Continuing Medical Education Article

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Magnesium and the anaesthetist

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Background

In 1695, Dr. Nehemiah Grew took water from a well in Epsom, England and prepared magnesium sulphate, hence the term "Epsom Salts." Black recognised magnesium as an element in 1755 and it was isolated by Sir Humphrey Davy in 1808.

Magnesium's biological significance has been known since the 18th century when it was recognised to be a constituent of plants. Indeed chlorophylls are magnesium-centred porphyrins.[1]

The clinical significance of magnesium has only been demonstrated in this century, the first clinical report of symptoms and signs of hypomagnesaemia being in 1934.[2] Shils in 1969 produced experimental magnesium depletion and those patients who were symptomatic demonstrated hypomagnesaemia, hypokalaemia and hypocalcaemia.[3] The first known application of magnesium in cardiology was in 1935 when Zwillinger used it intravenously to treat paroxysmal tachycardia.[4]

Magnesium hydroxide (milk of magnesia), chloride, sulphate and citrate are all used in medicine today.

A renewed interest in the clinical importance of elemental magnesium has been observed in this decade. There have been many recent articles including the effects of magnesium on the heart,[5-7] the role of magnesium as a calcium channel blocking agent,[8] the clinical importance of hypomagnesaemia,[9,10] magnesium flux during open-heart surgery,[11] and the implications of hypomagnesaemia for the critical care specialist.[12,13]

These have stemmed from an awareness that hypomagnesaemia is probably the most underdiagnosed deficiency in current medical practice.[14] Compared to the other cations less emphasis is placed on the importance of magnesium and its effects are often forgotten by practising physicians.

Magnesium homeostasis

Magnesium is the fourth most plentiful cation in the body (approximately 1000 mmol in a 70 kg man) and the second most plentiful intracellular cation after potassium. Only one per cent of magnesium (about 15 mmol) is in the extracellular fluid compartment and 30 per cent of this is protein-bound. Fifty to sixty per cent is in bone (approximately 500 mmol) and 20 per cent is in skeletal muscle. The remainder is found in other body tissues, especially the liver and the heart. The largest amount of magnesium which is active in magnesio-kinetics is within the cells of the body in various concentrations.[15] Normal serum magnesium values are between 0.7 to 1.05 mmol·L^{-1}. Magnesium balance is achieved by absorption through the small intestine and renal excretion. The average daily magnesium intake is about 12.5 mmol, mostly derived from green vegetables, two-thirds of this being unab-

sorbed and excreted in the faeces.[16] Absorbed magnesium is excreted primarily by the kidney, 125 mmol of magnesium being filtered in 24 hours. Most of this is reabsorbed primarily at the level of the ascending limb of the loop of Henle, so that about one per cent will appear in the urine depending on magnesium intake. The kidney is capable of reducing renal magnesium loss to less than 0.5 mmol per day when intake is nil. Aldosterone increases, and parathormone (PTH) reduces renal excretion of magnesium. PTH also enhances gut absorption of magnesium.[16]

Role of magnesium at the cellular level

The importance of magnesium, an obligatory cofactor in all animal cells which contain adenosine triphosphate (ATP), cannot be understated. Membrane Na-K dependent ATP-ase, necessary for the maintenance of normal intracellular potassium, requires magnesium. Adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) is magnesium-dependent. Magnesium by this mechanism effects the release and action of parathyroid hormone, consequently having an influence on calcium metabolism.[17] The hypocalcaemia which is common in hypomagnesaemic states may actually represent a direct effect on bone, independent of PTH activity.[18]

Alkaline phosphatases and pyrophosphatases are all activated by elemental magnesium. Oxidative phosphorylation, glucose utilisation, protein synthesis, and activation of aminoacids all require magnesium. Magnesium also has a direct effect on calcium uptake, content, distribution and binding in smooth muscle cells. The effect of calcium is opposite to that of magnesium in muscle, but a fall in either serum calcium or magnesium will result in increased neuronal activity. Magnesium, in large doses, has a curariform action at the neuromuscular junction[19] (see below), and is thought by some authors to be able to produce general anaesthesia.[20,21]

Therefore many aspects of physiology and metabolism relevant to anaesthetists can be significantly affected by alterations in magnesium homeostasis.

