

Magnesium—Essentials for Anesthesiologists

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ABSTRACT

Magnesium plays a fundamental role in many cellular functions, and thus there is increasing interest in its role in clinical medicine. Although numerous experimental studies indicate positive effects of magnesium in a variety of disease states, large clinical trials often give conflicting results. However, there is clear evidence for magnesium to benefit patients with eclampsia or torsades de pointes arrhythmias. In addition, magnesium seems to have antinociceptive and anesthetic as well as neuroprotective effects, yet well-designed large clinical trials are required to determine its actual efficacy in pain

management or in the state of stroke or subarachnoid hemorrhage. The current review aims to provide an overview of current knowledge and available evidence with respect to physiologic aspects of magnesium and proposed indications and recommendations for its use in the clinical setting.

MAGNESIUM has a key role in numerous physiologic processes. Although experimental studies have demonstrated beneficial effects of magnesium administration in a variety of disease states, the results of clinical studies frequently are a matter of controversy. The current review aims to summarize the current knowledge on the physiology and pathophysiology of magnesium and on the proposed indications and recommendations for its use in different clinical settings.

Using MEDLINE, the Cochrane Library, and ClinicalTrials.gov, a search was performed for studies addressing experimental and clinical effects of magnesium. Key words entered were: magnesium, physiology, toxicity, anesthesia, analgesia, pheochromocytoma, preeclampsia and eclampsia, asthma, myocardial infarction, cardiac arrhythmias, stroke, and neuroprotection. The search was limited to articles in the English and German language published within the time frame of the last 30 yr. Electronic searches were updated until September 2010 and were complemented by screening bibliographies of retrieved articles and reviews.

Physiologic Properties and Homeostasis of Magnesium

Magnesium is the fourth most abundant essential ion in the human body and plays a fundamental role in many cellular functions, such as storage, metabolism, and energy utilization.¹ It serves as a cofactor for various biologic processes, including protein synthesis, neuromuscular function, and nucleic acid stability.² Magnesium is an intrinsic component of many adenosine 5'-triphosphatases and an endogenous regulator of several electrolytes.³ Being a noncompetitive inhib-

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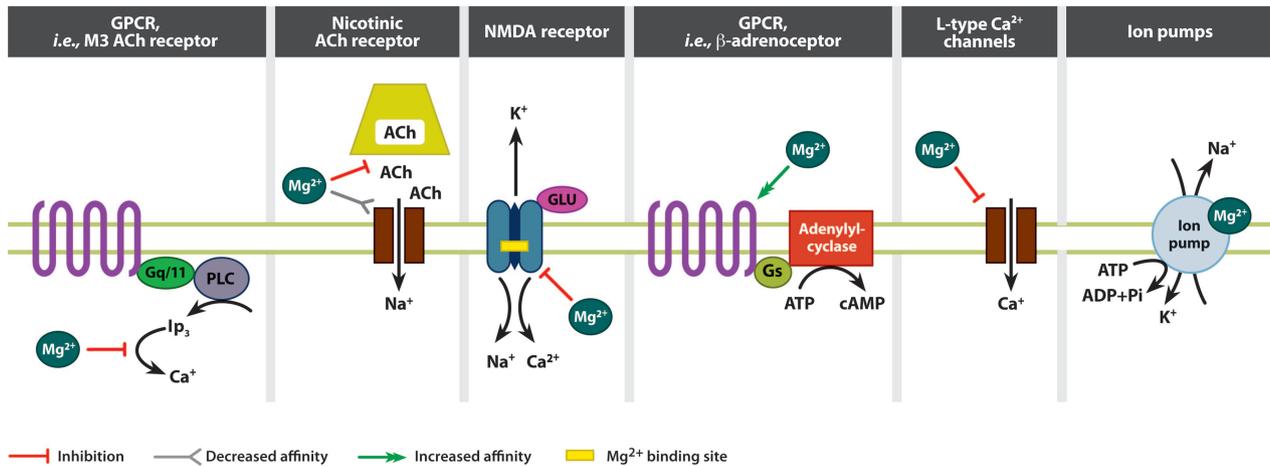


