

The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review

[L'usage thérapeutique du magnésium en anesthésiologie, réanimation et médecine d'urgence]

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Purpose: To review current knowledge concerning the use of magnesium in anesthesiology, intensive care and emergency medicine.

Methods: References were obtained from Medline® (1995 to 2002). All categories of articles (clinical trials, reviews, or meta-analyses) on this topic were selected. The key words used were magnesium, anesthesia, analgesia, emergency medicine, intensive care, surgery, physiology, pharmacology, eclampsia, pheochromocytoma, asthma, and acute myocardial infarction.

Principal findings: Hypomagnesemia is frequent postoperatively and in the intensive care and needs to be detected and corrected to prevent increased morbidity and mortality. Magnesium reduces catecholamine release and thus allows better control of adrenergic response during intubation or pheochromocytoma surgery. It also decreases the frequency of postoperative rhythm disorders in cardiac surgery as well as convulsive seizures in preeclampsia and their recurrence in eclampsia. The use of adjuvant magnesium during perioperative analgesia may be beneficial for its antagonist effects on N-methyl-D-aspartate receptors. The precise role of magnesium in the treatment of asthmatic attacks and myocardial infarction in emergency conditions needs to be determined.

Conclusions: Magnesium has many known indications in anesthesiology and intensive care, and others have been suggested by recent publications. Because of its interactions with drugs used in anesthesia, anesthesiologists and intensive care specialists need to have a clear understanding of the role of this important cation.

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Principaux résultats : Les hypomagnésémies sont fréquentes en postopératoire et en réanimation. Elles sont responsables d'une augmentation de la morbidité et de la mortalité et devraient être détectées et corrigées. Le magnésium diminue la libération des catécholamines, il permet ainsi un meilleur contrôle de la réponse adrénérique lors de l'intubation ou au cours de la chirurgie du phéochromocytome. En chirurgie cardiaque, il diminue la fréquence de survenue des troubles du rythme postopératoires. Il diminue la survenue des crises convulsives chez les femmes ayant une pré-éclampsie et diminue les récurrences convulsives chez les femmes ayant une éclampsie. Il possède des effets antagonistes des récepteurs N-méthyl-D-aspartate et on pourrait assister à un développement de ses indications en tant qu'adjuvant dans l'analgésie périopératoire. En urgence, sa place dans le traitement de la crise d'asthme et de l'infarctus du myocarde mérite d'être précisée.

Conclusion : Cet ion important de l'organisme a de nombreuses indications reconnues en anesthésie réanimation et de nouvelles indications pourraient apparaître au vu de publications récentes. Ces interactions avec les drogues utilisées en anesthésie en font une molécule importante à connaître des anesthésistes-réanimateurs.

Objectif : Mise au point sur les indications du magnésium en anesthésie, en réanimation ou en service d'urgence.

Méthode : Réalisation d'une revue de la littérature récente (1995 à 2002) concernant le magnésium, par le système Medline. Les articles, type étude clinique prospective, revue ou méta-analyses ont été recherchés. Les mots clés utilisés étaient : "magnesium, anesthesia,

MAGNESIUM (Mg) is the fourth most common mineral salt in the human organism and second among intracellular cations. It has calcium antagonist effects, is involved in the regulation of different ion channels and phosphorylation reactions, and serves as a cofactor in many enzymatic systems. Dymagnesemia,

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particularly hypomagnesemia, is frequent perioperatively and in intensive care and causes considerable morbidity. Different serum Mg concentrations and dosages will be used, depending on whether they are intended to correct a deficit or for pharmacological purposes. Mg is used in different surgical situations, obstetrics and perioperative analgesia and has various interactions with the drugs used in anesthesia. In emergency departments, it is being studied in the treatment of myocardial infarction and asthmatic attacks. This review considers Mg physiology and the implications of dysmagnesemia for anesthetic practice. Recent studies of known indications or promising developments of Mg therapy in anesthesiology, intensive care and emergency medicine are reviewed and discussed.

Mg physiology

Mg in the organism

Mg is a bivalent ion, like calcium, with an atomic weight of 24.312. The human body contains 1 mole (24 g of Mg). It is the fourth most common mineral salt in the organism after phosphorus, calcium and potassium,¹⁻³ the second intracellular cation after potassium, and the fourth plasma cation after sodium, potassium and calcium.⁴ It is concentrated mainly in bone (60%), muscle (20%) and soft tissues (20%). Only a fourth of the Mg contained in bone and muscle is exchangeable.² Extracellular Mg represents only 1% of the total. In serum, Mg is divided into three fractions: ionized (active form), protein-bound and that contained in anion complexes (phosphates and citrates). These three fractions account respectively for 65, 27 and 8% of serum content. Three-fourths of plasma Mg is ultrafiltrable.^{2,4}

The daily recommended Mg requirement is 250 to 350 mg (10.4–14.6 mmol) in adults^{4,5} and an additional 100 to 150 mg in children and pregnant or nursing women.² Food input is ensured essentially by cocoa powder, chocolate, almonds, peanuts, walnuts, vegetables, cereals and seafood. From 30 to 50% of ingested Mg is absorbed (5 mmol·day⁻¹) in decreasing quantity from the small intestine to the colon. Fibres, phytates and oxalic acid appear to reduce Mg absorption moderately through the formation of a complex that cannot be easily dissociated. The binding of Mg to anions (phosphates) or fatty acids reduces the quantity of absorbable Mg. The fraction of absorbed Mg decreases as the quantity ingested increases.² Mg depletion corresponds to obligatory and uncontrollable digestive losses (around 60% of ingested Mg) and variable losses through renal excretion. Digestive losses are increased by diarrhea or biliary fistula. Urinary excretion of Mg is normally 5 mmol·day⁻¹,

but can be reduced to 0.5 mmol·day⁻¹ in the event of severe deficiency. The level is regulated by variations in renal reabsorption, as a function of magnesemia, relative to inputs and bone mobilization.² Around 75% of plasma Mg is filtered at the glomerular level. Only 5% of filtered Mg is excreted, with reabsorption of 15 to 25% in the proximal convoluted tubule and 50 to 60% in the ascending limb of Henle's loop. Diuretics, thiazides, cisplatin, gentamicin and cyclosporine inhibit renal reabsorption.^{3,5}