Hypomagnesaemia

Definition and relationship to magnesium depletion

Normal serum magnesium concentrations range from $0.7–1.05$ mmol·L^{-1}. Hypomagnesaemia exists when the concentration is less than 0.7 mmol·L^{-1}.

Magnesium depletion may exist in the presence of a normal or high serum magnesium concentration, and can be detected by measuring cellular magnesium concentrations or measuring urinary magnesium excretion after a magnesium infusion. While no constant ratio exists between serum magnesium and total body magnesium, a low serum magnesium is generally indicative of a total body magnesium deficiency. Some authors believe that a serum magnesium concentration of less than 0.5 mmol·L^{-1} in combination with a 24 hour urine magnesium of less than 0.5 mmol·day^{-1} is indicative of a body depletion of magnesium.[22] The 24 hour urine magnesium levels vary, depending on the magnesium intake.

A magnesium load test is used clinically to diagnose magnesium depletion. In our centre this involves giving 20 mmol (5 g) magnesium sulphate intravenously (which is 10 ml of a 50 per cent solution of magnesium sulphate), in 500 ml crystalloid, over a period of not less than three hours and usually between 8 to 12 hours. The patient voids prior to the load, and a 24 hour urine collection is started with the initiation of the load.[9] Magnesium-deficient patients will excrete less than 70 per cent of this load over 24 hours, assuming normal renal function. Magnesium-replete patients will excrete a greater percentage, usually 100 per cent of the load in the same period. Hypomagnesaemia is almost always associated with a total body depletion of magnesium. Exceptions to this occur in patients with severe hypo-albuminaemia, or from dilution after massive crystalloid infusions. In these cases the measured magnesium concentration is low in the face of a normal serum content of ionised magnesium.

A high urinary magnesium excretion, in the presence of hypomagnesaemia, implies renal magnesium wasting. Magnesium deficiency from one of the other causes (Table I) is suggested when there is renal conservation of magnesium in the presence of hypomagnesaemia.

Where available, confirmation of body depletion of magnesium is by assay of white blood cell magnesium content, although bone or muscle magnesium would reflect body values more accurately. These are rarely measured in practice.

Aetiology

Hypomagnesaemia can be caused by a variety of conditions many of which are listed in Table I. There are some groups of patients who merit special attention.

Chronic alcoholics often have (1) magnesium-poor diets; (2) increased renal magnesium losses from alcohol; (3) decreased intestinal absorption of magnesium, especially if there is pancreatic or liver dysfunction. Magnesium deficiency may contribute to the cardiac dysfunction associated with alcoholism.[15]

Another group who are at risk from developing magnesium deficiency are patients in critical care areas.[12,13] There may be many causes in such patients, including magnesium-free intravenous replacement therapy, total parenteral nutrition (TPN), and the use of drugs such as the aminoglycosides and diuretics. Indeed many of the causes listed in Table I contribute to magnesium

TABLE I   Causes of hypomagnesaemia

Decreased intake
1 Deficient intake
  - magnesium-poor diet (e.g., chronic alcoholism)
  - prolonged fasting/malnutrition
  - soft-water area
2 Decreased intestinal absorption
  - short-bowel syndrome
  - ileal bypass
  - pancreatic insufficiency
  - rarely: inherited primary malabsorption of magnesium in infancy

Internal redistribution
- massive transfusion with citrated blood
- with insulin therapy in severe diabetic ketoacidosis

Increased losses
1 Gastro-intestinal losses
  - prolonged diarrhoea
  - prolonged naso-gastric suction
2 Renal
  - Intrinsic tubular dysfunction
    - interstitial nephritis
    - diuretic phase of ATN
    - drug damage from aminoglycosides, cisplatin and amphotericin B
    - rare inherited (autosomal recessive) renal wasting of Mg $\pm$ K
    - Bartter's syndrome
  - Extrarenal causes of increased renal magnesium loss
    - hyperaldosteronism
    - hypercalcuria
    - hypokalaemia
    - hypophosphataemia
    - digoxin therapy
    - ethanol toxicity
    - diuresis

Other
1 Spurious hypomagnesaemia (with normal serum content of ionised Mg) from severe hypoalbuminaemia or dilutional effect (e.g., on CPB).
2 Iatrogenesis
  - administration of Mg-free IV solutions or TPN in critically ill patient

deficiency in this sub-group of patients. Today we see more critically ill patients coming to the operating room for a variety of surgical procedures, so it behoves the anaesthetist to be aware of the potential for hypomagnesaemia and its clinical implications.

