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REVIEW ARTICLE

Magnesium: physiology and pharmacology

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Physiology

Magnesium is the fourth most common cation in the body, and the second most common intracellular cation after potassium. It has a fundamental role as a co-factor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis. It is also involved in several processes including: hormone receptor binding; gating of calcium channels; transmembrane ion flux and regulation of adenylate cyclase; muscle contraction; neuronal activity; control of vasomotor tone; cardiac excitability; and neurotransmitter release. In many of its actions it has been likened to a physiological calcium antagonist.[6 81]

The significance of magnesium and its relationship to the origin of life has been traced from the composition of the earth's crust (rich in iron–magnesium silicate) and the primeval ocean rich in magnesium, to the formation of chlorophyll with magnesium at the centre of the molecule, and finally to its incorporation into the animal cell containing adenosine triphosphate (ATP) with its dependence on magnesium.[4] The central role of magnesium within the chlorophyll molecule and as a co-factor for the enzymes in the 12 transphosphorylation reactions in photosynthesis makes it probably the most important inorganic element in the production of food and fossil fuels.[51]

In humans, less than 1% of total body magnesium is found in serum and red blood cells. It is distributed principally between bone (53%) and the intracellular compartments of muscle (27%) and soft tissues (19%).[52] Ninety percent of this intracellular magnesium is bound to organic matrices. Serum magnesium comprises only approximately 0.3% of total body magnesium, where it is present in three states—ionized (62%), protein bound (33%), mainly to albumin, and complexed to anions such as citrate and phosphate (5%).[51] Equilibrium between tissue pools is reached slowly with a half-life for the majority of radiolabelled magnesium varying between 41 and 181 days.[52] Thus serum magnesium estimations may not provide representative information on the status of other stores.

Magnesium units are commonly expressed in mg, mmol or mEq. A method of conversion is shown in Table 1. While there is an absolute requirement for magnesium, the daily estimated average requirement (EAR) is 200 mg for females and 250 mg for males.[115] Rich sources of magnesium in the diet include cereals and legumes, but the processing of the former may lead to marked depletion of inherent magnesium, leaving only 3–28% of the original content.[113] Magnesium absorption is inversely proportional to intake and occurs principally from the ileum and colon. Excretion and serum magnesium control occur via the kidney. In common with other cations, magnesium is filtered at the glomerulus but differs in that reabsorption is predominantly in the ascending limb of the loop of Henle and not in the proximal convoluted tubule.

It has been estimated that magnesium intake has declined by more than half during this century.[6] Although modern food processing has caused loss of magnesium found in food, there are several other factors which have reduced magnesium within the ecosystem as a whole. Acid rain causes exchange between magnesium and aluminium in the soil. This, coupled with intensive farming of the soils, has lead to a reduction in magnesium within the food chain. This has been implicated in a number of environmental issues, including the death of forests, and in lactating cows a condition variously known as grass staggers or spring tetany whereby hypomagnesaemia causes twitching and later convulsions.[32]

Measurement of magnesium

Assessment of magnesium status is a complex area. Older methods such as serum magnesium estimation are criticized

This article is accompanied by Editorial II.

Table 1 Conversion table for magnesium units

1 g of magnesium sulphate is equivalent to:
4 mmol, 8 mEq or 98 mg of elemental magnesium

Table 2 Causes of magnesium deficiency

● Reduced dietary intake
● Poor gastrointestinal absorption
● Increased losses from the gastrointestinal tract
Diarrhoea
Vomiting
Laxative use
● Increased renal losses
Congenital or acquired tubular defects
Diabetes mellitus
Alcoholism
Drug-induced (diuretics, angiotensin converting enzyme (ACE) inhibitors, aminoglycosides, amphotericin, cyclosporin and cisplatin)
Others
Increased requirements (growth, pregnancy)
Excessive sweating

because only 0.3% of total body magnesium is found in serum. Moreover, the sample could be affected by magnesium from red blood cells (which have three times the magnesium concentration of serum) should haemolysis occur. Urinary magnesium estimates throughput of magnesium, but does not focus on total body assessment.[51] However, serum magnesium is used commonly and has a place in the acute situation or for monitoring levels during therapy. Normal concentrations are debated, but taking a mean concentration of 0.860 mmol litre^{-1}, and assuming normal distribution, a reference range of 0.76–0.96 mmol litre^{-1} can be calculated.[32] Red cell and muscle magnesium concentrations have also been studied, but the relationships between these and total body magnesium are unresolved. Another approach for assessment of magnesium status is urinary magnesium excretion. A 24-h estimation is of principal use in identifying aberrant renal excretion with a normal daily urinary loss of 3.6 mmol for females and 4.8 mmol for males.[46] A further refinement is the magnesium retention test. After a baseline 24-h urine collection, a parenteral load of magnesium is administered and a further 24-h urine collection obtained. Although there is no standardization of the test, excretion of greater then 60–70% of the magnesium load suggests that magnesium depletion is unlikely. This test principally quantifies the major exchangeable pool of magnesium, such as bone.[149]

Perhaps the most useful tests rely on estimation of ionized magnesium in serum, blood or plasma. This is an area of expanding interest and has led to the development of ion-selective electrodes.[6] However, these are prone to interference from other cations, particularly calcium. A more complex area is the assessment of intracellular ionized magnesium (Mg^{++}_i). Two methods that have received particular interest recently are fluorescent probes and nuclear magnetic resonance.[108]

Magnesium deficiency

Magnesium deficiency is common and is frequently multifactorial. Epidemiological studies trace the prevalence of cardiovascular disease and cardiac deaths to the degree of magnesium depletion induced by a diet and drinking water low in magnesium.[149] Magnesium deficiency has been demonstrated in 7–11% of hospitalized patients and is found to co-exist in up to 40% of patients with other electrolyte abnormalities, particularly hypokalaemia or hypophosphataemia and, to a lesser extent, hyponatraemia and hypocalcaemia.[187] The common causes of magnesium deficiency are listed in Table 2, with renal losses accounting for the majority of cases.

The co-existence of secondary electrolyte abnormalities plays a key role in the clinical features of magnesium depletion. Of these the relationship between magnesium and calcium has been the best documented.[9 32 200] Absorption of both magnesium and calcium appears to be inter-related, with concomitant deficiencies of both ions well described. A common link is that of parathyroid hormone (PTH), secretion of which is enhanced by hypocalcaemia. Hypomagnesaemia impairs hypocalcaemic-induced PTH release, which is corrected within minutes after infusion of magnesium. The rapidity of correction of PTH concentrations suggests that the mechanism of action of magnesium is enhanced release of PTH.[9] Magnesium is also required for the sensitivity of the target tissues to PTH and vitamin D metabolites. In contrast, calciotrophic hormones (PTH and calcitonin) have a profound effect on magnesium homeostasis, with PTH release enhancing magnesium reabsorption in the kidney, absorption in the gut and release from bone.[200]

A more fundamental interaction between magnesium and other ions occurs at the cellular level. Intracellular calcium concentrations are controlled within narrow limits, with transient increases rapidly giving way to a return to normal levels. The release of intracellular calcium plays a key role in many cell functions, both basic (cell division and gene expression) and specialized (excitation, contraction and secretion).[182] A common pathway for the release of intracellular calcium from many stimuli such as hormones, growth factors and neurotransmitters is phospholipase C activation and hydrolysis of phosphatidylinositol 4,5-biphosphate into inositol 1,4,5-triphosphate (IP_3).[18] IP_3 acts by binding to the transmembrane IP_3 receptor causing opening of a calcium channel, which is part of the same molecule.[19] Magnesium acts as a non-competitive inhibitor of the IP_3-gated calcium channel and of IP_3 binding. Therefore, it may be considered as an intracellular calcium antagonist acting at IP_3 sensitive calcium release channels. It may also have a role as a calcium antagonist at other cell sites such as the ryanodine subgroup of calcium release channel receptors in the sarcoplasmic reticulum.[182]

In addition to interactions with calcium, magnesium has a marked effect on the regulation of transmembrane sodium and potassium movement. This area has been reviewed by Bara, Guiet-Bara and Durlach.[14] The importance of both

Table 3 Treatment of magnesium deficiency

Emergency—i.v. route
8–16 mmol immediately
40 mmol over the next 5 h
Severely ill (i.m. route)
48 mmol on day 1
17–25 mmol on days 2–5
Other cases (oral route)
15 mmol day^{-1}

Mg^{++}_i and extracellular magnesium ion concentration (Mg^{++}_o) are emphasized. Mg^{++}_i blocks outward sodium and potassium currents whereas Mg^{++}_o generally has an activator effect on ionic transport. Both Mg^{++}_i and Mg^{++}_o stimulate sodium–potassium ATPase at low concentrations and cause inhibition at high concentrations.