Fig. 1. Sites and mechanisms of action for magnesium. By modulating not only ion channels and ion pumps but also receptor signaling, magnesium affects numerous cellular processes. Ach = acetylcholine; ADP = adenosine diphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; Glu = glutamate; GPCR = G-protein-coupled receptor; IP₃ = inositol triphosphate; NMDA = *N*-methyl-D-aspartate; Pi = inorganic phosphate; PLC = phospholipase C.

itor of inositol triphosphate-gated calcium channels, magnesium functions as an endogenous calcium antagonist by affecting its uptake and distribution.^{1,4} Magnesium also shows modulatory effects on sodium and potassium currents, thus influencing membrane potential.^{5,6} In the central nervous system, magnesium exerts depressant effects, acting as an antagonist at the *N*-methyl-D-aspartate (NMDA) glutamate receptor and an inhibitor of catecholamine release (fig. 1).^{7,8}

A human adult body contains an average of 24 g (1 mol) magnesium, stored mainly in bone (60%) and the intracellular compartments of muscle (20%) and soft tissues (20%), primarily bound to chelators, such as adenosine 5'-triphosphate and DNA.² Two to three percent of intracellular magnesium is ionized and regulates intracellular magnesium homeostasis.² The extracellular space comprises only 1% of total body magnesium, including 0.3% found in plasma. Plasma magnesium is ionized (60%), complexed to anions (7%), or protein-bound (33%), with normal concentrations of total plasma magnesium ranging from 0.7 to 1.0 mM (1.7–2.4 mg/dl).

Maintenance of magnesium homeostasis is largely regulated by intestinal absorption and renal excretion. Magne-

sium is mainly absorbed in the small intestine *via* two different pathways depending on dose and formula of dietary intake: at low intraluminal concentrations predominantly by a saturable active transcellular transport and with rising concentrations through nonsaturable passive diffusion (table 1).⁹ The bioavailability of organic compounds, such as magnesium aspartate or magnesium citrate, is suggested to be considerably better than that of inorganic mixtures. When magnesium content is normal, approximately 40–50% is absorbed. Underlying mechanisms of altered fractional magnesium absorption in the state of hypo- or (less commonly) hypermagnesemia remain to be identified.

In the kidneys, approximately 80% of plasma magnesium is ultrafiltered through the glomerulus, with more than 95% being reabsorbed by the consecutive segments of the nephron (fig. 2). The predominant site is the cortical thick ascending limb of the loop of Henle (70%), with the proximal and distal convoluted tubule accounting for only 15–25% and 5–10% of reabsorption, respectively.¹⁰ In the loop of Henle, magnesium is passively reabsorbed *via* paracellular diffusion, driven by an electrochemical gradient, resulting from reabsorption of sodium chloride. The tight junction protein claudin 16 is believed to facilitate paracellular magnesium reabsorption because mutations in its encoding gene paracellin-1 cause a human hereditary magnesium-wasting syndrome.^{11,12}

Little is known about the mechanisms underlying magnesium reabsorption in the distal convoluted tubule. As demonstrated for the small intestine, an active transcellular transport involving TRPM6, a member of the transient receptor potential family of cation channels, localized along apical distal convoluted tubule membranes and at brush-border membranes of the duodenum, seems to play a role.¹³ Patients with mutation in the TRPM6 gene experience severe hypomagnesemia and secondary hypocalcemia.¹⁴ Regulation of magnesium transport lacks a specific endocrine control, although several hormones have been suggested to alter mag-

Table 1. Gastrointestinal Absorption of Magnesium

Anatomical Site	Magnesium Absorption (mg/day)	% Absorption of Intake
Stomach	0	0
Duodenum	15	5
Jejunum	30	10
Proximal ileum	45	15
Distal ileum	30	10
Colon	15	5
Total	135	45

The data represented refer to a normal dietary intake of 300 mg/day. Approximately 40–50% of the dietary magnesium is absorbed.