Mg is mainly intracellular, existing largely (90%) in bound form in adenosine triphosphate (ATP) molecules of the cytoskeleton (nucleus, mitochondria and reticulum), in nucleotides, or in enzyme complexes. A small portion of intracellular Mg (5–14%, depending on the cells) is found in ionized free form within the cell. Heart muscle cells have a high concentration of total Mg (11–17 mmol·L⁻¹ of intracellular water).^{2,6}

Knowledge about the hormonal regulation of Mg homeostasis is incomplete. Several hormones are involved in the regulation of Mg metabolism, namely parathyroid hormone (PTH), calcitonin, vitamin D, insulin, glucagon, epinephrine, antidiuretic hormone, aldosterone and sex hormones. PTH and vitamin D increase intestinal absorption, PTH favours renal reabsorption of Mg and facilitates its bone reuptake, insulin increases cellular uptake of Mg, and glucagon is conducive to its renal reabsorption.^{7,8}

Biological considerations

Assay of total plasma Mg by spectrophotometry is precise and easy to perform (0.7–1.1 mmol·L⁻¹ or 1.4–2.2 mEq·L⁻¹, or 16.8–26.4 mg·L⁻¹). However, owing to the intracellular nature of this ion, these values are not exactly indicative of the Mg pool in the organism or of a possible state of deficiency.⁴ Other concentrations have been studied to allow better assessment of true Mg deficiencies, namely intracellular (8–10 mmol·L⁻¹)⁶ and ionized plasma Mg (0.65 ± 0.1 mmol·L⁻¹) concentrations. Interferences with calcium ions at the level of the Mg electrode reduce the relevance of the ionized Mg assay.⁴ Because of the long life of Mg and its slow turnover, erythrocytic Mg might be a better indicator of deficiency (values in the literature: 2.10 ± 0.4 mmol·L⁻¹)^{1,3} Lymphocytic Mg would appear to be a better indicator of the Mg content of muscle and myocardium and of ionized Mg.¹ However, the relation between these last evaluations and the Mg pool of the organism remains uncertain.⁴

Urinary excretion of Mg is highly variable, ranging from 5 mmol·day⁻¹ in the normomagnesimic subject to 0.5 mmol·day⁻¹ in the deficient subject. Measurement of urinary excretion helps separate renal

from non-renal causes of hypomagnesemia. In the presence of hypomagnesemia, high urinary excretion suggests that increased renal loss is the mechanism of Mg depletion, whereas low urinary excretion suggests miscellaneous or gastrointestinal causes. Studies of the urinary excretion of Mg after a loading test can help diagnose Mg deficiency when magnesemia is normal: the subject without deficiency excretes more than 60–70% of Mg input, whereas the subject with a deficiency excretes less than 50%.^{9,10}

Various changes in Mg can occur during the perioperative period. Plasma concentrations are decreased after abdominal^{11,12} or orthopedic surgery.¹³ After heart surgery, mean magnesemia is reduced,^{14,15} and the frequency of hypomagnesemia increased from 19.2% preoperatively to 71% immediately after surgery before dropping slightly to 65.6% 24 hr later.¹⁶ For Zuccala *et al.*, the depletion of intracellular Mg would appear to be closely correlated with reduced serum concentrations. These authors found that both concentrations decreased after orthopedic surgery.¹⁷

Cellular physiological properties of Mg

ACTION ON MEMBRANE AND MEMBRANE PUMPS

Mg intervenes in the activation of membrane Ca ATPase and Na-K ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases. Mg deficiency impairs the action of ATPase pumps and leads to a reduction of intracellular ATP as well as to increased concentrations of sodium and calcium and decreased concentrations of potassium within the cell.⁵ It would thus appear to act as a stabilizer of cell membrane and intracytoplasmic organelles.¹⁸

ACTION ON ION CHANNELS

Mg is considered to act as a regulator of different ion channels. A low intracellular Mg concentration allows potassium to leave the cell, thereby altering conduction and cellular metabolism.^{5,18} Mg also exerts its effects on calcium channels of potential-dependent L type in membrane and on those of sarcoplasmic reticulum. A competitive antagonist action is directed against calcium inflows. By inhibiting the calcium activation dependent on the sarcoplasmic channel, Mg limits the outflow of calcium from the sarcoplasmic reticulum, the main site of intracellular calcium storage.¹⁸ Thus, Mg is a calcium channel blocker and a modulator of calcium channel activity, which means that a rise in intracellular calcium occurs during hypomagnesemia.^{2,5}

ENZYMATIC ACTIVATION

Intracellular free Mg is involved in the energy reactions of phosphorylation and is necessary for the activation of hundreds of enzymatic reactions concerning ATP.¹⁸ Inorganic phosphate and ATP within the cell reduce free Mg, whereas the conversion of ATP to adenosine diphosphate (ADP) increases it.³ In fact, Mg interacts with the outer two phosphate groups of ATP to form the enzymatic substrate. Intracellular Mg deficiency is correlated with the impaired function of many enzymes utilizing high-energy phosphate bonds, as in the case of glucose metabolism.²