Magnesium therapy

Magnesium dosage for replacement therapy is poorly understood and recommendations vary. A suggested procedure is given in Table 3. Before administration, it is necessary to ascertain that renal function is adequate. The i.v. route should be used only in an emergency (such as hypomagnesaemic convulsions or life-threatening cardiac arrhythmia) and treatment should be stopped if hypotension or bradycardia occurs, if serum concentrations exceed 2.5 mmol $litre^{-1}$ or if the deep tendon reflexes disappear. The oral route should be used wherever possible, although this route takes six times longer for repletion to occur.[57] (Other references to magnesium repletion are given later in this article under the various sub-headings.)

Magnesium has had a suggested role in nearly every physiological system. Key underlying mechanisms of action are that of calcium antagonism via calcium channels, regulation of energy transfer (such as the production and function of ATP, and controller of glycolysis and the Krebs cycle in oxidative phosphorylation) and membrane sealing or stabilization.[81 149 200] This has led to several studies on the central and peripheral nervous systems, and cardiovascular, respiratory, endocrine and reproductive systems. In the nervous system, magnesium has a depressant effect at synapses and has been used as an anticonvulsant. The mechanism of action at synapses is related to competition between calcium and magnesium in the stimulus–secretion coupling processes in transmitter release.[21] The most well described of these is presynaptic inhibition of acetylcholine release at the neuromuscular junction. Its action as an anticonvulsant is secondary to magnesium antagonism at *N*-methyl D-aspartate (NMDA) receptors.[116] These are a subgroup of glutamate receptors, stimulation of which is known to lead to excitatory postsynaptic potentials (EPSP) causing seizures; magnesium has been used successfully as an anticonvulsant in eclampsia.[168] However, in other circumstances it appears to be a much less effective anticonvulsant. Other more speculative areas where magnesium may have a role are in dementia, restless legs syndrome and chronic fatigue syndrome where deficiency of magnesium may cause excess activity at NMDA receptors, loss of cell fluidity and decreased calcium release and effect.[103]

In sports medicine, the effect of magnesium supplementation has been shown to increase workload duration and enhance membrane function (shown by decreased release of muscle enzymes into serum). The effect of the former is postulated to be secondary to its role as a co-factor in intracellular energy production. The latter effect is produced by binding of magnesium to the phosphate groups of phospholipids on cell and organelle membranes, thus stabilizing membranes from exercise-induced injury.[64]

Magnesium has a depressant effect on the release of catecholamines. This has been studied in animals; magnesium obtunds some of the features of the porcine stress syndrome whereby transportation and slaughter induce hypermetabolic changes resulting in a reduction in pork quality. The carcass muscles classically have PSE (pale soft and exudative) syndrome.[50] In humans, neuronal hyperexcitability syndrome (NHS), the symptoms of neuromuscular, autonomic and psychological excitability, can be relieved with the use of magnesium.[114] The mechanism is attributed to interference with storage and release of catecholamines. Moreover, the situation in NHS can be exacerbated by catecholamine-induced magnesium loss, further depleting the ion from soft tissues. The use of magnesium as an agent to decrease catecholamine release during phaeochromocytoma surgery is discussed below.

The use of magnesium in immunology has been studied: in allergic rhinitis and asthma it has been suggested that intracellular calcium concentrations increase in response to IgE stimulation leading to histamine release. This can be antagonized by magnesium.[184] In asthma, bronchospasm (requiring increased intracellular calcium) is antagonized by magnesium. This is discussed below.

Magnesium has been used as a therapeutic agent for several hundred years. Its earliest use was as a cathartic, for which it is still used most commonly. Magnesium-rich waters (such as those of the Epsom Spa) have been thought to be beneficial since the early 17th century. The dangers of excessive magnesium intake were also recognized, with the first case of magnesium poisoning recorded in 1891 when 4 ounces of Epsom salts caused complete muscular paralysis in a 35-yr-old woman.[32] There are a large number of theoretical benefits of magnesium therapy, from laxative and antacid therapy to cytoprotection for organs destined for transplantation.[47] However, the use of magnesium in obstetrics and cardiology provides the most compelling evidence. These areas, together with other current interest in magnesium therapy, are now discussed in greater detail.

Magnesium in obstetrics

Magnesium sulphate has been advocated for the treatment of both pre-eclampsia (a multi-system disorder characterized by hypertension, oedema and proteinuria) and eclampsia

(the association of one or more seizures with pre-eclampsia) since 1906.[101] More recently it has been recommended as a tocolytic. In the USA, it is the most common drug for the treatment of convulsions associated with eclampsia,[137] but is used less commonly in the UK where diazepam and phenytoin are the two main choices.[80] However, randomized, prospective studies of its use were limited until the Eclampsia Trial Collaborative Group reported the results of a multinational study showing a beneficial effect of magnesium sulphate over diazepam or phenytoin in eclampsia.[168] However, there is little direct evidence for a beneficial effect of magnesium sulphate in pre-eclampsia.

Eclampsia

Eclampsia is believed to complicate 1 in 100 to 1 in 1700 pregnancies in developing countries and 1 in 2000 pregnancies in Europe and the developed world.[43 196] In the last UK figures, it was a contributing factor in 15% of direct maternal deaths[38] and world-wide caused 50 000 deaths per year.[45] The mortality rate varies from 2 to 5%.[43] Magnesium sulphate has been the first-choice drug in the USA since the 1930s for controlling the first fit and for preventing further fits,[137] yet only 2% of UK obstetricians admit to having used it.[79] The use of magnesium in the USA was largely founded on uncontrolled reports until recently. However, there are now three randomized, controlled studies that support the use of magnesium in eclampsia.

Crowther compared diazepam with magnesium sulphate in 51 eclamptic patients.[36] The study showed an association between the use of magnesium and less serious morbidity (convulsion recurrence, acute renal failure, cardiopulmonary problems and disseminated intravascular coagulation) but these differences were not significant. There was a significant increase in the number of infants born with Apgar scores of less than 7 in the diazepam group. The second study compared magnesium sulphate with phenytoin in 22 eclamptic patients.[42] This was terminated early when four of 11 patients in the phenytoin group had recurrent convulsions compared with none of 11 in the magnesium group.

The study that provides the most compelling evidence for the role of magnesium in eclampsia is from the Eclampsia Trial Collaborative Group (ETCG), co-ordinated by the Perinatal Trials Service in Oxford.[168] In total, 1687 women with eclampsia from 28 centres in South America, India and Africa were included in a randomized study comparing magnesium sulphate with phenytoin in one limb of the study, and magnesium sulphate with diazepam in the other limb. Magnesium sulphate was given i.v. in a loading dose of 4 g, with subsequent doses given by i.v. infusion or i.m.

The results showed that women given magnesium sulphate had a 52% lower relative risk of developing recurrent convulsions compared with those given diazepam (13.2% *vs* 27.9%), and a lower relative risk of recurrent seizures (5.7% *vs* 17.1%). Maternal mortality was reduced in the magnesium group compared with the diazepam and phenytoin groups but the difference was not significant. The magnesium group were less likely to require intensive care facilities or develop pulmonary problems, and their babies were significantly less likely to require special care facilities or intubation than the phenytoin group.