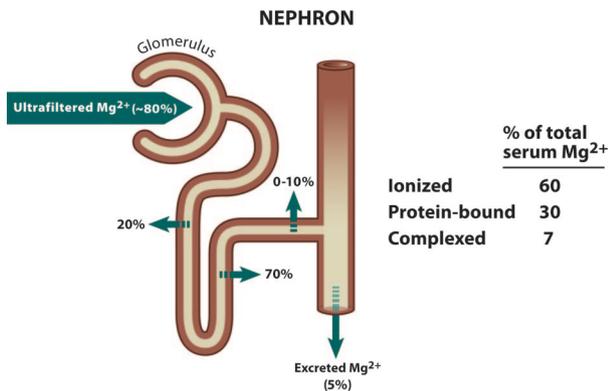


Fig. 2. Schematic representation of the renal handling of magnesium. Normally 95% of the filtered magnesium is reabsorbed by the nephron.

nesium homeostasis. Parathormone and vitamin D stimulate magnesium renal and intestinal reabsorption, respectively, whereas insulin may decrease renal excretion of magnesium and enhance its cellular uptake.¹⁵ The human body is not able to rapidly mobilize magnesium stores and exchange them with circulating magnesium to keep plasma concentrations within normal limits. Urinary excretion of magnesium is normally 5 mmol/day if renal function is adequate but can be decreased to less than 0.5% (~ 0.03 mmol/day) in the event of magnesium deprivation caused by extrarenal losses. However, individuals are highly vulnerable to hypermagnesemia with loss of renal function.

Clinical Relevance of Magnesium Disturbances

Hypomagnesemia is defined as a plasma magnesium concentration of less than 0.7 mM and results mainly from inadequate dietary intake and/or gastrointestinal and renal losses. Clinically significant magnesium deficiency (symptoms usually occur at plasma concentrations less than 0.5 mM) is commonly associated with diarrhea, vomiting, and laxative abuse; the use of loop and thiazide diuretics, angiotensin-converting enzyme inhibitors, cisplatin, aminoglycosides, or other nephrotoxic drugs; and several endocrine disorders, such as parathyroid disease, hyperaldosteronism, and chronic alcoholism.^{16,17} Diabetes mellitus is strongly associated with hypomagnesemia, possibly because of increased urinary losses. Low magnesium may aggravate insulin resistance and predispose diabetic patients to cardiovascular disease.¹⁵ Hypomagnesemia also occurs perioperatively and is commonly found in patients undergoing cardiothoracic or major abdominal surgery or thyroidectomies.^{18–21} During abdominal cancer surgery, serum magnesium concentrations have been shown to correlate with the extent of resection, but underlying mechanisms also may be factors.²⁰ Preoperative bowel preparation, intraoperative serum loss, and chelation of magnesium by transfusion of citrate-rich blood products as reported for liver transplantation have been proposed as contributing.²² However, perioperative volume expansion of the extravascular fluid may decrease pas-

sive magnesium transport, thereby decreasing plasma magnesium concentrations.

Magnesium depletion has been demonstrated in 7–11% of hospitalized patients. The incidence increases to as high as 65% for patients in an intensive care unit (ICU), where hypalbuminemia, total parenteral nutrition, and the use of magnesium-wasting medications are commonly present.^{23,24} Surgical ICU patients with severe head injury also seem to be at high risk for hypomagnesemia, potentially because of polyuria induced by cerebral injury.²⁵ Initial low serum magnesium concentrations were suggested to correlate with poor outcome after traumatic brain injury.²⁶ Cerebrospinal fluid magnesium appears to be increased in these patients, yet this increase does not necessarily correlate with low serum magnesium.^{26,27} Mechanisms underlying the increased cerebrospinal fluid magnesium remain unclear but may include the penetration of serum magnesium into the cerebrospinal fluid because of blood–brain barrier disruption or magnesium release from damaged brain cells secondary to hypoxia.²⁶ In a prospective observational study, Rubeiz *et al.* reported a significantly higher in-hospital mortality in hypomagnesemic (serum magnesium [Mg] ≤1.5 mg/dl) patients on a general ward and a medical ICU than in their normomagnesemic counterparts, despite similar Acute Physiology and Chronic Health Evaluation II scores.²³ Similar results, at least for severe hypomagnesemia (serum Mg ≤1.0 mEq/l), were demonstrated for surgical ICU patients and for hypomagnesemic (serum Mg, less than 1.4 mEq/l) children in a pediatric ICU.^{24,28} However, studying the role of extracellular and intracellular magnesium in outcome prediction of critically ill patients, Huijgen *et al.* could show no association of low extra- and intracellular values with increased mortality and thus suggested that hypomagnesemia is merely an epiphenomenon.²⁹

Considering its physiologic properties, deficiency of magnesium typically manifests as cardiac and/or neuromuscular disorders. Clinical symptoms include nausea and vomiting, weakness, convulsions, tetany, muscle fasciculations, and changes in the electrocardiogram, for example prolonged PR and/or QT interval, diminution of the T wave, or certain arrhythmias, such as torsades de pointes and others.³⁰ Electrolyte abnormalities, such as hypokalemia and hypocalcemia, also are frequently associated with hypomagnesemia.