Clinical effects of Mg

CARDIOVASCULAR EFFECTS

The action of Mg on calcium channels and pumps actually serves as a regulator of transmembrane and intracellular flows. In addition, Mg has an indirect effect on cardiac muscle cells by inhibiting calcium uptake on the troponin C of myocytes and thereby influencing myocardial contractility. In a preparation of isolated animal heart, Mg, because of its anticalcium properties, caused a dose-dependent negative inotropic effect.¹⁹ Rasmussen *et al.* observed a moderate positive inotropic effect after infusion of Mg into healthy volunteers,²⁰ which could have been related to the vascular effect of Mg in reducing systemic arterial²⁰ and pulmonary artery pressures through a decrease of vascular resistance.¹⁸ In *in vitro* studies on isolated aorta, the absence of Mg potentiated the vasoconstrictive effect of angiotensin and acetylcholine, and hypermagnesemia induced the relaxation of smooth muscle.²¹ The role of Mg in transmembrane movements of calcium and the activation of the adenylate cyclase involved in the synthesis of cyclic adenosine monophosphate (AMP; a vasodilator) could account in part for this effect. A reduction of cyclic AMP in hypomagnesemia induced an increase of vascular tone.²² Mg deficiency may also play a role in the pathogenesis of variant angina or coronary spasm,²³ and infusion of Mg can produce coronary dilatation and suppress acetylcholine-induced coronary spasm in patients with vasospastic angina.²⁴

In anesthetized dogs, a dose-dependent decrease in heart rate and systolic and diastolic arterial pressures was observed after the infusion of Mg.²⁵ In humans, hemodynamic studies have shown a peripheral (predominantly arteriolar) vasodilator effect.^{26,27} After the rapid infusion of a dose of 3 or 4 g of sulfate (MgSO₄), a reduction of systolic arterial pressure occurred, in relation to decreased systemic vascular resistance. Positive inotropic and chronotropic effects compensated for the former by increasing the heart

index, whereas pulmonary vascular resistance remained unchanged. In the study by Vigorito *et al.*, coronary vascular resistance decreased as coronary blood flow increased.²⁶

Disturbances in cellular ionic movements induced by dysmagnesemia could affect the excitability of the heart cells of nodal tissue responsible for cardiac rhythm disorders.¹⁸ In electrocardiographic studies in anesthetized dogs, a dose-dependent lengthening of the PR and RR intervals was noted, as well as a dose-dependent increase of QRS duration, without any modification of the QTc interval. A dose-dependent lengthening of atrioventricular conduction time was also observed.²⁵

MUSCLE AND NEUROMUSCULAR TRANSMISSION

Calcium and Mg have opposite effects on muscle. Hypomagnesemia stimulates contraction, whereas hypocalcemia induces relaxation. Hypomagnesemia causes rapid, passive release of calcium by the sarcoplasmic reticulum as a result of the opening of calcium channels, whereas high concentrations of Mg block this process.²⁸ Neuromuscular transmission is altered by a preponderant presynaptic effect as well as a postsynaptic effect. Mg acts competitively in blocking the entry of calcium into presynaptic endings. Presynaptic release of acetylcholine is reduced by high Mg concentrations, thereby altering neuromuscular transmission.^{4,28} Mg decreases the effects of acetylcholine on postsynaptic muscle receptors and has been shown to increase the threshold of axonal excitation. Hypomagnesemia induces neuromuscular hyperexcitability,³ while hypermagnesemia causes neuromuscular weakness as well as a reduction or even an abolition of deep tendon reflexes. Excess serum Mg concentrations produce progressive inhibition of catecholamine release from adrenergic nerve endings, adrenal medulla and adrenergic postganglionic sympathetic fibres.^{28,29}

CENTRAL NERVOUS SYSTEM

The property of Mg as an antagonist of N-methyl-D-aspartate (NMDA) receptors is the basis for studies of its adjuvant effect in perioperative analgesia. This calcium inhibitory effect causes central arteriolar vasodilation and acts against vasospasm. The inhibition of NMDA receptors and the increased production of vasodilator prostaglandins induced by Mg could account for the anticonvulsant action of Mg.

OTHER CLINICAL EFFECTS

The postulated mechanisms for the bronchodilator effects of Mg include inhibitory action on smooth

muscle contraction, histamine release from mast cells and acetylcholine release from cholinergic nerve terminals.^{4,30} The precise mechanism of action for the tocolytic effects^{31,32} of Mg sulfate is not clearly defined, but may be related to the action of Mg as a calcium blocker in inhibiting muscle contractions.

Posology and administration of Mg

Mg can be administered orally or intravenously. Intramuscular injection is also possible but painful. Oral administration of a daily dose of more than 50 mmol can cause vomiting and diarrhea. In anesthesia and intensive care, the preferred administration route is *iv*. Two injectable forms of Mg are available, namely Mg chloride and sulfate. Ten millilitres of a 10% Mg chloride (MgCl₂) solution provide 1 g of Mg salts (= 118 mg Mg = 9 mEq = 4.5 mmol), and 10 mL of a 10% Mg sulfate (MgSO₄) solution provide 1 g of Mg salts (= 98 mg Mg = 8.12 mEq = 4.06 mmol).^{5,9}

Posology differs according to indications, and several dosage recommendations have been proposed. When Mg sulfate is used to correct a Mg deficit, the objective is to restore normal serum concentrations, in which case slow infusion of up to 10 g·day⁻¹ is appropriate. When Mg is used for its pharmacological properties, more rapid infusion is often necessary to obtain the high plasma concentrations desired. The recommended procedure is rapid infusion of 1 to 2 g of MgSO₄ *iv* over a ten-minute period followed by continuous *iv* infusion of 0.5 to 1 g·hr⁻¹ (reduced to 0.25 g·hr⁻¹ for patients with renal insufficiency). Administration is performed under continuous electrocardiographic control, and serum concentrations of Mg or ionized Mg are determined every six hours.^{5,9} If Mg is given too quickly, flushing can occur, and bradycardia, cardiac arrhythmia, or cardiac arrest have been reported.³³⁻³⁵ There is also the increased risk of the toxic effects of Mg resulting in renal impairment.³⁵

When Mg was used for tocolysis, adverse effects (flushing and headache) were more frequent with high (5 g·hr⁻¹) than with low doses (2 g·hr⁻¹), and pulmonary edema occurred in two patients in the high-dose group *vs* none in the low-dose group.³² In the MAGPIE trial, the risk of pulmonary edema was similar in the Mg and placebo groups (0.63 and 0.65%, respectively).³⁶