This study has been acclaimed widely as a landmark in multicentre research, and as an example of what can be achieved with limited hospital resources and skills. Not only this, but the high significance level of the results has led to a number of editorials in the UK demanding the instatement of magnesium sulphate over other therapies in eclampsia. The 'time of reckoning' for magnesium sulphate is now here.[45 141]

Pre-eclampsia

While the evidence for the use of magnesium sulphate in eclampsia is strong, there is less support for a prophylactic or therapeutic role in pre-eclampsia. First, the proportion of women with pre-eclampsia who progress to eclampsia is very small, making it difficult to produce a study with high enough power to detect differences. Second, the side effects of any treatment must be borne in mind when conducting a study in which only a small proportion of participants are likely to benefit. By examining studies of the rate of progression from pre-eclampsia to eclampsia after magnesium sulphate use, it has been calculated that if magnesium sulphate reduced the rate of eclampsia by 50%, 675 patients would have to be treated to prevent one convulsion.[46] A more recently published study has demonstrated that magnesium may have a role in patients with severe pre-eclampsia, when the number of women who needed treatment with magnesium to prevent one convulsion was 34.[33]

There have been several recent randomized studies which may show some further beneficial effects of magnesium sulphate in pre-eclampsia. Belfort and Moise showed a significant reduction in the pulsatility index of the middle cerebral artery (assessed by Doppler ultrasonography) in six patients with pre-eclampsia given a bolus dose of magnesium sulphate 6 g i.v., compared with six similar patients given placebo.[16] The carotid artery waveforms were unaltered by magnesium sulphate. Their interpretation was that the reduction in pulsatility index of the middle cerebral, as opposed to carotid arteries, was a result of relief of vasospasm in the distal cerebral circulation. They have found similar results for the retinal circulation in pre-eclampsia. However, these were small studies and interpretation of pulsatility indices is difficult without some indication of the effects of magnesium sulphate on cardiac output, which was not measured.

As mentioned above, large sample sizes would be needed to show a beneficial effect of any treatment in terms of reducing the rate of progression from pre-eclampsia to eclampsia. In a large study, women with pre-eclampsia were allocated randomly to receive either magnesium sulphate or phenytoin as prophylaxis against developing eclampsia.[109]

The results showed that 10 of 1089 women given phenytoin developed convulsions compared with none of 1049 given magnesium sulphate. In other respects, maternal and infant outcomes were the same and the groups were similar in terms of other treatments received. The study was stopped early because it was felt that phenytoin might be having a harmful effect. Of even greater interest was the group of women who declined to consent to take part in the study. Only one of 1300 such women developed a convulsion, which would cause most people to question the validity of prophylactic treatment in pre-eclampsia. Neilson points out that as only 0.5% of the women in the study went on to have convulsions, the estimated rate of 5% of pregnant women receiving anticonvulsant treatment in the USA is surely far too high,[127] given the possible side effects of treatment. Unfortunately, there are still no certain predictors of which pre-eclamptic women are likely to progress to eclampsia.

Action of magnesium sulphate in eclampsia

The precise site of action of magnesium sulphate in eclampsia is not known. Experimentally, magnesium has been shown to block the NMDA subtype of glutamate channel through which calcium enters the cell and causes neuronal damage during cerebral ischaemia.[116 147] Ischaemia leads to lowering of the transmembrane potential allowing calcium ion influx across the membrane and from the endoplasmic reticulum and mitochondria. This leads to further calcium influx as membrane phospholipids are hydrolysed by activated enzymes. Magnesium blocks calcium at intracellular sites in addition to the outer lipid membrane. This could make it superior to conventional calcium antagonists that act only on the outer membrane. Magnesium has been shown to protect hippocampal cell cultures from anoxia[146] and glutamate,[56] and has also been shown to prolong the ischaemic time before irreversible cell damage in the rabbit spinal cord.[177] Direct neuromuscular block has also been suggested as a mechanism of action in eclampsia, but this seems unlikely as serum concentrations well below those needed to suppress neuromuscular transmission exert anti-eclamptic effects.

Pathological findings from brains of patients with eclampsia reveal evidence of cerebral vasospasm; these findings have been backed by cerebral angiography and CT findings and agree with findings in the systemic vasculature.[105] Calcium and magnesium act as antagonists of each other in blood vessel tone regulation. Increases in calcium ion concentration cause vasospasm which is reversed by magnesium and worsened by lowering magnesium concentrations.[7]

Magnesium and tracheal intubation

Tracheal intubation of patients with hypertensive disorders in pregnancy causes marked increases in systemic arterial, pulmonary arterial and pulmonary capillary wedge pressures leading to increased risks of intracerebral hypertension and haemorrhage.[35] Conventional strategies for obtunding the hypertensive response to intubation, such as β block, topical local anaesthesia, opioids and vasodilators appear to be less effective in pre-eclampsia.[122] Magnesium sulphate has been shown to obtund the hypertensive response to intubation in patients with pre-eclampsia. Allen, James and Uys showed no increase in systolic arterial pressure for 5 min after intubation in women pretreated with magnesium sulphate 40 mg kg^{-1} or alfentanil 10 μg kg^{-1}, but a significant increase in women pretreated with lidocaine 1.5 mg kg^{-1}.[5] Both magnesium sulphate and alfentanil had side effects at these doses, with magnesium causing tachycardia and alfentanil causing neonatal depression and failing to control arterial pressure in 25% of patients. Ashton and colleagues showed even better control of arterial pressure and heart rate with a combination of alfentanil 7.5 μg kg^{-1} and magnesium sulphate 30 mg kg^{-1}, without causing significant neonatal depression.[12] The mechanism of action appears to be inhibition of catecholamine release from the adrenal medulla[44] with epinephrine concentrations unchanged from baseline and a significant decrease in the increase in norepinephrine concentrations compared with controls.[87]

Haemodynamic effects of magnesium sulphate in obstetrics

Magnesium sulphate may have beneficial haemodynamic effects in pre-eclampsia. In a study comparing 15 patients with pre-eclampsia with 11 patients in preterm labour before and after a high dose magnesium sulphate bolus and infusion, it was found that patients with pre-eclampsia had increased baseline systemic vascular resistance almost twice that of the preterm labour patients, and a concomitant reduction in cardiac index. For the first 4 h of the magnesium sulphate infusion, systemic vascular resistance decreased and cardiac index increased in pre-eclamptic patients, but it had little effect in preterm labour patients.[152]

The uteroplacental unit may also be affected favourably by magnesium sulphate. Gravid ewes receiving magnesium sulphate towards the end of gestation showed a decrease in mean arterial pressure but an increase in uterine blood flow and fetal Pa_{O_2}.[179] In humans, fetal heart rate variability *in utero* showed no significant change during infusion of magnesium sulphate and only a small increase after a bolus dose was given to pre-eclamptic patients.[24]

Anaesthetists will be particularly concerned by the haemodynamic effects of magnesium sulphate when given in the presence of regional local anaesthetic block. Studies in gravid ewes showed a significant decrease in mean arterial pressure in ewes receiving an infusion of magnesium sulphate compared with controls given an infusion of saline, after epidural block with lidocaine to the T10–11 sensory level. However, maternal cardiac output and uterine blood flow remained at baseline levels.[179] In a later study by the same group,[161] gravid ewes were given magnesium sulphate, an epidural to thoracic sensory levels and were then treated with ephedrine, phenylephrine or normal saline. In contrast

Table 4 Treatment regimens in eclampsia

Magnesium 4 g i.v. over at least 5 min, followed by either:
(a) I.v. infusion of magnesium 1g h^{-1} for 24 h after the last fit or
(b) Magnesium 5 g i.m., and then magnesium 2.5 g i.m. every 4 h until 24 h after the last fit
Recurrent fits may require an additional bolus of 2–4 g i.v.

to their earlier study, epidural block after magnesium sulphate caused a decrease in cardiac index and uterine blood flow in addition to mean arterial pressure. This was reversed only by ephedrine, while uterine systemic vascular resistance and fetal pH were worsened by phenylephrine. In a study of 11 severe pre-eclamptic patients already receiving magnesium sulphate, lumbar epidural analgesia resulted in a significant decrease in mean arterial pressure but no change in cardiac index, pulmonary vascular resistance, central venous pressure or pulmonary capillary wedge pressure.[129] It was also noted that these patients had supranormal cardiac indices before epidural block which may have been caused by magnesium sulphate.

Magnesium sulphate may have beneficial effects on both maternal and uteroplacental haemodynamics in pre-eclampsia, and regional block appears safe in the presence of magnesium sulphate.

Treatment regimens and monitoring

Although there have been many different treatment regimens over the past 70 yr for the use of magnesium sulphate in pregnancy, it is now being suggested that the regimens used in the Eclampsia Trial Collaborative Groups study should be used as standard, as they have been proved to produce a beneficial effect without risk of side effects.[45] These regimens are the i.m. regimen described by Pritchard, Cunningham and Pritchard[138] and the i.v. regimen described by Zuspan,[201] and are shown in Table 4. Although magnesium slightly increased bleeding times in pre-eclampsia, which may in theory make the risk of post-partum haemorrhage (PPH) and epidural haematomata more likely,[83] the ETCG showed that there was no increase in PPH, and the risks are probably very small.