In contrast, hypermagnesemia (plasma concentrations more than 1.6 mM) is rather uncommon and occurs mainly in patients with renal failure during therapeutic administration of magnesium-containing drugs or other treatment-related causes, for example in patients treated for eclampsia.³¹ However, magnesium is relatively safe to apply because toxicity may not occur before oral intake of 30 g magnesium sulfate (MgSO₄). At that moment, cardiac and neuromuscular changes may be observed clinically, starting with electrocardiogram changes, such as widened QRS complexes. Further increasing magnesium plasma concentrations may result in hypotension, respiratory depression, and narcosis. Cardiac

arrest occurs at blood concentrations greater than 6.0–7.5 mM.^{32,33} Treatment of severe magnesium toxicity consists of intravenous administration of calcium gluconate and, if required, ventilatory and/or circulatory support. Renal excretion of magnesium might be increased by application of loop diuretics when renal function is adequate. For patients with hypermagnesemia and renal insufficiency, hemodialysis remains a valuable tool.

Magnesium Dosing and Formulation

Magnesium supplements are available in a variety of oral and parenteral formulations. When using magnesium, the following aspects should be considered: dosing, as suggested in the literature, varies in response to the magnesium formulation used. A 10-ml vial of a 10% MgSO₄ solution contains 1g MgSO₄·7H₂O and thus an available magnesium fraction of 0.4 mM or, according to its molecular weight, 9.72 mg/ml. The dosing recommended for magnesium chloride or magnesium aspartate may vary because of differences in complex size, but if osmolarity is the same, the free magnesium fraction delivered will be the same. Data regarding pharmacokinetics of various magnesium salts are limited, making it difficult to recommend one preparation more than another. However, small studies suggest bioavailability of organic compounds, such as magnesium aspartate or magnesium citrate, to be considerably better than that of inorganic mixtures (except magnesium chloride), potentially because of greater water solubility. Recommended treatment regimens for different clinical settings are given in table 2. Magnesium should be applied orally whenever possible; however, in emergency situations, the intravenous route should be used. Renal function should be assessed before magnesium is administered. Contraindications are known allergies to the compound, atrioventricular block, and neuromuscular disease, such as myasthenia gravis.

Table 2. Dosing Magnesium Sulfate, Adults

Preeclampsia or eclampsia	4–6 g IV loading dose over 15–20 min (5 min in severe cases), followed by 1–2 g IV continuous infusion or 4–5 g IM in each buttock every 4 h
Torsades de pointes arrhythmia	Pulseless: 1–2 g IV over 5–20 min With pulse: 1–2 g IV over 5–60 min
Asthma	Life-threatening or severe exacerbation (unlabeled use): 2 g IV over 30–60 min
Severe deficiency	1–2 g/h IV for 3–6 h, followed by 0.5–1 g/h IV as needed

Slow administration of IV magnesium sulfate is preferable in stable patients. Renal impairment requires close monitoring for signs of hypermagnesemia.

IM = intramuscular; IV = intravenous.

Magnesium and Anesthesia

At the beginning of last century, magnesium was proposed to induce anesthesia effectively.³⁴ Although later studies could not support this hypothesis and seriously questioned sufficient blood–brain barrier penetration of intravenous magnesium (and thus a true central nervous system effect of the drug itself), magnesium has been suggested for reducing anesthetic requirements, attenuating cardiovascular effects from laryngoscopy and intubation, and exerting muscle-relaxing effects.^{35–37}