Approximately seven per cent of patients with severe diabetic ketoacidosis will have hypomagnesaemia due to the catabolic action of insulin deficiency causing release of magnesium from cells and increasing urinary magnesium losses. This effect is enhanced by the concomitant ketoacidosis and osmotic diuresis induced by glycosuria. Furthermore, treatment with insulin can exacerbate hypomagnesaemia by shifting magnesium back into the cell. It has been reported that 50 per cent of these patients become transiently hypomagnesaemic after 12 hours of

insulin therapy, and a fatal arrhythmia has been reported in this situation.[23]

Hypomagnesaemia has been shown to occur in association with hyperaldosteronism, inappropriate ADH secretion and rare congenital states characterised by renal magnesium wasting.[9] It can also be a feature of Bartter's syndrome.[24]

Pathophysiology
Cardiovascular and neuromuscular functions are those significantly affected by hypomagnesaemia (Table II).

In the same way that patients with acute potassium losses are more likely to be symptomatic, so it is that patients with acute hypomagnesaemia will show early symptoms. An example is the patient who has been taking diuretics and is then given intravenous gentamycin therapy and develops ventricular dysrhythmias. In contrast, a chronic alcoholic may have a greater total body deficiency of magnesium. Because of the chronicity, the extracellular magnesium concentration may remain within normal limits because the intracellular to extracellular magnesium ratio remains constant. This patient may not have any signs or symptoms of magnesium depletion unless subjected to another magnesium-losing stimulus.

Alterations in intracellular potassium and calcium homeostasis play a role in mediating the clinical manifestations of hypomagnesaemia, secondary to magnesium's role as a cofactor for ATP-ase. Hypokalaemia is caused by decreased renal tubular reabsorption of potassium secondary to hypomagnesaemia. Therefore treatment of the hypokalaemia will not be successful until the magnesium deficiency is corrected. Hypocalcaemia associated with hypomagnesaemia will correct gradually without calcium supplementation once the magnesium deficit is corrected.

Tetany, dysrhythmias, and seizures in the setting of hypomagnesaemia may be induced by alkalosis or hypocalcaemia. Conversely acidaemia may prevent these sequelae.

Cardiovascular manifestations
Hypomagnesaemia can affect many aspects of cardiac function. This can result in digoxin-mediated dysrhythmias,[6,25] electrocardiographic changes,[26] ventricular dysrhythmias including torsade de pointes,[15,27,28] and, less commonly, supraventricular dysrhythmias.[29]

There is evidence for a role of magnesium deficiency in sudden death from coronary artery disease,[30] coronary artery spasm[31] and hypertension.[32] Hypomagnesaemia in patients recovering from acute myocardial infarction is associated with increased morbidity and mortality, which can be reduced if treated with intravenous magnesium.[33]

Digoxin uptake into the myocardial cell is enhanced in

TABLE II Symptoms and signs of hypomagnesaemia

Cardiovascular	Neuromuscular	Psychiatric
Ventricular dysrhythmias	Chvostek's sign	Apathy
(VT, VF, torsade de pointes)	Trousseau's sign	Depression
Nodal tachycardia	Stridor	Anxiety
Premature atrial or	Dysphagia	Restlessness
ventricular beats	Tremor	Hallucinations
Enhancing digitalis –	Myoclonic jerks	Psychosis
induced dysrhythmias	Tetany ⎫	Wernicke's encephalopathy
Hypertension	Seizures ⎬ rare	
Coronary artery spasm	Coma ⎭	
ECG changes		
↑ PR, ↑ QT intervals		
T wave changes		

magnesium-depleted states and both factors hinder the cell's sodium-potassium pump mechanism. Consequently, the cardiac cell's ability to conserve potassium against an ionic gradient is affected; the resting membrane potential becomes less negative so that the threshold potential is more easily reached and cardiac irritability is induced. Digoxin-mediated dysrhythmias in this setting are often resistant to conventional therapy, but may respond to treatment with intravenous magnesium.