Monitoring of serum magnesium has been used to assess therapeutic concentrations and adverse effects. Target serum concentrations have been suggested to range from 2 to 4 mmol $litre^{-1}$,[141] with side effects such as loss of reflexes and respiratory depression occurring at concentrations of more than 5 and 7 mmol $litre^{-1}$, respectively. However, serum monitoring was not undertaken in the Eclampsia Trial Collaborative Groups study, but data on similar regimens suggest that serum concentrations of magnesium would have been less than 2 mmol $litre^{-1}$.[159] The results of this study suggest that serum monitoring may be of little benefit and that therapeutic serum concentrations may be well below previously accepted values. Monitoring of patellar reflexes and ventilatory frequency may be of equal benefit to monitoring serum concentrations, as loss of the patellar reflexes occurs well before respiratory depression and arrest.[45] As magnesium is cleared by the kidneys, extra caution is needed in renal failure. In the Eclampsia Trial Collaborative Groups study, the magnesium dose was halved if urine output decreased to less than 100 ml h^{-1} and there were no other signs of toxicity. Although no untoward events were reported in the study from this strategy, in the presence of renal failure, monitoring of serum concentrations might be of benefit.

Magnesium sulphate in tocolysis

Magnesium has been used for nearly 40 yr to treat premature labour and is the most commonly used agent in the USA,[104] but evidence for its use is unconvincing. In a recent review, Macones and colleagues examined the evidence comparing ritodrine, beta agonists and magnesium. Compared with placebo, magnesium was no better in achieving a delay in delivery, although ritodrine, beta agonists and magnesium were comparable in achieving clinically significant tocolysis.[110] In addition, when used in the prior treatment of pre-eclampsia, magnesium did not prolong or affect duration of labour, although it necessitated a higher dose of oxytocin.[190]

Magnesium in cardiology

Magnesium has been studied extensively in cardiology. The three areas of particular relevance to anaesthetists are myocardial infarction, arrhythmia and cardiac surgery.

Magnesium and acute myocardial infarction

Interest in the therapeutic potential of magnesium in the management of patients with acute myocardial infarction (AMI) followed reports of decreased arrhythmias and improved survival from uncontrolled studies in South Africa, Australia and Europe. Epidemiologists later noted that patients dying suddenly from ischaemic heart disease (IHD) had lower concentrations of myocardial tissue magnesium and potassium than controls (death after acute trauma)[93] and that there was a greater proportion of deaths in cities with soft water, which is relatively lacking in magnesium and calcium.[10] The results of randomized studies were generally inconclusive and the possible benefits of magnesium in AMI were not evaluated on a large scale. Despite major advances in the management of AMI in recent years, there has been little impact on deaths resulting from cardiogenic shock. Attempts to improve current strategies, to search for less expensive therapies and new evidence that magnesium may be an effective pharmacological agent for the treatment of reperfusion injury have lead to a renewed interest in this agent.

Magnesium has many functions which could be of importance in AMI, not only in ischaemic–infarcted tissue but also during reperfusion (whether spontaneous, pharmacological or by angioplasty). During ischaemia, aerobic metabolism ceases and intracellular ATP is depleted. As the majority of ATP within the cell is in the form of

the magnesium salt, cellular magnesium is also depleted. Moreover, anaerobic metabolism leads to intracellular acidosis and an increase in mitochondrial uptake of calcium which further inhibits ATP synthesis. Calcium overload is central in ischaemic myocardial cell death and this is exacerbated during reperfusion. Magnesium administration may provide cellular protection during ischaemia. Magnesium drives calcium into the sarcoplasmic reticulum, reduces mitochondrial calcium overload[54] and competes with calcium for binding to troponin C. Magnesium also inhibits calcium influx into myocytes and thus prevents increases in intracellular concentrations of calcium which are known to be detrimental to cellular function. Magnesium helps to conserve cellular ATP as the magnesium salt[71] and therefore preserves energy-dependent cellular activity, particularly in the face of adrenergic overstimulation occurring during ischaemic episodes. Other beneficial effects include improvement of the contractile response of stunned myocardium[49] and limitation of infarct size[30] by a mechanism yet to be elucidated. Infusions of magnesium increase the threshold for electrical excitation of myocardial cells.[69] The likelihood that an injury current will create an abnormal focus near ischaemic or infarcted tissue is reduced by magnesium, and as a co-factor for sodium–potassium ATPase, magnesium inhibits cellular potassium loss which may also be important in the prevention of arrhythmia.[178] Magnesium may also reduce reperfusion injury by inhibiting calcium overload and laboratory studies indicate that magnesium may protect cells from free radical damage.[192]

Many of the actions of magnesium have been likened to calcium antagonism.[81] When infused, magnesium causes a decrease in peripheral resistance of approximately 20–35% in association with a secondary increase in cardiac index of 25%, with little change in arterial pressure or heart rate. Inhibition of the sinus node by magnesium is probably offset by inhibition of acetylcholine release at the vagal nerve terminals. Gomez has recently compared published data on the haemodynamic effects of magnesium administration in awake subjects.[65] Coronary vasodilatation was accompanied by a significant increase in coronary perfusion. Clinically, i.v. magnesium suppressed exercise-induced angina caused by coronary artery spasm by improving regional myocardial blood flow.[97]

Magnesium inhibits basal, myogenic and hormone-induced smooth muscle contraction and also has a direct vasodilator effect.[8] Magnesium blocks calcium entry into vascular smooth muscle cells via voltage- and receptor-operated channels and it diminishes the reactivity of these cells to a variety of pressor agents. In the same way, magnesium competes with calcium to inhibit the contractility of coronary arteries. *In vitro* withdrawal of magnesium increases coronary artery tone and potentiates the contractile response to angiotensin, 5-HT, norepinephrine, acetylcholine and potassium.[173] Magnesium has other important actions within the context of AMI, such as inhibition of release of catecholamines.[44] It also modulates coagulation by inhibition of platelet function at high concentrations[125] and stimulation of the release of prostacyclin from vascular endothelium. Thrombus formation is also modified by administration of magnesium.[2]

Given the effects of magnesium in terms of vasodilatation, improved contractility, limitation of infarct size, reduced frequency of arrhythmias, coagulation modification and sympatholysis, it is not surprising that magnesium therapy has been studied extensively in the context of AMI. Moreover, AMI may markedly reduce magnesium concentrations in some patients over the first 24–48 h.[1] The decline in serum magnesium with the onset of chest pain is probably caused by uptake of magnesium into adipocytes to form soaps as a result of catecholamine-induced lipolysis to free fatty acids. Magnesium deficiency may predispose to myocardial irritability and contractile failure of the heart as it is essential for the replenishment of ATP. It is likely that both acute and chronic depletion of extracellular magnesium are harmful to the myocardium in the setting of AMI. Whether magnesium therapy is merely replacing a deficit or acting as a pharmacological agent is pivotal to our understanding of magnesium therapy.

Two studies concerning the use of magnesium and mortality after AMI predated the introduction of thrombolysis. Horner reported that i.v. administration of magnesium was associated with a 49% reduction in the incidence of ventricular tachycardia (VT) and ventricular fibrillation (VF) and that there was a smaller non-significant reduction in the incidence of asystole and electromechanical dissociation (EMD) in the treatment groups. Overall, there was a 54% reduction in mortality associated with administration of magnesium.[79] Teo and colleagues also demonstrated that administration of magnesium was a safe and effective method of reducing arrhythmias and mortality in AMI.[167] Horner suggested that the anti-arrhythmic effect of magnesium was the main mechanism by which it reduced mortality.

More recently, the results of two much larger studies have been published. In 1994, in the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT 2), 2316 patients with AMI were allocated randomly to receive magnesium or placebo.[194] Treatment consisted of magnesium 8 mmol over 5 min, before thrombolytic therapy, followed by 65 mmol as an infusion over the next 24 h. Serum magnesium concentrations were approximately doubled for 24 h after admission but returned to normal by 48 h. There was a 24% relative reduction in mortality after 28 days (10.3% *vs* 7.8%) and a 25% lower incidence of left ventricular failure (LVF 14.9% *vs* 11.2%) in the treatment group. There was no difference in the incidence of hypotension, arrhythmias (particularly early VF) or requirements for anti-arrhythmic agents. The reduction in LVF was associated with a corresponding reduction in mortality from IHD over a mean follow-up period of 2.7 yr.[193] Side effects of treatment included an increase in bradyarrhythmias and skin flushing on administration. The

conclusion of this study was that early i.v. magnesium is a useful addition to standard therapy in AMI.