Dysmagnesemia

Hypomagnesemia

Hypomagnesemia, defined as a plasma concentration below 0.7 mmol·L⁻¹, is considered severe when under 0.5 mmol·L⁻¹. This condition is most often associated with a true depletion of Mg in the organism, although

a Mg deficit can exist even when magnesemia is normal. Thus, measurement of the urinary excretion of Mg and possibly a loading test can help establish the diagnosis.³⁷ As the bone and intracellular Mg reserves of the organism cannot be easily mobilized toward the extracellular sector, a negative Mg balance rapidly leads to hypomagnesemia.⁶

A deficit was found in 11, 19 and 47% of blood samples obtained from hospitalized patients with increasing Mg thresholds of < 0.6 mmol·L⁻¹, < 0.62 and < 0.74 mmol·L⁻¹ respectively.³⁸⁻⁴⁰ The incidence of deficit was much higher in patients sampled in surgical and medical intensive care units, reaching 61 and 65% for thresholds of 0.75 and 0.7 mmol·L⁻¹ respectively.^{41,42} The high rates for these patients were due to an association of several causes of hypomagnesemia. This disorder is often overlooked, although it should probably be searched for systematically because of its significance for the prognosis of patients.⁴⁰ In fact, a prospective study of patients hospitalized in wards and intensive care units (ICU) showed that the death rate was twice as high for the group with hypomagnesemia on admission as for the group without a deficit but an equivalent APACHE II score.³⁹ These data were confirmed by Chernow *et al.* in a study of postoperative ICU patients, for whom the death rate was 41% *vs* 13% for patients without hypomagnesemia.⁴¹ Other studies after heart surgery showed that patients with hypomagnesemia experienced more rhythm disorders. Time on the ventilator was longer,^{16,43} and morbidity was higher than for patients with normal magnesemia.⁴³ Another study showed that a greater than 10% reduction of serum and intracellular concentrations was associated with a higher rate of postoperative ventricular arrhythmias.¹⁷

As the regulation of Mg homeostasis is ensured by the digestive tube or the kidney, the main causes of hypomagnesemia are digestive (lack of input or absorption, or excessive elimination) or renal (increased excretion), as summarized in Table I.⁶

In human clinical conditions, it is difficult to define the symptomatology of hypomagnesemia specifically, as it is often associated with other metabolic disorders. For example, a Mg deficit was associated with a potassium deficit in 61% of patients with hypokalemia.⁴⁰ Administration of potassium alone often fails to remedy kalemia, and only simultaneous correction of Mg and potassium deficits restores normal levels. The role of Mg in transmembrane potassium transport systems accounts for this phenomenon.⁴⁴ A calcium deficit is also often associated with a severe Mg deficit.

When experimental Mg depletion is induced in human volunteers, the clinical manifestations and

metabolic abnormalities of Mg deficiency are anorexia, generalized weakness, positive Trousseau and Chvostek signs, hypokalemia and hypocalcemia.⁶ The main clinical manifestations of hypomagnesemia are summarized in Table II.

Oral administration of 5 to 15 mmol·day⁻¹ is sufficient to eliminate moderate deficits and can be increased to 15 to 28 mmol·day⁻¹ for severe deficits. The usual *iv* dose is 25 mmol administered as a continuous infusion in eight to 24 hr.⁶ In severe, but non-life-threatening hypomagnesemia, it is advisable to begin with an infusion of 1 to 2 g·hr⁻¹ of Mg sulfate for three to six hours and then decrease the rate to 0.5 to 1 g·hr⁻¹ as a maintenance infusion. In the treatment of acute life-threatening arrhythmias, it is advisable to inject 1 to 2 g (4-8 mmol) of *iv* Mg sulfate over five minutes. This

TABLE I Causes of hypomagnesemia

| | |
|---|--|
| Gastrointestinal causes | |
| <i>Decreased intake</i> | |
| | Chronic alcoholism |
| | Malnutrition |
| | Prolonged administration of magnesium-free intravenous fluids |
| <i>Decreased absorption</i> | |
| | Short bowel syndrome |
| | Small bowel bypass surgery |
| | Malabsorption |
| | Inflammatory bowel disease |
| | Primary intestinal hypomagnesemia |
| <i>Gastrointestinal losses</i> | |
| | Vomiting |
| | Prolonged nasogastric suction |
| | Acute or chronic diarrhea |
| | Biliary or intestinal fistula |
| | Acute pancreatitis |
| | Chronic laxative abuse |
| Renal causes: increased urinary excretion | |
| | <i>Chronic alcoholism</i> |
| | <i>Diuretics</i> |
| | <i>Diuretic phase of acute tubular necrosis</i> |
| | <i>Post-obstructive diuresis</i> |
| | <i>Post-renal transplantation</i> |
| | <i>Nephrotoxic drugs: aminoglycoside antibiotics, amphotericin B, cisplatin, cyclosporine, pentamidine</i> |
| | <i>Hypercalcemia</i> |
| | <i>Primary hyperparathyroidism</i> |
| | <i>Bartter's syndrome</i> |
| | <i>Gitelman's syndrome</i> |
| | <i>Primary renal magnesium wasting</i> |
| | <i>Hyperaldosteronism</i> |
| Miscellaneous | |
| | <i>Diabetes mellitus</i> |
| | <i>Insulin infusion</i> |
| | <i>Hypoparathyroidism</i> |
| | <i>Hungry bone syndrome following parathyroidectomy or thyroidectomy</i> |
| | <i>Mg-free dialysis</i> |

TABLE II Signs and symptoms of hypomagnesemia

| | |
|--------------------------|---|
| General signs: | Generalized weakness Anorexia Apathy, depression |
| Neuromuscular signs: | Chvostek's and Trousseau's signs Muscular fasciculations and cramps Tremor Tetany Generalized convulsions Respiratory muscle weakness or paralysis |
| Cardiovascular signs: | Cardiac arrhythmias: Frequently: torsades de pointes, ventricular tachycardia Supra- and ventricular arrhythmias Digitalis-associated arrhythmias Hypertension Sudden death Coronary artery vasospasm Progressive changes in the electrocardiogram: Widening of the QRS complex and peaking of the T wave Prolongation of the PR interval and flattening of the T wave |
| Metabolic abnormalities: | Hypokalemia Hypocalcemia Metabolic alkalosis |

bolus should be followed by an infusion of 1 to 2 g of Mg sulfate per hour for the next few hours and then be reduced to 0.5 to 1 g Mg sulfate per hour as a maintenance infusion. Potassium and Mg levels should be monitored during therapy. These dosages should be reduced in patients with renal insufficiency.⁹