Electrocardiographic changes seen with hypomagnesaemia are non-specific, but can be similar to those seen in hypokalaemia. These may include, in the early stages, low voltage P waves, normal QRS and peaked "spinous" T waves. In severe magnesium deficiency these may progress to prolonged PR and QT intervals, with flattened T waves and U wave formation.[15,34]

Electron microscopic evidence of myocardial damage has been demonstrated, even in the early stages of magnesium deficiency. These include: mitochondrial swelling and vacuolisation, distortion of cristae, derangement of myofibrillae, and various nuclear changes. It is thought that interference with magnesium-dependent enzymes involved in oxidative phosphorylation plays an important role in producing these observed changes.[35]

Neuromuscular manifestations
Some authors feel that while it is uncommon for hypomagnesaemia to be associated with obvious clinical signs, neuromuscular changes are often the earliest signs of hypomagnesaemia. These include Chvostek's and Trousseau's signs, lateral peroneal nerve tap sign, carpopedal spasm, muscle weakness, fasciculations and muscle cramps. Other important presentations include tremors, paraesthesiae and stridor from laryngeal spasm. Concomitant hypocalcaemia and hypokalaemia may contribute to these findings.

Magnesium itself decreases presynaptic acetylcholine release and depresses the excitability of nerve and muscle

membranes. Magnesium also plays an important role in muscle relaxation and contraction by regulating calcium channels, effecting re-uptake of calcium into the sarcoplasmic reticulum via magnesium-dependent ATP-ase and cAMP, and by facilitating actin-myosin interaction, again via magnesium-dependent ATP-ase.

Other manifestations of magnesium deficiency
Neuropsychiatric manifestations such as apathy, depression, agitation, confusion and delirium have all been described. Magnesium is necessary for thiamine utilisation and hypomagnesaemia can precipitate Wernicke-Korsakoff's syndrome.[36]

Less commonly magnesium deficiency leads to movement disorders such as choreoathetosis, myoclonic jerks, seizures and coma.[9]

Anaesthetic implications (Table III)
Patients at risk should have a preoperative serum magnesium estimation and, when indicated, a magnesium load test as outlined above, particularly in those individuals with low serum concentrations of the other commonly measured electrolytes. In one study of patients who were hypomagnesaemic, 23 per cent were hyponatraemic, 29 per cent hypophosphataemic, 23 per cent hypocalcaemic and 40 per cent were hypokalaemic.[17] In a separate study by Wong,[37] routine monitoring of serum magnesium revealed low levels in 11 per cent of hospitalised patients. In patients from intensive care units the incidence of hypomagnesaemia may be as high as 20 per cent.[13] Once diagnosed, the magnesium deficit should be replaced prior to surgery (see treatment below).

The hypomagnesaemic patient should have routine ECG, CXR, CBC, serum electrolytes, calcium, albumin, BUN and creatinine, and liver function tests prior to replacement therapy and any scheduled surgery.

As in all preoperative patients, a full drug history should be taken and special attention paid to those

TABLE III   Anaesthetic considerations of hypomagnesaemia

Preoperative

1 Be aware
  - hypomagnesaemia common in hospitalised patients
  - especially in critical care areas
  - often associated with ↓ serum Na, K, Ca
  - can affect CVS, CNS and neuromuscular junction
2 Tests
  - check 24 hr urine Mg, after IV Mg-load
  - ECG, CXR, serum albumin, liver function
  - BUN, creatinine, CBC, electrolytes
3 Drug history
  The following can ↓ serum Mg:
  - digoxin, thiazide diuretics, aminoglycosides
  - amphotericin B, cisplatin, cyclosporin
4 Treatment
  - delay non-essential surgery
  - treat deficiency with parenteral $MgSO_4$

Intraoperative

1 Monitors
  - ECG, BP, peripheral nerve stimulator
  - end–tidal CO_2, oxygen saturation
2 Avoid
  - hyperventilation and respiratory alkalosis
  - hypoxaemia
  - airway irritation (risk of laryngospasm)
3 Dysrhythmias
  - conventional treatment
  - often responsive to IV $MgSO_4$
  - defibrillator available
  - correct any pre-existing hypothermia or acidaemia
4 High-risk operations
  - open-heart procedures
  - organ transplantation (donor and recipient)

Postoperative risks

1 Laryngeal spasm and stridor
2 Paraesthesiae, tetany, seizures, coma
3 Ventricular dysrhythmias

receiving digoxin, diuretics, aminoglycosides, amphotericin B, cisplatin or cyclosporin.

Preoperative medication and aspiration prophylaxis will depend on the type, site and urgency of the surgery, choice of anaesthetic, and the general condition of the patient.