However, the publication of ISIS 4 in 1995 showed no benefit of magnesium therapy in a study population of 58 500.[82] In addition to magnesium, patients were allocated randomly to receive thrombolytic therapy, captopril or mononitrates. The results showed a trend towards increased mortality at 35 days with an excess incidence of cardiogenic shock and heart failure in the magnesium group (7.6% *vs* 7.2%) although there was a significant reduction in the early occurrence of VF. No benefit was seen in the treatment group across all major subgroups, whether they were treated early or late and whether or not they received thrombolysis. In this study, however, thrombolytic therapy was given and lysis completed before treatment with magnesium in contrast to LIMIT 2 where they were given concurrently.

These differences in the results between LIMIT 2 and ISIS 4 have led to some confusion as to whether or not magnesium should be administered routinely as first-line therapy during the acute phase of myocardial infarction. Clinically important differences have been noted between the two studies and in some of the small earlier studies. There are differences in the time of administration of magnesium and its relationship to thrombolytic therapy, variation in the doses administered in the first 24 h and duration of magnesium therapy, and differences in patient risks in control and treatment groups.

If magnesium protects the contractile function of the myocardium from reperfusion injury, then the timing of administration may be important. During the first few minutes of reperfusion, calcium accumulates in the myocardium, in particular in the mitochondria, and there is depletion of high-energy phosphates and contractile dysfunction. For protection to occur, magnesium concentrations must be increased before reperfusion occurs. The timing of magnesium administration in relation to either spontaneous reperfusion or after thrombolysis is likely to be critical. The therapeutic time window for modifying the external concentration of magnesium is probably confined to the first 1–2 min of reperfusion; it has been shown that the beneficial effects of magnesium are diminished when it is administered 1 h after reperfusion.[15] DuToit and Opie demonstrated in a rat model that magnesium attenuated calcium influx only when administered within 15 min of reperfusion.[48] Hence magnesium should probably be given before thrombolytic therapy. Those patients not given thrombolysis should receive an infusion of magnesium to maintain high serum concentrations when spontaneous reperfusion is most likely to occur. Also, the mortality of the control group influences the perceived benefit from the treatment: in ISIS 4, the mortality of the control group was very low whereas the higher control group mortality in LIMIT 2 may be because fewer control subjects received thrombolysis or aspirin.

In both LIMIT 2 and ISIS 4, a proportion of patients received thromobolytic therapy. In general, only about one-third of patients with AMI receive this treatment, despite its proven benefit on outcome. Shechter and colleagues performed a study to assess magnesium therapy in patients with AMI not receiving thrombolysis: 194 high-risk patients unsuitable for thrombolysis were allocated randomly to receive magnesium or placebo.[157] Therapy was started a mean of 5 h earlier than in the ISIS 4 study and there was 17% mortality in the placebo group compared with 4% in the magnesium group. Ejection fraction was higher at 72 h in the magnesium group than in those given placebo and the high mortality in the placebo group was caused mainly by myocardial failure. These data support the hypothesis that magnesium is cardioprotective in AMI.

It would appear that the beneficial effect of magnesium in AMI is not suppression of life-threatening rhythm disturbances but myocardial protection, particularly during reperfusion,[194] as evidenced by a 25% reduction in LVF in the treatment group in LIMIT 2 and the results of the study of Shechter and colleagues. It is not clear if antiplatelet effects and improved coronary perfusion are important but it would appear that afterload reduction resulting from administration of magnesium is probably too brief to be clinically important. Despite large studies examining the effect of magnesium on outcome after AMI, clear recommendations for its use are still lacking. Antman reviewed all randomized controlled studies of magnesium in AMI.[11] He concluded that patients at low risk of mortality from AMI and who benefit from thrombolysis and aspirin probably gain little benefit from magnesium therapy. In high-risk patients who may not be suitable for thrombolysis, magnesium appears to be useful. In a commentary in the *Lancet*, Cassells stated that patients with subnormal magnesium concentrations should be given magnesium in AMI.[26] Administration of magnesium 10 mmol as an i.v. bolus after oral aspirin should be standard for all patients seen within 6 h of the acute event, except those with hypotension, bradycardia or AV block. Overall, the treatment of AMI patients with magnesium is debatable. If it does have a place, evidence to date supports its administration before spontaneous reperfusion or thrombolysis and in high-risk patients.

Magnesium and arrhythmias

Extensive investigations, both in the laboratory and in clinical studies, have been undertaken to define the role of magnesium in the genesis and treatment of cardiac arrhythmia. While both atrial and ventricular arrhythmias have been associated with hypomagnesaemia,[49] this relationship is complicated by the poor correlation between serum and myocyte magnesium concentrations[95 139] and the close interaction of magnesium with potassium metabolism. The multiple roles of the magnesium ion in cardiac muscle has confounded interpretation of available data on hypomagnesaemia as a cause or precipitant of arrhythmia.[82]

In a review of arrhythmias associated with hypomagnesaemia, Millane, Ward and Camm found that concurrent hypokalaemia was a consistent feature.[118] Causes of magnesium and potassium depletion are similar and hypomagnesae-

mia results in renal wasting of potassium. There appears to be no evidence that isolated hypomagnesaemia is pro-arrhythmic or that myocardial magnesium depletion precipitates arrhythmias, but it may exacerbate potassium-mediated arrhythmias by a complex interaction which modifies the action potential. In most reports of hypomagnesaemic-related arrhythmia, there is a good response to magnesium therapy which is sustained when both potassium and magnesium concentrations are normalized and it is recommended that both potassium and magnesium are administered for rapid control of arrhythmias associated with potassium depletion. The mechanism by which magnesium acts is probably by slow inward calcium current block, which decreases sinus node rate, prolongs AV conduction time and increases AV node refractoriness without major changes in ventricular physiology.[40]

Atrial arrhythmias

Wesley and colleagues described the effect of a single bolus dose of magnesium 2 g in supraventricular tachycardias and demonstrated slowing or termination when the AV node was part of a re-entrant circuit in seven of 10 patients.[185] However, in a later study, adenosine was significantly better than magnesium at terminating induced tachycardias, acting by anterograde AV nodal block whereas with magnesium, no specific mode of action was evident.[181] Nevertheless, in critically ill patients, magnesium was more effective than amiodarone in conversion of acute atrial tachyarrhythmias, although slowing of ventricular rate in non-converters was the same in both groups.[121]

Ventricular arrhythmias

Magnesium has been used successfully in the treatment of ventricular arrhythmias associated with AMI, long QT syndromes and digoxin toxicity. Ventricular arrhythmias, particularly following AMI, are not well established as being related to low magnesium concentrations, whereas the evidence linking ventricular arrhythmias and hypokalaemia is substantial.[131] The place of magnesium therapy also awaits confirmation, but it has been successfully demonstrated to increase the threshold stimulus required to provoke either VT or VF,[61] and magnesium has been incorporated into the algorithm for management of broad complex tachycardia in the Resuscitation Council Advanced Life Support Manual (1994). The recommended dose in this situation is 10 ml of a 50% solution of magnesium sulphate given over 1 h.[140]

However, the use of magnesium as a first-line drug in the treatment of polymorphic ventricular tachycardia can be associated with marked prolongation of the QT interval (torsades de pointes). Tzivoni and colleagues reported the successful use of magnesium in three patients with drug-induced torsades de pointes.[175] Despite normal serum potassium and magnesium concentrations, all patients responded to i.v. boluses (1–2 g) of magnesium. Perticone, Adinolfi and Bonaduce reported a further six cases of torsades de pointes treated with magnesium (50 mg min^{-1} until 2 h after the arrhythmia stopped, then 30 mg min^{-1} for 90 min twice daily for 3–4 days).[136] In all patients, the arrhythmias disappeared after 20–30 min of magnesium infusion. There were no documented adverse side effects, and heart rate and QT interval remained unchanged from baseline values. None of the patients was hypomagnesaemic at the time. The mechanism of action of magnesium is not clear as it has no effect on heart rate or QT interval, which suggests that it does not shorten delayed repolarization of the myocardium. However, magnesium is ineffective in polymorphic VT not associated with long QT intervals.[77] This area has been reviewed recently by Roden.[143]

