium potentiates the effects of all non-depolarising muscle blockers and that a reduced dose of muscle relaxant should be used. Further administration should be cautious and the requirements should be governed by the results obtained using a peripheral nerve stimulator.

Cardiopulmonary bypass

Hypomagnesaemia is particularly common following cardiopulmonary bypass (CPB) and is associated with clinically important postoperative morbidity. Other ischaemic events that can occur during critical illness often result in depletion of cellular magnesium. Thus, magnesium is widely advocated in the treatment and prophylaxis of arrhythmias particularly after CPB.

Epidural blockade

The vasodilator properties of magnesium sulphate could theoretically increase the likelihood of maternal hypotension particularly when used in conjunction with epidural anaesthesia. There has been considerable debate as to which vasopressor is the most suitable in such circumstances. However, anecdotal evidence suggests that epidurals have been successfully administered to patients with pre-eclampsia being treated with magnesium without significant problems. Animal studies have shown that magnesium infusion slightly decreases maternal blood pressure during epidural lignocaine infusion and that ephedrine both restores and/or protects uterine blood flow and fetal well being.

Phaeochromocytoma

Magnesium therapy has proved very useful during surgery for a phaeochromocytoma due to its calcium channel blocking properties allied to its effect on the release of catecholamines. An initial bolus of 40–60 mg kg⁻¹ intravenously followed by an infusion of 2 g h⁻¹

has been suggested. It has also been used as a useful adjunct to anaesthesia for patients with phaeochromocytoma complicating pregnancy.

Calcium channel blockers

A patient may be treated with both magnesium and nifedipine in a pregnancy complicated by PIH. Since both exert an effect on calcium channels, interaction between these two agents may occur. An increased hypotensive effect has been observed. Perhaps of more concern is the suggestion that nifedipine may potentiate neuromuscular blockade and the toxic effects of magnesium. In practice, significant clinical effects are relatively uncommon, but caution should be exercised when this particular combination is used.

Post extubation and recovery

Provided that the muscle power has returned to normal there should be no problems. However, if the ionised fractions are abnormal, it is possible that there will be both muscle and cardiovascular complications which would depend on whether hypo- or hypermagnesaemia was the underlying cause.

Intensive care unit

Magnesium replacement therapy is particularly important in the critically ill and it is recommended that the plasma concentrations are measured regularly and appropriate therapy introduced.

Other clinical settings

Magnesium has been used in a number of other clinical settings which may be of interest to the anaesthetist either in the theatre or ITU. These include its use in the management of severe bronchospasm (refractory to more conventional agents), tetanus and autonomic dysfunction despite heavy sedation.

Finally, it was hoped that magnesium therapy after myocardial infarction would be beneficial. Activities of magnesium considered to be potentially protective in the setting of ischaemia induced cardiac dysfunction include antiplatelet aggregation, vasodilating effects, calcium blocking actions, reduction of potassium loss and protection against free radical injury. Although earlier smaller studies revealed beneficial effects with respect to mortality, left ventricular function and infarct size, results from the ISIS-4 trial have proved disappointing.

See multiple-choice questions 6 and 7.