Hypermagnesemia

Hypermagnesemia, which is less frequent than hypomagnesemia, was found in 9.3, 5.7 and 3.5% of blood samples obtained from hospitalized patients with increasing Mg thresholds of $> 0.95 \text{ mmol}\cdot\text{L}^{-1}$, > 0.99 and $> 1.07 \text{ mmol}\cdot\text{L}^{-1}$ respectively.^{38,40} In postoperative intensive care, hypermagnesemia was observed in 5.2% of patients with a threshold of $1 \text{ mmol}\cdot\text{L}^{-1}$.⁴¹ Moderate hypermagnesemia is frequent in patients with chronic renal insufficiency,² both during rhabdomyolysis (due to release of Mg from disintegrating muscle) and after excessive use of antacids or laxatives containing Mg salts.⁴⁵ Severe hypermagnesemia is most often observed during the therapeutic administration of Mg sulfate in patients with chronic renal insufficiency or during treatment of eclampsia.³⁴

Neuromuscular and cardiovascular manifestations are predominant in the clinical symptomatology of hypermagnesemia. However, clinical severity is not always correlated with the degree of hypermagnesemia.³⁴ Flushing, nausea and/or vomiting can be early signs. Central neurological signs range from somnolence to deep coma. Deep tendon reflexes may be reduced or totally lost. Breathing may be decreased or even stopped because of paralysis of the respiratory muscles. Cardiovascular abnormalities may include hypotension because of peripheral vasodilatation, conduction disorders (lengthening of the PR and/or QT intervals or the QRS complex, and atrioventricular block), bradycardia and even cardiac arrest.¹⁰

Treatment is based on stopping Mg inputs. An infusion of calcium salts, which momentarily antagonizes some Mg effects, can be initiated in emergency conditions (2.5–5 mmol in a slow *iv* infusion until disappearance of conduction disorders) when neurological and cardiovascular complications are life-threatening.^{9,10,28,29} Loop diuretics inhibit renal reabsorption of Mg and induce an increased urinary excretion of Mg, but also of calcium, which can cause hypocalcemia and thereby intensify the clinical signs of hypermagnesemia. Calcemia needs to be monitored, and some authors recommend preventive administration of calcium salts when diuretics are used. For patients with renal insufficiency, recourse to dialysis involving a Mg-poor fluid is frequent.

Therapeutic indications for Mg in anesthesiology

Anesthetic induction

The stress of intubation is associated with catecholamine release. Mg reduces this release by the adrenal medulla and adrenergic nerve endings. In a comparative study, patients received thiopental and succinylcholine with or without Mg sulfate $60 \text{ mg}\cdot\text{kg}^{-1}$ at anesthesia induction. Patients treated with Mg showed a lower increase of heart rate and systolic blood pressure after intubation. Plasma concentrations of epinephrine and norepinephrine were markedly lower after intubation in the Mg-treated group.⁴⁶

In a prospective study concerning coronary patients, Puri *et al.* compared hemodynamic changes during anesthesia induction and intubation after infusion of Mg or lidocaine. The group treated with Mg showed a slight increase in mean arterial pressure (MAP) and systemic vascular resistance and no decrease in cardiac output, as compared to the lidocaine group, with equally good control of increased heart rate.⁴⁷ In another study, the group treated with Mg showed a lesser hypertensive response during induction compared to placebo, whereas early reflex

tachycardia was not controlled by Mg.⁴⁸ Ashton *et al.* found no increase in arterial pressure or heart rate and a moderate decrease of plasma catecholamine concentrations after intubation in a group treated with Mg alone before intubation.⁴⁹ In all these studies, Mg administration before anesthesia induction was associated with a good control of the adrenergic response during intubation.

Surgery for pheochromocytoma

The use of Mg in pheochromocytoma surgery is based on the inhibitory action of catecholamine reuptake by the adrenal medulla, which reduces the sensitivity of adrenergic receptors in the context of peripheral vasodilatation and decreases antiarrhythmic effects.^{50,51}

Several clinical cases have demonstrated the advantage of supplementing conventional treatment with Mg sulfate to improve control of arterial pressure and heart rate. Hemodynamic balance was achieved during anesthesia induction and intubation, but frequently remained unstable during tumour resection.⁵¹⁻⁵³ In a study of 17 cases, James clearly showed that catecholamine concentrations were reduced after Mg infusion and, especially, that they did not increase after intubation. However, Mg did not prevent a considerable rise in catecholamine levels at the time of tumour resection. Before tumour removal, control of arterial pressure and heart rate was obtained in 12 cases after the infusion of Mg alone. For four of the other five patients, sodium nitroprusside was required to control arterial pressure at the time of tumour handling, including one case in which phentolamine was added. The patient for whom hemodynamic control could not be obtained had a serum Mg concentration (1.3 mmol·L⁻¹) below desired values, which may have been responsible for clinical failure. Serum Mg concentrations were high in the other patients (2-4 mmol·L⁻¹), corresponding to inputs of 8 to 18 g of Mg in a period of 60 to 150 min.^{50,54}

With such high doses and serum concentrations of Mg, the effects of curares were increased and it was necessary to counteract these at the end of the operation, before extubation.^{50,51} After tumour resection, vascular filling generally allowed correction of low arterial pressure,⁵¹ so that recourse to vasopressors was only necessary in one of the 17 cases studied by James.⁵⁰ As this type of surgery is infrequent, no controlled prospective study has evaluated the role of Mg during surgery for pheochromocytoma.