Table 5 Treatment of cardiac arrhythmias with magnesium

Indications:
Emergency treatment of:
(a) Torsades de pointes
(b) Digoxin toxicity
(c) Any serious atrial or ventricular arrhythmia, especially when hypokalaemia co-exists
Dose:
2 g over 10–15 min
Repeat once if necessary

Cardiac glycosides

The cardiac glycosides, which inhibit membrane-bound sodium–potassium ATPase, are used in the treatment of atrial arrhythmias but toxicity can also be arrhythmogenic. Magnesium is a co-factor for this enzyme. Normomagnesaemia is essential for digoxin to be effective in controlling atrial arrhythmias,[17] and hypomagnesaemia facilitates digitalis-induced arrhythmias which may be terminated by administration of magnesium.[156] Young and colleagues studied 81 patients with and without digoxin toxicity and found that subjects with toxic symptoms had lower serum and monocyte magnesium concentrations than those with no evidence of digitalis toxicity.[198] The mechanism by which magnesium depletion increases the risk of digoxin toxicity is uncertain. It might be anticipated that in the presence of hypomagnesaemia, inhibition of Na–K ATPase by digoxin is inhibited and magnesium therapy should reactivate the enzyme. However, animal studies suggest that magnesium has a direct membrane stabilizing effect on the cell membrane.[158]

Overall, the relationship between magnesium and the genesis and treatment of atrial and ventricular arrhythmias is far from clear. It has an established place in the treatment of long QT syndromes and digoxin toxicity (Table 5). However, i.v. magnesium should be considered for all refractory arrhythmias, even in the presence of normal serum concentrations, particularly if the patient has been receiving digoxin and diuretics.[95] Caution should be exercised in administering magnesium to patients with compromised renal function, bradycardia and atrioventricular conduction abnormalities. Further evidence of the use of magnesium comes from the MAGICA study where the prophylactic use of oral magnesium and potassium was

evaluated: a 50% increase in intake over 3 weeks of these two minerals in patients with frequent and stable ventricular tachyarrhythmias resulted in a significant anti-arrhythmic effect, although supraventricular tachyarrhythmias and patient symptoms remained unchanged.[199]

Magnesium and cardiac surgery

Patients undergoing heart surgery are at risk of magnesium deficiency because of pre-existing diuretic therapy and heart failure.[187] Hypomagnesaemia is common after cardiopulmonary bypass surgery (CPB) and may contribute to postoperative arrhythmias.[3] Its administration has been shown to decrease the occurrence of postoperative hypomagnesaemia.[183] Opinion is divided as to whether or not there is an association between adverse events and low magnesium concentrations[53 174] in cardiac surgical patients.

A decrease in magnesium in patients undergoing CPB was recognized nearly 30 yr ago.[154] More recently, Satur and colleagues evaluated the patterns of magnesium deficiency that develop during and after CPB without cardioplegia.[151] Haemodilution at the start of CPB caused a 17% decrease in plasma magnesium which persisted until the first postoperative day, but by day 5, the concentration had increased to almost 20% greater than the preoperative value. The content of magnesium in cardiac muscle decreased by 13%. Fluxes in plasma magnesium concentration were reflected in the pattern of urinary excretion. They described three patterns of magnesium depletion: haemodilution, intraoperative cellular depletion and postoperative cellular depletion. Suggested causes were a bypass prime low in magnesium, intermittent ischaemia and release of intracellular magnesium by catecholamine-induced β receptor stimulation. Turnier and colleagues demonstrated a significant increase in magnesium concentration in pump samples after CPB compared with pre-bypass levels and suggested that catecholamine-induced lipolysis and FFA chelation of magnesium may contribute to low circulating concentrations.[174] Brookes and Fry found that at 24 h after CPB, plasma ionized magnesium was reduced significantly with no change in total magnesium.[22] They suggest the presence of a magnesium binding ligand of unknown origin in the plasma which may be related to solutions used after operation, such as hetastarch or an acute phase protein.

The effect of prophylactic administration of magnesium during the perioperative period has been a subject of much debate and recommendations vary. Colquhoun and colleagues administered magnesium chloride 50 mmol or placebo to patients after coronary artery vein grafting (CAVG).[34] The incidence of SVT was twice as great in the placebo group but there was no difference in the incidence of ventricular arrhythmias. However, Harris and Crowther demonstrated that the incidence of atrial arrhythmias was similar in both groups but ventricular arrhythmias occurred three times more frequently in the control group.[68] England and colleagues attempted to determine if magnesium was effective in reducing morbidity and mortality after CAVG surgery.[53] One hundred patients were included in a placebo-controlled, double-blind study of magnesium chloride 16 mmol given during operation after termination of CPB; 16% of the treatment group had ventricular arrhythmias compared with 34% in the placebo group. Magnesium-treated patients also had higher cardiac indices and were less likely to require prolonged mechanical ventilatory support. Recently, the study of Jensen, Alstrup and Klitgard provided further evidence for the use of magnesium for cardiac surgical patients: there was a reduction in the duration of atrial and ventricular arrhythmias, although not the overall number of patients developing these arrhythmias.[92] Liebscher, Shapiro and Barner showed that patients in whom adenosine triphosphate–magnesium chloride was administered after cardiac surgery had higher cardiac indices than patients treated with sodium nitroprusside, and suggested that the cardioprotective effects of magnesium were responsible for improved myocardial performance in the magnesium treated group.[106] More recently, refractory cardiogenic shock after cardiac surgery resolved promptly after administration of magnesium.[165]

Despite this, there is evidence suggesting that administration of magnesium may be detrimental. Parikka and colleagues suggested that correcting the postoperative decline in magnesium by infusing 70 mmol on the first 2 days after operation did not reduce the incidence or relapse rate of atrial fibrillation.[135] They found that patients with high serum magnesium (treatment group) had AF more frequently and that supra-physiological concentrations of magnesium led to a slowing of sinus rhythm rate that may predispose to AF. Hecker and colleagues indicated that administration of magnesium was deleterious because more DC higher energy shocks were required to defibrillate the heart after CPB than when magnesium is not given.[75]

Another area of interest is the use of magnesium in cardioplegic solutions. Effective myocardial protection is an essential part of successful cardiopulmonary bypass techniques. A variety of magnesium-containing cardioplegic solutions have been studied experimentally and clinically with regard to their efficacy as cardioprotective agents. The St Thomas' solution has been subject to the most detailed analysis. The cornerstone of myocardial preservation is a reduction in energy requirements of the ischaemic myocardium. In 1976, Hearse, Stewart and Braimbridge investigated the extent to which various protective agents could increase the resistance of the heart to periods of transient ischaemia.[72] The aim was to produce a solution which, if infused into the coronary vessels before the onset of ischaemia, would rapidly induce arrest and counteract some of the deleterious effects of ischaemia. They developed an infusate with a pH of 7.4, potassium 12 mmol litre^{-1}, magnesium 16 mmol litre^{-1}, creatine phosphate 10 mmol litre^{-1} and procaine 1 mmol litre^{-1}. Later, Hearse, Stewart and Braimbridge showed that magnesium exerts, in a complex dose-related manner, a marked protective effect on ischaemic rat myocardium and that fluctuations within

narrow limits of the concentrations of ionized magnesium and magnesium adenine nucleotide complexes can profoundly affect the contractile performance of the cell.[73] The St Thomas' solution has since been modified but is the most widely used crystalloid cardioplegic solution and can facilitate safe cardioplegic arrest for up to 3 h.

Hearse, Stewart and Braimbridge suggested a mechanism for the beneficial effects of magnesium. After the onset of ischaemia, there is an abrupt reduction in oxidative metabolism and ATP production. The decrease in ATP leads to a transient increase in intracellular magnesium which leaks out of the cell as a result of changes in membrane permeability. This magnesium loss restricts the energy available during post-ischaemic reperfusion. The ability of extracellular magnesium to protect the ischaemic myocardium is because of a reduction in passive magnesium loss. Intracellular stores are conserved, facilitating high-energy phosphate production.