Routine intraoperative monitoring is mandatory with an emphasis on ECG for rhythm disturbances (lead II), peripheral nerve stimulator, end–tidal CO_2 monitor and oxygen saturation monitor. These patients may be at increased risk from laryngeal spasm with any airway manipulation, but how severe the magnesium deficiency has to be before stridor develops is uncertain. Hyperventilation and respiratory alkalosis should be avoided as they will tend to shift magnesium into the cell.

The anaesthetist should be prepared to deal with intraoperative dysrhythmias in these patients. Conven-

tional antiarrhythmics, magnesium sulphate, and a defibrillator should all be readily available.

Common sense dictates that non-essential surgery should be deferred until the magnesium depletion has been corrected.

There is one sub-group of patients who deserve special consideration with regard to perioperative magnesium flux. Patients undergoing open-heart surgery, requiring cardiopulmonary bypass and the use of cardioplegia solution, have intraoperative hypomagnesaemia and protracted postoperative hypomagnesaemia.[11,38-40] This occurs from a variety of factors.

1 There may be pre-existing undiagnosed hypomagnesaemia from digoxin and diuretic therapy or magnesium-poor diets associated with chronic debility or alcohol ingestion. Also, secondary aldosteronism associated with heart failure increases urinary magnesium losses;
2 A marked dilutional effect occurs intraoperatively from intravenous crystalloid infusion and pump priming solution;
3 Acid-base disturbances with intracellular transfer of magnesium have been described in this setting,[11] although the mechanism is obscure. It has been demonstrated that the stress response can deplete body stores of magnesium,[41] but there is no evidence of an extrarenal device mediated through the adrenergic system to account for intracellular movement of magnesium, as has been described for potassium.[42]

Postoperative hypomagnesaemia may persist for up to a week in some cases.[11] If not treated it has the potential to increase morbidity from cardiac dysrhythmias which may not respond to conventional anti-dysrhythmic therapy or defibrillation.[6,38,43] Magnesium therapy for these refractory dysrhythmias is effective assuming that hypothermia and acidaemia have been corrected.

The fall in serum magnesium levels in these situations occurs despite attempts to correct it by adding up to 16 $mmol \cdot L^{-1}$ Mg^{++} to the cardioplegic solution. Even high-magnesium cardioplegic solutions result in very little elevation of serum magnesium levels above the normal range.[40]

All the commonly used calcium-channel blocking agents have shown beneficial effects when used in cardioplegia solutions. This lends credence to the concept of trying to maintain normal serum magnesium levels by adding magnesium to cardioplegic solutions, in view of the action of magnesium as a calcium blocking agent.[8] Cardioplegic solutions have three main functions: (1) rapid institution of diastolic ischaemic arrest prior to depletion of intramyometrial energy stores; (2) minimising ischaemic injury, and (3) prevention of myocardial injury during re-perfusion. Cardioplegia is obtained with a high concentration of potassium (30 $mmol \cdot L^{-1}$), and by

increasing extracellular magnesium levels the beneficial effects of cardioplegia are potentiated by controlling calcium influx. This limits the deleterious effects of excess calcium at the sarcolemmic and mitochondrial levels. Isolated heart studies have suggested that a magnesium concentration of 15 mmol·L^{-1} in cardioplegic solutions is optimal in terms of myocardial protection.[44] The use of magnesium to treat early ischaemic contracture of the myocardium at the end of bypass has recently been described.[45] Magnesium has also been shown to be essential for the inotropic action of catecholamines[45] and is known to be a coronary vasodilator. Thus, normal extracellular magnesium levels in patients on cardiopulmonary bypass can enhance myocardial recovery by a variety of mechanisms.

Another specific area where anaesthetists may experience problems with large fluxes of magnesium is in the brain-dead patient being stabilised and prepared for organ donation. Hypomagnesaemia may occur, in part, from (1) dilution caused by the large volumes of dextrose in water infused to prevent the hypernatraemia that can occur secondary to diabetes insipidus;[47] (2) stress caused by the CNS injury contributing to increased renal wasting and intracellular transfer of magnesium; (3) a large osmotic diuresis contributing to both magnesium and potassium renal wasting; (4) intermittent positive pressure ventilation causing respiratory alkalosis and further intracellular movement of magnesium.