Cardiac surgery

The high rate of hypomagnesemia after cardiac surgery is well established.^{14-16,43} Lower serum Mg levels have been found to be associated with an increased incidence

of atrial fibrillation,^{43,55,56} which was decreased in several studies by the prophylactic administration of Mg after coronary artery bypass grafting.^{14,15,56,57} In a group treated with Mg postoperatively, England *et al.* found a non-significant reduction of supraventricular dysrhythmias, a significant decrease of ventricular dysrhythmias and a significant increase of postoperative cardiac indices.⁴³ There were no differences between groups for the various forms of ventricular arrhythmia.¹⁴ Two other studies including only small numbers of patients found a non-significant reduction of postoperative atrial fibrillation²⁷ or rhythm disorders.⁵⁸ One study reported no decrease of postoperative atrial tachyarrhythmias, although Mg was only initiated postoperatively.⁵⁹ Among the four studies with positive results, Mg was initiated postoperatively in one,¹⁴ and intraoperatively in the other three.^{15,56,57}

A high rate of postoperative hypomagnesemia has also been observed in pediatric heart surgery. Junctional ectopic tachycardia occurred in 27% of children who were not given Mg postoperatively, whereas those who received Mg had no rhythm disorders.⁶⁰

With respect to its vascular properties, the role of Mg has been studied in the context of controlling intraoperative hypertension. In a population of hypertensive patients who underwent cataract surgery under local anesthesia, a comparative study showed that preoperative administration of Mg (*vs* placebo) allowed stabilization of intraoperative variations in systolic and diastolic pressures.⁵⁸ In cardiac surgery, Mg has proved to be as efficient as nifedipine in controlling arterial pressure during cardiopulmonary bypass procedures. As cardiopulmonary bypass output was constant, the reduction of MAP observed was attributed to decreased systemic arterial resistance.²⁷

As Mg has a stabilizing effect on membranes, it can be used in the treatment of cardiac rhythm disorders. The best indication is for the treatment of torsades de pointes,⁶¹ but Mg is also indicated for ventricular arrhythmias related to digitalis toxicity.⁴ In critically ill patients, Mg proved more effective than amiodarone for the conversion of acute atrial tachyarrhythmias.⁶²

Obstetric anesthesia

High Mg doses produce a tocolytic and hypotensive effect in preeclampsia.^{32,63,64} In an animal model, Mg lowered maternal arterial pressure, while maintaining uterine arterial flow and fetal oxygenation.⁶⁵ Mg has an inhibitory effect on NMDA receptors and increases the production of vasodilator prostaglandins, thereby affecting cerebral vasodilatation.^{66,67} Mg causes vasodilatation of smaller-diameter intracranial vessels in patients with preeclampsia,⁶⁸ which could account

for its anticonvulsant action.^{66,67}

The risk of onset of eclampsia in women with severe preeclampsia is about 1 to 3%.⁶⁹ Compared to placebo, administration of Mg was found to reduce the incidence of convulsions in this population.⁶⁹ An earlier work had reported no difference, but the number of patients in the two groups was low.⁷⁰ Mg was more efficient than phenytoin in preventing the onset of convulsive seizures.⁷¹ However, no difference was observed between Mg and phenytoin groups in two other studies with low numbers of subjects.^{72,73} The meta-analysis of Chien *et al.* found that Mg was superior to phenytoin in this population.⁷⁴ These data have been confirmed by the recent results of the Magpie Trial, which found a 58% reduction of the risk of eclampsia for Mg *vs* placebo.³⁶ The recommended doses are 4 g of Mg sulfate infused in 20 min, followed by a continuous infusion at a rate of 1 to 2 g·hr⁻¹.^{66,69}

In a multicentre prospective study including nearly 1,700 women with eclampsia, Mg, as compared to diazepam and phenytoin, did not reduce maternal death but decreased the recurrence of convulsions and of neonatal morbidity. Labour lasting more than eight hours was slightly more frequent in the group treated with Mg, but Mg had no incidence on the rate of Cesarean delivery, blood loss and transfusion.⁶⁷ Two studies found a decrease in recurrent convulsions in the group treated with Mg as compared to those treated with diazepam and phenytoin, but the difference was not significant because of the low number of patients involved.^{33,75} The meta-analysis by Chien *et al.* found a significant reduction of recurrent convulsions in patients treated with Mg as compared to diazepam and phenytoin.⁷⁴

Mg administered to the mother may have a neuroprotective effect for the newborn. Neonatal morbidity was lower and an Apgar score below 7 at one minute was significantly less frequent in infants of mothers treated by Mg as compared to diazepam.³³ The multicentre study referred to above found a decrease in neonatal morbidity when Mg was used at the doses administered for eclampsia (loading dose of 4 g *iv* followed by an infusion of 1 g·hr⁻¹ or *im* administration of 5 g every four hours).⁶⁷ In a population of low birth weight infants, maternal treatment with Mg before delivery was associated with a reduced risk of cerebral palsy⁷⁶ and a decrease of ultrasonographically detected lesions of cystic periventricular leukomalacia.⁷⁷ This neuroprotective effect of Mg in premature infants was not found in other studies.⁷⁷⁻⁸⁰ The discrepancies in the results of these retrospective studies led several researchers to undertake prospective studies. One of these investigations was discontinued early because of

a significant increase in the deaths of newborns whose mothers had been given Mg at tocolytic doses (loading dose of 4 g followed by infusion of 2-3 g·hr⁻¹).⁸¹ A correlation seemed likely between high ionized Mg concentrations in cord blood and death.⁸² However, an abnormally low death rate was noted in the control group, and the deaths occurring in the Mg group were often attributable to marked prematurity.⁸¹

Mg can be recommended for anticonvulsant treatment,³⁵ and the studies cited above confirm its efficacy in preeclampsia and eclampsia. However, data to date seem inadequate to determine its usefulness and safety at higher (tocolytic) doses.³²