While the role of magnesium in preventing perioperative arrhythmias is still debated, it appears to be a desirable part of myocardial protection during CPB. However, despite reports of improved myocardial preservation with magnesium-containing cardioplegia solutions in addition to an improvement in maximal post-ischaemic ventricular performance,[23] the addition of magnesium has not been accepted universally.

Other clinical uses

Magnesium and neuromuscular block

Research from the early 1950s first elucidated the nature of the effects of calcium and magnesium ions at the neuromuscular junction. By making allowance for some minor postjunctional effects of magnesium, studies of endplate potentials showed that it competed for a prejunctional site with calcium ions.[91] The ions antagonized each other; high magnesium concentrations inhibited release of acetylcholine and high calcium concentrations increased release from the presynaptic nerve terminal. These studies also showed that magnesium ions had an inhibitory effect on postjunctional potentials and caused a decrease in muscle fibre membrane excitability, although these effects were relatively minor in comparison with presynaptic inhibition of acetylcholine release. The nature of the presynaptic channel has been elucidated further in the past 20 yr. There are a variety of different calcium channels now known to exist, named after specific ligands which bind to them. Interest has centred on the N-, L- and P-channels in neuromuscular research. In humans, there is strong evidence for the P-channel being the most important site. Studies using funnel web spider toxin and other synthetic toxins specific to the P-channel have shown that they bind to the presynaptic motor nerve terminals in humans,[176] while binding by known ligands of N- and L-channels was not demonstrated.

The widespread use of magnesium sulphate has implications for anaesthetists, especially when used in conjunction with conventional neuromuscular blocking agents. Lee, Zhang and Kwan studied the effects of magnesium sulphate-induced neuromuscular block on the electromyogram (EMG) and mechanomyogram (MMG) in pigs.[102] The single twitch response at 0.1 Hz was reduced, with the MMG more depressed than the EMG. There was no evidence of fade after train-of-four at 2 Hz and, with tetanic stimulation at 50 Hz, the contractile force increased (not decreased) at 5 s. These results suggested a presynaptic action of magnesium. Magnesium has been shown to potentiate non-depolarizing neuromuscular blocking agents. After a dose of magnesium sulphate 40 mg kg^{-1}, the ED_{50} of vecuronium was reduced by 25%, onset time was nearly halved and recovery time nearly doubled.[59] Prolonged neuromuscular block has been reported with magnesium sulphate and vecuronium,[160] and a more formal study showed recurarization 1 h after vecuronium block in 100% of patients treated with magnesium sulphate 60 mg kg^{-1}.[58] The reduction in onset time of non-depolarizing block has been used clinically to produce intubation conditions more rapidly. The concept of 'priming' to produce a more rapid onset of block involves sequential administration of 20–30% of the ED_{95} of a non-depolarizing agent followed 4–6 min later by the ED_{95}.[155] Magnesium sulphate has been shown to produce rapid onset of block when used as the priming agent with pancuronium,[90] although it had no effect on the onset time of rocuronium.[100] As recovery times are prolonged after magnesium, it has little place in rapid sequence intubation as an alternative to succinylcholine.

The interaction of magnesium with depolarizing neuromuscular blockers is uncertain. Initial reports suggested potentiation of depolarizing block[62] or little clinical effect.[88] However, the most recent study suggests that magnesium may antagonize the block produced by succinylcholine.[172] This study found a 20% reduction in twitch suppression produced by succinylcholine $1.25 \times ED_{50}$ after pretreatment with magnesium sulphate 90 mg kg^{-1}, and a 20% increase in the ED_{50} of succinylcholine after the same dose of magnesium sulphate. An increase in twitch height was also found when succinylcholine $1.25 \times ED_{50}$ was given in the presence of 50% neuromuscular block produced by magnesium sulphate. The authors postulated that some of the earlier reports of potentiation of succinylcholine by magnesium sulphate may have been caused by the development of dual block.

Magnesium and the central nervous system

Magnesium appears to play an important role in conduction in the nervous system with its main mechanism of action appearing to be via a voltage-gated antagonist action at the NMDA receptor. Recent interest has focused on the role of NMDA receptor antagonists in the protection of the central nervous system (CNS) from ischaemic damage.

In experimental systems, ischaemic damage in brain cells was induced and the results of pre- and post-treatment with

NMDA receptor antagonists, such as magnesium, were observed or concentrations of magnesium after ischaemic damage and treatment with NMDA receptor antagonists were measured. Several animal experiments have shown a reduction in ischaemic damage when magnesium was given at or near the time of injury.[78 112] Intracellular magnesium concentrations have been shown to decrease after traumatic brain injury in rats[180] and this decline is attenuated by non-competitive NMDA receptor antagonists,[63] with a corresponding improvement in neurological outcome.[74]

While there is good evidence for a protective role of magnesium in animal models, translating this to humans has proved more difficult. The main problems with human research are attempting to give a treatment before irreversible damage has occurred and selecting suitable end-points to give significant results. Observational studies in very low-birth weight infants suggest that the risk of cerebral palsy may be reduced in mothers treated with magnesium sulphate during pregnancy.[128] Results of large, randomized, prospective studies are awaited. Magnesium sulphate has not been shown to produce significant benefits when given within 12 h of suspected stroke.[123] Similarly, magnesium sulphate has not yet been shown to alter neurological outcome or survival after cardiac arrest.[169]

Magnesium sulphate is of little benefit in the treatment of epilepsy or status epilepticus although there is some evidence that it may be of use in the treatment of some types of seizures other than eclamptic seizures.[116] It has been argued that the mechanism of action of magnesium in treating seizures is by neuromuscular block, but this seems unlikely given that the serum concentrations used are well below those that produce neuromuscular block.[41]

Recent studies suggested a role for NMDA receptor antagonists (such as magnesium or ketamine) in the management of postoperative pain, as NMDA receptor antagonism inhibits induction and maintenance of central sensitization after nociceptive stimuli.[195] In a double-blind study, patients receiving a preoperative bolus and postoperative infusion of magnesium sulphate had lower morphine requirements, less discomfort and less subjective sleep disturbance than control patients in the first 48 h after operation.[171] Wilder-Smith, Knopfli and Wilder-Smith demonstrated that magnesium, fentanyl and ketamine reduced spinal excitation after hysterectomy and produced similar pain scores and morphine consumption.[189] However, the same group have also demonstrated an antanalgesic effect with magnesium.[188]

Phaeochromocytoma

Magnesium is known to have a marked anti-adrenergic effect. This is mediated by a variety of mechanisms, of which the most important is probably calcium antagonism. Calcium plays a fundamental role in stimulus–response coupling of catecholamine release from the adrenal medulla and adrenergic nerve terminals, and its role in adrenal catecholamine release has been well described for more than 30 yr.[44] However, it is only in the past few years that detailed studies of magnesium on this process have been undertaken. In rat phaeochromocytoma cell lines, magnesium produces a discrete block, probably at high-affinity calcium binding sites within the calcium channel pore.[99]

These anti-adrenergic actions, in addition to its vasodilator and anti-arrhythmic actions, have lead to the use of magnesium during surgery for phaeochromocytoma. In this condition, marked cardiovascular changes can occur during induction of anaesthesia, tracheal intubation, tumour handling and after devascularization (where vasoactive support may be required). In spite of the rarity of this condition, James and colleagues have produced a series of 17 anaesthetics in 16 patients who received magnesium in addition to conventional α and β adrenergic block (usually phenoxybenzamine and propanolol or atenolol).[84] Patients received magnesium 1–2 g h^{-1} supplemented with a bolus dose of 40 mg kg^{-1}, and a target magnesium concentration of 2–4 mmol $litre^{-1}$ was obtained in all but one patient. Overall, magnesium sulphate was effective in reducing catecholamine concentrations in the five patients in whom these measurements were undertaken, and was generally effective at controlling cardiovascular changes at induction of anaesthesia and during tracheal intubation, although in four anaesthetics, additional measures (such as sodium nitroprusside) were required during tumour handling. In one patient, magnesium therapy was ineffective and this was attributed to a pre-existing magnesium deficiency and failure to achieve target concentrations of serum magnesium.