The organ recipient may develop hypomagnesaemia after transplantation as a result of cyclosporin therapy. This drug is administered in order to suppress the immune response and lessens the likelihood of graft rejection. One of its side effects is to cause renal magnesium wasting. It has been reported that the hypertension seen in the early postoperative period in such patients is a result of cyclosporin-induced magnesium deficiency.[48,49]

Treatment

Prophylactic measures include: using a diet high in magnesium-containing food, such as green vegetables, meat, seafood and cereals; using potassium/magnesium-sparing diuretics such as amiloride and triamterene, if diuretics are required; considering magnesium supplementation in diabetic ketoacidosis, and ensuring that TPN

TABLE IV   Aetiology of hypermagnesaemia

Iatrogenic (excessive IV $MgSO_4$ therapy)
Excess ingestion of Mg-containing laxatives/antacids
Renal dysfunction (GFR < 30 ml·min^{-1})
Addison's disease
Myxoedema
Concurrent lithium therapy

contains adequate magnesium to maintain normal serum magnesium levels.

Oral replacement, using magnesium glucoheptonate 20–50 mmol·day^{-1} in divided doses, is used when magnesium losses are continuous.

The typical deficit required to produce symptomatic hypomagnesaemia is 0.5–1.0 mmol·kg^{-1}. Replacement should be twice the estimated deficit, as 50 per cent or more of administered parenteral magnesium will be excreted in the urine.

A typical replacement regimen in a patient with normal renal function would be 40 mmol (10 g) magnesium sulphate in the first 24 hours by controlled infusion, followed by 24 mmol (6 g) per day over the next two to five days again by pre-set infusion, since intracellular magnesium equilibrates slowly. The patient's clinical status, including reflexes and the serum magnesium, should be followed. During the infusion the serum magnesium will be supernormal, but unless tendon reflexes disappear or the serum level is greater than three times the normal upper limit, this is of little consequence and should be expected. For the emergency treatment of convulsions or malignant tachyarrhythmias, 8 mmol (2 g) of magnesium in 10 ml five per cent dextrose in water can be injected intravenously over ten minutes, followed by 20 mmol in 500 ml over three hours.

Hypermagnesaemia

Definition
Hypermagnesaemia exists when the serum magnesium concentration exceeds 1.05 mmol·L^{-1}. (This value will vary depending on the laboratory. Some texts give a value of 1.25 mmol·L^{-1}.)

Aetiology
The most common cause is iatrogenesis from magnesium sulphate therapy for toxaemia of pregnancy. Other causes include excessive intake of magnesium-containing laxatives and antacids, renal dysfunction (especially if the glomerular function rate is less than 30 ml·min^{-1}), Addison's disease, myxoedema, and concurrent lithium therapy (Table IV).

Hypermagnesaemia is less common than hypomagnesaemia and rarely poses a problem except at very high levels and in association with other disease states.

Hypermagnesaemia affects the same organ systems that are affected by hypomagnesaemia: the central nervous system, neuromuscular junction and cardiovascular system. The signs and symptoms of hypermagnesaemia are listed in Table V.

The following sections deal with the clinical effects and

TABLE V   Signs and symptoms of hypermagnesaemia

Warmth, flushing, headache
Nausea, dizziness
Depression of deep tendon reflexes
Hypotension
Flaccid weakness
Non-specific ECG changes –   ↑ PQ interval
– wide QRS
Hypothermia
Respiratory depression
Coma
Cardiac arrest in diastole

anaesthetic implications of hypermagnesaemia by re-viewing magnesium sulphate therapy.

Magnesium sulphate therapy
Minor side effects of IV magnesium therapy include warmth, flushing, nausea, headache and dizziness. The more serious side-effects are dose-related and will depend on the serum magnesium concentration (Table VI). Symptoms may be present at serum levels in excess of 2 mmol·L^{-1}, but levels up to 3 mmol·L^{-1} are frequently seen in chronic renal failure and seldom give rise to problems.[50] Concurrent hypocalcaemia, impaired clot-ting mechanisms, somnolence and disappearance of deep tendon reflexes have been described.[10] Atrio-ventricular and intra-ventricular conduction are inhibited with a level greater than 2.5 mmol·L^{-1}. A level between 6 to 7.5 mmol·L^{-1} will cause progressive muscle weakness. A serum magnesium level in excess of 12.5 mmol·L^{-1} can produce cardiac arrest in diastole which is said to respond to pacemaker treatment,[25] assuming ventilation is main-tained. Cardiac arrest at levels between 8–10 mmol·L^{-1} can occur in the acidaemic patient.