Interaction of Mg with drugs used in anesthesia and intensive care

A lengthening of neuromuscular blockade has been reported in patients treated by Mg and confirmed experimentally.⁸³ In two prospective studies, a lower use of curare during surgery was observed in the group treated with Mg.^{12,84} Mg blockade at the neuromuscular junction is the result of (i) a reduction of the amount of acetylcholine released from motor nerve terminals; (ii) a decrease in the depolarizing action of acetylcholine at the endplate; or (iii) depression of muscle fibre membrane excitability.⁸³ In a rat phrenic nerve-diaphragm preparation, Mg potentiated neuromuscular blockade produced by d-tubocurarine, decamethonium and succinylcholine.⁸³ Prolonged curarization may require more frequent recourse to anticholinesterases to counteract neuromuscular blockade.^{11,83}

In a halothane anesthetized rat model, continuous infusion of Mg led to a reduction of halothane minimum alveolar concentration, which was nonlinearly dependent on plasma Mg level.⁸⁵ Volatile anesthetic effects on NMDA receptors can be potentiated significantly by Mg, ketamine, or most profoundly by both. The analgesic effects of ketamine and Mg are likely to be enhanced in the presence of volatile anesthetics.⁸⁶

Hypomagnesemia increased ketamine sensitivity in a rat Mg deficiency model.⁸⁷ NMDA receptors are important components of pain processing, and their response can be inhibited by ketamine and Mg, which have a super-additive effect in combination. This may explain in part why analgesia is more effective for the combination than for either compound alone.⁸⁸

The vasodilator properties of Mg theoretically increase the risk of hypotension and this risk could be augmented by the vasoplegic effects of anesthetic drugs or during epidural anesthesia.^{66,85} In epidural anesthesia of gravid ewes, an initial high dose of Mg sulfate decreased maternal MAP, but increased uterine artery blood flow and fetal PaO₂.⁶⁵ In large studies in

humans, the risk of hypotension was moderately increased compared to placebo (0.75 vs 0.4%) when half of the patients in each group had received concomitantly antihypertensive drugs.³⁶ The clinical manifestations of hypermagnesemia included hypotension.^{10,28}

Clinical situations in which glycemia remains elevated despite increased insulin doses are frequent in intensive care. In fact, insulin resistance increases as the serum Mg concentration decreases, with Mg acting as a second messenger for insulin.² Diuretics increase renal excretion of Mg and can cause hypomagnesemia.² Gentamicin treatment can also induce hypomagnesemia through renal loss of Mg, which ceases once treatment is stopped.²

Perioperative analgesia

The use of Mg as an adjuvant in the context of perioperative analgesia is novel. This application is based on the antagonist properties of Mg for the NMDA receptor and its inhibitory properties for calcium channels. Calcium channel blockers have shown antinociceptive effects in animals and morphine potentiation in patients with chronic pain. NMDA receptor antagonists can prevent the induction of central sensitization due to peripheral nociceptive stimulation and abolish hypersensitivity.¹¹

The double-blind prospective study of Tramèr *et al.* clearly shows the value of Mg as an adjuvant in postoperative analgesia. Patients receiving Mg required less morphine, had less discomfort and slept better during the first 48 hr than those receiving morphine alone. The quality of postoperative analgesia was, of course, equivalent. Three respiratory depressions occurred in the patient-controlled analgesia group receiving morphine only vs none in the group treated by morphine and Mg.¹¹ Koinig *et al.* reported similar results, with a reduction of analgesic use both intra- and postoperatively in the group receiving Mg pre- and intraoperatively.¹³ In both studies, plasma Mg concentration was markedly reduced postoperatively in the control group (values close to hypomagnesemia), but was significantly increased in the treatment group.^{11,13}

Wilder-Smith *et al.* conducted a comparative study of pain intensity and postoperative use of morphine in three groups. In each group, patients received ketamine, Mg or fentanyl pre- and intraoperatively. No differences were found between groups for the effects of these products.⁸⁹

In another report, Mg infusion after anesthesia induction reduced intraoperative use of remifentanyl.⁸⁴ In two other studies, the trend toward reduced use of fentanyl intraoperatively⁹⁰ and morphine postoperatively^{90,91} was confirmed, but not sta-

tistically significant. In the study of Wilder-Smith *et al.*, lack of significance was probably due to the low numbers of patients in the groups.⁹¹

Ko *et al.* found no reduction of analgesic use during the postoperative period. However, Mg was the only analgesic used intraoperatively in their treatment group and only initiated after anesthesia induction.¹²

It seems clear that Mg reduces the use of classic morphine-based drugs, as well as their side effects, when administered pre- and intraoperatively and associated with these drugs during the operation. Future studies will undoubtedly define the precise role of Mg as adjuvant in perioperative analgesia.

A recent study suggested that the intrathecal administration of Mg sulfate might be a useful adjunct to spinal morphine analgesia in a rat model.⁹² These findings could lead to studies defining the benefit of adjuvant Mg in obstetrical or postoperative analgesia.

Myocardial infarction

Two meta-analyses studied the impact of Mg treatment on reduction of the death rate and rhythm disorders in the acute phase of myocardial infarction before initiation of reperfusion treatments. Both reports found a 54% reduction of the death rate,^{93,94} and one noted a decreased incidence (49% less) of ventricular fibrillation or tachycardia in the population treated by Mg.⁹³ Several mechanisms of Mg action were proposed, as the death rate observed corresponded to the expected rate: coronary and systemic vasodilatation, prevention of rhythm disorders, reduction of platelet aggregation, and improvement of myocardial metabolism.⁹³ A recent study not involving reperfusion therapy confirmed these data, showing a reduction of rhythm disorders and the death rate. These authors found that serum Mg levels of patients with acute myocardial infarction were lower than those of controls.⁹⁵

Since the appearance of reperfusion techniques, the results of studies have been divergent. The LIMIT-2 trial found a reduction of the death rate and left-ventricular failure at 28 days and a lower death rate at four years for patients treated early with Mg.^{96,97} Subsequently, the ISIS-4 trial, including more than 58,000 patients, found a non-significant increase of the death rate at five weeks and one year in the group treated with Mg. Ventricular fibrillation was reduced in the treatment group, whereas other forms of cardiac arrest (heart failure and cardiogenic shock) were increased.⁹⁸ Methodological differences may account for these conflicting results. In the ISIS-4 trial, the death rate in the control group was low, and Mg was administered later (after reperfusion). Therefore, a

study has recently been initiated to include 10,400 high-risk patients for whom Mg treatment will be started early.⁹⁹ The recently published results of this study confirm the ISIS-4 data. In a population of high-risk patients with acute myocardial infarction, early Mg treatment was neither beneficial nor harmful and failed to decrease the 30-day mortality and the need for treatment of heart failure or dysrhythmias.¹⁰⁰ The usefulness of Mg treatment in acute myocardial infarction appears to be controversial.