Further support for the use of magnesium in the prevention of catecholamine release is found in a study of males pretreated with magnesium sulphate 60 mg kg^{-1} before tracheal intubation. Compared with the control group, magnesium treated patients had significantly lower epinephrine and norepinephrine concentrations after intubation, and less change in heart rate and systolic arterial pressure.[87] The results of this study would suggest that pretreatment with magnesium sulphate is of benefit in other areas such as phaeochromocytoma and pre-eclampsia, particularly if there is a wish to avoid the use of opioids, and indeed magnesium has been used successfully where phaeochromocytoma and pregnancy co-exist.[67 89]

Asthma

Magnesium therapy in asthma was first reported more than 50 yr ago.[70] Recent anecdotal reports and limited series have revived interest in magnesium as an adjunct to standard bronchodilator therapy. Widespread availability, low cost and minimal side effects make magnesium a potentially attractive therapeutic option in asthma. Disparity between study populations, clinical status, therapeutic protocols, methods of assessment and end-points in some studies, together with the small numbers involved, have made it difficult to draw firm conclusions about the place of magnesium in the management of asthma.

The mechanism of action of magnesium in asthmatics is probably multifactorial. The magnesium ion has an

inhibitory action on smooth muscle contraction,[164] on histamine release from mast cells[144] and on acetylcholine release from cholinergic nerve terminals.[37] Magnesium has been shown to relax bronchial smooth muscle *in vitro* by modulating calcium ion transport at the cellular level. Support for this comes from studies with calcium channel blockers which have been shown to blunt the bronchoconstrictor response to exercise,[27] histamine and methacholine, and the effect of magnesium is similar.[111] Magnesium also appears to influence the function of respiratory muscles; low serum concentrations have been associated with diminished respiratory muscle power that improves with administration of magnesium.[120] There is some evidence that prostaglandin- and isoprenaline-mediated vascular smooth muscle relaxation may be magnesium-dependent[8] and that magnesium may potentiate the effect of β agonists on adenyl cyclase.[163] Exposing activated neutrophils from adult asthmatics to magnesium results in a decrease in superoxide production,[25] indicating that magnesium may modulate the inflammatory process and decrease the release of free radicals. The cellular effects of magnesium are diverse and this may explain why such a wide range of responses result from its administration.

Several clinical studies of magnesium therapy have been undertaken. Noppen and colleagues studied six patients presenting with acute asthma in whom there was an improvement in symptoms and signs after magnesium, but it was less than the subsequent effect of β_2 therapy.[130] A study by Rolla and colleagues suggested that the effects of magnesium may be limited only to the duration of the infusion, with respiratory variables returning to control thereafter.[146] Three studies have evaluated the effect of magnesium therapy on hospital admission rates for asthma. Skobeloff and colleagues treated 38 patients with magnesium (PEFR $<$200 litre min^{-1}) who were unresponsive to β_2 agonists, i.v. steroids and aminophylline.[162] The magnesium group demonstrated an increase in mean PEFR from 225 to 297 litre min^{-1} compared with 208 to 216 litre min^{-1} in the placebo group. Hospital admission rates were 37% and 79%, respectively. However, a later study showed no reduction in admission rates with magnesium therapy in a mixed group of asthmatics.[66] However, it is debatable as to the usefulness of admission rates as a measurable endpoint of success or failure of treatment.

Bloch and colleagues seemed to indicate a differential effect of magnesium depending on asthma severity.[20] Patients with acute asthma were treated with regularly inhaled β_2 agonists and i.v. steroids. Thirty minutes after arrival in the emergency room, patients received either magnesium sulphate or placebo. In the initial analysis, hospital admission rates were 35% for the placebo group and 25% for the magnesium treated group. Further analysis revealed that patients who had a severe asthma attack (FEV_1 less than 25% predicted on presentation) had admission rates of 33% compared with 78% in the placebo group. In contrast, in those who had a moderate attack (FEV_1 of 25–75% predicted), admission rates were 22% in both groups. From this study, magnesium seemed to have a beneficial effect in severe acute asthma. Further evidence comes from a case report of a severe, ventilated asthmatic who responded to magnesium therapy.[119] However, routine use of magnesium was not recommended by Tiffany and colleagues who found only minimal improvement in a group of severe asthmatics.[170]

The majority of studies have been conducted in adults and have examined the effect of parenteral magnesium administration. A more recent area of interest has been inhaled magnesium, which shows inconsistent effects. It attenuated metabisulphite-induced bronchoconstriction in asthmatic subjects,[126] but other studies showed no benefit,[28 76] and even increased airway reactivity to histamine.[76]

In children, Pabon, Monem and Kissoon cited four cases in which i.v. magnesium treatment was associated with improvement when conventional bronchodilator therapy had failed.[134] A larger study demonstrated that magnesium achieved earlier improvement in clinical signs and symptoms in patients not responding to conventional therapy alone.[39] In children, however, nebulized magnesium had no beneficial effect and indeed blunted the bronchodilatory and chronotropic effects of inhaled beta agonists.[31]

Current knowledge suggests that the response to magnesium in asthmatics is very variable and factors which determine which patients will benefit from its administration are unknown. In acute exacerbations of asthma, the response to magnesium, although theoretically attractive, is unreliable. But magnesium has been reported to produce immediate and dramatic improvement in anecdotal reports in which life-threatening bronchoconstriction failed to respond to standard therapy.[98]

Magnesium and critical care

Current estimates of hypomagnesaemia may be as high as 65% in adult intensive care patients[150] and 30% in neonatal intensive care patients,[124] compared with 11% in general hospital inpatients.[192] The reasons for these high rates of magnesium deficiency are multifactorial and include: decreased absorption caused by impaired gastrointestinal activity; malnutrition; renal wasting of various drugs (e.g. digoxin, gentamicin, cyclosporin and loop diuretics); diabetes mellitus; hypokalaemia; and hypocalcaemia.[117] Various authors have suggested that supranormal concentrations of magnesium may be required to produce a clinical effect.[85 133] There are several recommendations for the treatment of magnesium deficiency: James recommended slow infusion of magnesium sulphate 10 g over 24 h,[86] while Flink recommended infusion of up to 2 mmol kg^{-1} over 5 days.[57] Magnesium deficiency in low-birth weight infants may be minimized by the addition of magnesium 0.3 mmol kg^{-1} day^{-1}.[153]

Other interesting uses of magnesium include the treatment of respiratory failure, neonatal pulmonary hypertension and tetanus. Magnesium deficiency has also been shown to be

important as a cause of respiratory muscle failure.[142] Patients with low muscle magnesium concentrations but normal serum levels are common in pulmonary intensive care units (47% of patients). These patients have longer stays than patients with normal muscle magnesium concentrations.[55] Magnesium replacement therapy has been shown to increase respiratory muscle power in patients with hypomagnesaemia,[120] but routine magnesium replacement therapy in mechanically ventilated patients has not been proved to be of benefit.[94]

Magnesium sulphate has been studied extensively in the treatment of neonatal pulmonary hypertension. While there are anecdotal reports and series of cases which may show a beneficial effect of magnesium sulphate in premature human neonates,[197] randomized studies in lambs and piglets with induced pulmonary arterial hypertension suggest that systemic vasodilator effects of magnesium may be pronounced at doses required to cause pulmonary artery vasodilatation, and therefore selective pulmonary artery dilators such as nitric oxide may be safer.[148] The mechanism of action of magnesium on the pulmonary artery appears to be via cAMP- and cGMP-mediated relaxation.[60] In tetanus, magnesium sulphate has been used to treat both muscle spasms (thus avoiding the need for sedation and artificial ventilation)[13] and autonomic dysfunction, which leads to large increases in catecholamine release.[107] However, some reports suggest that other agents such as clonidine may be superior for the latter.[166]

Miscellaneous

Magnesium treatment has also been described for a variety of other anaesthesia-related uses, such as prevention of postoperative shivering,[96] and intrathecal administration in rats where it produced spinal anaesthesia and sedation without apparent neurotoxicity.[29] It has also been demonstrated that magnesium deficiency increases ketamine sensitivity in rats, both agents probably exerting their effects via NMDA receptor antagonism.[132]

Summary

Magnesium has an established role in obstetrics and an evolving role in other clinical areas, in particular cardiology. Many of the effects involving magnesium are still a matter of controversy. Over the next decade, it is likely that improvements in the measurement of magnesium, a clearer understanding of the mechanisms of its actions and further results of clinical studies will help to elucidate its role, both in terms of treating deficiency and as a pharmacological agent.

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