The hypocalcaemia which can co-exist with hyper-magnesaemia is due to increased urinary calcium loss, but severe depression of serum calcium levels are prevented by a concomitant increase in parathormone levels.[51]

ECG changes from hypermagnesaemia are non-specific but can include prolongation of the P-Q interval and widening of the QRS complex.[52]

The obstetric anaesthetist is probably most familiar with magnesium sulphate therapy but, as this paper

TABLE VI   Dose-related side-effects of hypermagnesaemia

Serum Mg concentration		
0.7 – 1.01 mmol·L^{-1} Normal range		
2 – 3	"	Range during parenteral treatment
4 – 5	"	Arreflexia
6 – 7.5	"	Respiratory arrest
>12.5	"	Cardiac arrest in diastole

suggests, anaesthetists may also see patients from the intensive care area on magnesium replacement therapy.

In obstetrics, the use of magnesium sulphate is empiric and is infrequently used in Britain and Scandinavia. It is administered to decrease central nervous system irritabili-ty in the toxaemic patient in an attempt to prevent seizures. There is debate as to whether it is the seizure per se or the peripheral motor manifestations that are prevent-ed.[52] Even so, it is commonly used in this setting in North America, producing sedation, vasodilatation and decreas-ing uterine tone and contractility. Indeed magnesium sulphate is also a useful tocolytic agent and has been used as such for almost 20 years.[53]

A recent report has described the use of magnesium sulphate in the anaesthetic management of phaeochromo-cytoma complicating pregnancy.[54] Its usefulness in this setting is due, in part, to magnesium's ability to inhibit the release of catecholamines from the adrenal medulla and peripheral adrenergic nerve terminals.

Magnesium sulphate produces vasodilatation by a direct effect on blood vessels, decreasing vasospasm and lowering blood pressure, although only to a minor degree. Placental perfusion may increase due to reduced uterine vascular resistance, improving fetal nutrition and oxygen-ation. Magnesium sulphate readily crosses the placenta and may cause neonatal hypotonia and respiratory depres-sion.[55] Fetal levels reach 90 per cent of the maternal level within three hours of therapy.[56]

Magnesium sulphate can be given intravenously or intramuscularly, but the latter route is painful and produces less predictable blood levels. For toxaemia, 16 mmol of a 20 per cent solution is given IV over 20 minutes followed by a 4–8 mmol per hour maintenance infu-sion.[55] Deep tendon reflexes are checked every 30 minutes and the rate is adjusted according to the reflexes and serial serum magnesium levels. Adjustments should be made in the dose if there is renal dysfunction or diminishing urine output.

Anaesthetic implications (Table VII)
In the obstetric setting, magnesium sulphate administra-tion may need to be discontinued or decreased with initiation of lumbar epidural analgesia or during operative delivery, as it could aggravate hypotension caused by sympathectomy or haemorrhage. After delivery the infu-sion should be continued or recommenced for at least 24 hours or until the toxaemic process has resolved, which may take a few days.[57] Late seizures have occurred up to one week post-delivery.[58]

Neonatal hypotonia can be exacerbated by the interac-tion of local anaesthetics used for lumbar epidural analgesia and concurrent magnesium sulphate therapy, if there is significant placental transfer of the local anaes-

TABLE VII   Anaesthetic considerations in hypermagnesaemia

Preoperative
1 Common in patients with renal dysfunction treated with oral or parenteral magnesium
2 Symptoms and signs are dose-related
3 Avoid MgSO₄ therapy in
   – patients with A-V heart block
   – myocardial depression
4 Use MgSO₄ with care, especially in
   – patients with myaesthenia
   – muscular dystrophy

Intraoperative
1 Potentiates hypotension associated with
   – lumbar epidural anaesthesia
   – volatile anaesthetics
   – calcium channel blockers
   – butyrophenones
   – hypovolaemia
2 Discontinue intraoperative MgSO₄ unless being used to treat seizure, tetany or ventricular dysrhythmia
3 Neuromuscular blockade
   – avoid pre-treatment with non-depolarising agent
   – use full, single dose of succinylcholine
   – reduce dose of non-depolarising agent by one-third to one-half
   – titrate dose to train-of-four twitch response

Postoperative
1 May cause or aggravate neonatal hypotonia and hypotension
2 High levels may cause
   – excessive sedation
   – muscle weakness
   – respiratory depression
   – cardiac arrest
3 Treatment of significant side-effects
   – discontinue MgSO₄
   – IV calcium
   – if severe, dialysis

thetic.[59] This would be more important in the premature or acidaemic neonate.