Cardiac arrest

Retrospective reports have described successful resuscitation after Mg administration in refractory cases. In a randomized trial, a 5-g Mg sulfate bolus *vs* placebo failed to improve the return of spontaneous circulation, survival after emergency department management and survival to hospital discharge. The main limitation of this study was the small size of the groups.¹⁰¹ A second study comparing a 2-g bolus followed by 24 hr infusion (8 g) to placebo failed to improve the same endpoints. However, the median Karnofsky index was higher in patients who had received Mg and survived to hospital discharge. More of these patients were capable of independent living after discharge, which suggests that Mg may have a cerebral protective effect.¹⁰²

Asthma

Mg has bronchodilator effects apparently related to its calcium antagonist properties that inhibit the contraction of smooth muscle fibres.¹⁰³

Three meta-analyses have recently been published on this subject.¹⁰³⁻¹⁰⁵ That of Alter *et al.* (based on nine studies) determined that addition of Mg sulfate *vs* placebo to conventional asthma treatment led to a 16% improvement of peak flow.¹⁰⁴ The meta-analysis of Rowe *et al.* (based on seven studies) found that *iv* administration of Mg significantly reduced the length of hospital stays and improved the peak expiratory flow (PEF) rate, as compared to placebo, in the subgroup of patients with severe asthma treated in the emergency department.¹⁰³ In the different studies, Mg was administered as a loading dose by infusion of 1.2 or 2 g in 20 min, after initiation of treatment with oxygen, β -agonists, anticholinergic agents and corticosteroids.¹⁰³ The third meta-analysis (based on five studies) found that the very slight improvement of pulmonary function after Mg infusion and the decrease of the hospitalization rate were not significant compared to results for placebo groups.¹⁰⁵

Several observations can be made about these meta-analyses and the studies concerned. That of Rodrigo *et al.*¹⁰⁵ included only five studies, two of

which gave negative results, whereas two pediatric studies with positive results were excluded.^{106,107} Moreover, the patient populations were not homogeneous. Two of the studies concerned pediatric asthmatic populations^{106,107} and another a population with exacerbation of chronic obstructive pulmonary disease. All of the studies except one¹⁰⁸ used Mg sulfate as second-line therapy in patients who had usually not responded to conventional treatment. It is noteworthy that in the only study comparing Mg inhalation with salbutamol inhalation an equivalent bronchodilator effect was observed for both treatments, with an improvement in PEF of 35 and 42% respectively.¹⁰⁸

The role of Mg in the treatment of bronchospasm is controversial, but there appears to be a bronchodilator effect that improves PEF and reduces the hospitalization rate for asthmatic patients seen in emergency departments. These effects appeared to be more marked in a subpopulation with severe asthma that failed to respond to conventional therapy.^{106,107,109-111} A prospective study including a large number of patients in this subpopulation would be useful to confirm the role of Mg as a bronchodilator as second-line therapy and in association with conventional treatment.

Mg should not be used routinely in the treatment of moderate asthma, but *iv* Mg sulfate may be useful in addition to the usual therapy for refractory asthma.^{5,30,112}

Prospects

Recent studies could lead to the establishment of new indications for Mg. In patients with tetanus, Mg infused at doses providing serum concentrations of 2 to 4 mmol·L⁻¹ allowed good control of spasms and muscle rigidity. Intubation and ventilation were only required for 43% of patients, and the overall death rate was 12%.¹¹³

Fluoroquinolones, which are toxic for tendons and cartilage, are Mg ion chelators largely involved in cartilage biochemistry. A recent animal study found that fluoroquinolones induced a high rate of cartilaginous lesions in immature rats with Mg deficiency, whereas rats without deficiency had no lesions.¹¹⁴ A correction of hypomagnesemia might be necessary in this context.

Mg or calcium deficiency seems likely in those patients treated by oxaliplatin who show neurotoxic clinical side effects characteristic of tetany or myotonia. The toxicity of oxaliplatin for the neuron is related to a decrease in the inward sodium current amplitude resulting in a reduction of the action potential amplitude, e.g., in the case of calcium chelating substances. The role of Mg or calcium in preventing oxaliplatin neurotoxicity has been suggested,¹¹⁵ and a

prospective study has been initiated to confirm the neuroprotective effects of calcium and Mg.

Conclusion

Hypomagnesemia is frequent postoperatively and in the intensive care unit. As hypomagnesemia is responsible for increased morbidity and mortality, it should be detected and corrected systematically. Hypermagnesemia is relatively infrequent and often iatrogenic, particularly in the case of patients with renal insufficiency, for whom Mg should be prescribed with care.

Mg can be used in anesthesia during induction or pheochromocytoma surgery in order to control adrenergic response. It can reduce the incidence of postoperative rhythm disorders in cardiac surgery and prevent the onset or recurrence of convulsive seizures in preeclampsia and eclampsia. It could also be used more extensively as an adjuvant in perioperative analgesia. It is of particular importance to understand how Mg interacts with the therapeutic drugs used in anesthesia and intensive care.

Mg is used for its antiarrhythmic properties in treating torsades de pointes and arrhythmias induced by digitalis. Its role in the treatment of asthmatic attacks and myocardial infarction needs to be defined more precisely.

Mg can be used as second-line therapy in various clinical situations, particularly in hypertensive attacks for its vasodilator properties, in the correction of hypokalemia, and in situations involving insulin resistance.

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