The vasodilatation from butyrophenones, volatile anaesthetic agents, calcium channel blocking drugs and narcotics can be exacerbated by magnesium. Magnesium therapy should be avoided or used cautiously in patients with A-V heart block and myocardial depression.

Magnesium sulphate has been reported to potentiate the effects of both depolarising and non-depolarising neuromuscular blocking agents.[19] In Gonheim's study,[19] which looked at an isolated rat phrenic nerve-diaphragm preparation, magnesium sulphate potentiated the effects of succinylcholine by a factor of 1.9 and d-tubocurarine by a factor of 4.1. This is certainly the case in clinical practice as far as the non-depolarising drugs are concerned, especially vecuronium.[60,61] It was never apparent why this interaction would occur with succinylcholine. In fact, theory dictated that the depolarising block would be antagonised by magnesium. A recent clinical study[61] of the use of magnesium sulphate in eclamptic parturients compared with non-eclamptic controls showed that a full, single dose of succinylcholine can be safely used to facilitate tracheal intubation, without fear of delaying the onset of relaxation or causing prolonged paralysis. The *in vitro* results probably occurred because of the absence of pseudocholinesterase in the preparation, leading to the erroneous conclusion that magnesium potentiated the effects of succinylcholine.

One-half to one-third of the usual dose of non-depolarising agent should be used to maintain relaxation in the presence of magnesium sulphate. The muscle relaxant should be carefully titrated to twitch response with a peripheral nerve stimulator. Pre-treatment with a small dose of non-depolarising agent to reduce fasciculations and myalgia is not only unnecessary in these patients, but may be potentially dangerous by causing significant paralysis.

Magnesium has been thought to produce general anaesthesia by its central nervous system depressant action.[20,62] These claims were dismissed by Aldrete[63] who felt that although magnesium depresses nerves, insufficient magnesium crosses the blood-brain barrier to produce narcosis. He suggested that the anaesthetic effect of magnesium was the result of cerebral hypoxia secondary to progressive cardiac and respiratory depression.[64] If respiration and oxygenation were properly supported, volunteer subjects remained conscious even though there was complete neuromuscular paralysis from magnesium.[65]

A recent article though has demonstrated up to a 60 per cent reduction in halothane MAC in rats with high serum levels of magnesium, which was not due to either the cardio-respiratory or neuromuscular effects of the magnesium.[21]

If high serum levels of magnesium have occurred intraoperatively, there is a possibility of postoperative respiratory failure. Because of the curare-like effect of magnesium, it should be used cautiously in myaesthenics and patients with muscular dystrophy.

Treatment

Treatment of significant hypermagnesaemia will start by discontinuing any magnesium therapy. The specific antidote is calcium. In hypermagnesaemic neonates with hypotension, 100–200 mg·kg⁻¹ calcium gluconate IV over five minutes and a continuous infusion of 100–300 mg·kg⁻¹·day⁻¹ is the treatment of choice.[66] In adults calcium gluconate 1 g IV is a prompt effective antagonist to moderate magnesium intoxication,[67] but in severe cases the effect may be short-lived and dialysis could be necessary.[68]

Summary

Magnesium plays an important role as a cofactor in many of the body's critical functions and reactions. A deficiency or excess of extracellular magnesium can produce significant signs and symptoms. Hypomagnesaemia is a common finding in hospitalised patients, especially those in critical care areas. Anaesthetising hypomagnesaemic patients may exacerbate pre-existing cardiovascular disease and increase the risk of perioperative dysrhythmias. A low serum magnesium level usually suggests a total body deficiency of magnesium. Treatment of magnesium deficiency is by parenteral magnesium and should be instituted prior to surgery.

Hypermagnesaemia is often iatrogenic and is more likely in patients with renal dysfunction who are receiving oral or parenteral magnesium. The specific antidote is intravenous calcium. Anaesthetised patients with high serum magnesium levels are at risk from hypotension, potentiation of non-depolarising neuromuscular blockers, postoperative respiratory failure and cardiac arrest.

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