Mechanisms of Action

Details of the mechanisms underlying the anesthesia-enhancing effects of magnesium remain unknown. A competitive antagonism on hippocampal presynaptic calcium channels that regulate neurotransmitter release in the central nervous system has been suggested.³⁸ Volatile anesthetics, such as isoflurane, are thought to partially induce anesthesia by inhibition of these channels.³⁸ Attenuation of catecholamine release from the adrenal medulla and calcium antagonistic effects on vascular smooth muscle cells also may contribute to the anesthetic effects of magnesium.³⁹ In terms of neuromuscular blockade, the inhibition of calcium-mediated release of acetylcholine from the presynaptic nerve terminal at the neuromuscular junction plays an important role. A decrease of postsynaptic sensitivity to acetylcholine and direct effects on the membrane potential of myocytes also may contribute.^{40,41}

Experimental Data

Magnesium significantly potentiated the inhibitory effects of volatile anesthetics on NMDA receptor functioning, recombinantly expressed in *Xenopus* oocytes.⁴² Increasing magnesium concentrations were associated with nonlinear reductions in halothane minimal alveolar anesthetic concentration in rats.⁴³ In a study on the effects of MgSO₄-induced neuromuscular blockade in pigs, Lee *et al.* reported that the mechanomyogram response was more depressed than that of the electromyogram at 0.1 hertz.⁴⁴ In addition, the presence of a nonfading train-of-four response at 2 Hz, as well as a tetanic ascent instead of a descent, further supported the idea of prejunctional attenuated transmitter release by magnesium.⁴⁴

Clinical Data

There are greater differences in the results of clinical trials on anesthetic actions of magnesium. Two double-blind, randomized, and controlled trials demonstrated a reduction of propofol requirements guided by Bispectral Index monitoring after administration of intravenous MgSO₄ (bolus of 30 mg/kg, followed by continuous infusion of 10 mg · kg⁻¹ · h⁻¹ until end of surgery) in patients undergoing spinal surgery.⁴⁵ However, in one study magnesium also significantly delayed postoperative recovery (Bispectral Index more than 80; mean ± SD, 9.84 (1.14) *vs.* 7.52 (1.16) min for patients

receiving magnesium and control patients, respectively).⁴⁶ Pretreatment with 2.48 mmol intravenous MgSO₄ was found to reduce the incidence and intensity of etomidate-induced myoclonic movements during induction of anesthesia.⁴⁷ Moreover, catecholamine release and cardiovascular effects in response to tracheal intubation were found to be attenuated by intravenous magnesium in most clinical trials.^{36,48} However, Durmus *et al.* observed an increased minimal alveolar concentration of sevoflurane at the time of skin incision when magnesium was administered before anesthesia induction.⁴⁸ This study was performed in 60 elective surgery patients, who were not premedicated nor received any other drugs for induction of anesthesia. Agitation and flushing, side effects observed only in magnesium-treated patients, may have counteracted potential anesthetic effects.

A similar reduction in requirements as shown for anesthetic agents was described for muscle relaxants when magnesium also was administered.^{46–48} In cardiac surgery patients, MgSO₄ significantly prolonged duration of the intubation and maintenance dose of cisatracurium (mean ± SD, 74 (20) *vs.* 42 (6) min and 69 (16) *vs.* 35 (7) min) and thus reduced the total dose administered intraoperatively (mean ± SD, 0.19 (0.07) *vs.* 0.29 (0.01) mg/kg).⁴⁹ With rocuronium administration, the average onset of neuromuscular block was shown to be significantly shorter in patients receiving MgSO₄ compared with controls (mean ± SD, 77 (18) *vs.* 120 (48) s).⁵⁰ Accordingly, total recovery time, determined as time from injection until a train-of-four ratio of 0.9, was significantly longer after administration of MgSO₄ (mean ± SD, 73.2 (22) *vs.* 57.8 (14.2) min).⁵⁰ Similar effects were observed for several other nondepolarizing muscle relaxants, such as vecuronium.³⁷ The clinical effects of MgSO₄ on depolarizing muscle relaxants seem to be rather small. MgSO₄ does not interfere with onset and duration of succinylcholine-induced neuromuscular block but seems to prevent associated muscle fasciculations and may attenuate potential succinylcholine-induced increases of serum potassium.^{51,52}

Summary

Although a number of studies suggest a clinically relevant effect of magnesium, its actual efficacy as an adjuvant to analgesics and anesthetics to induce and maintain general anesthesia remains unclear and requires evaluation in large clinical trials. Because magnesium prolongs muscle relaxation, continuous monitoring of neuromuscular function during surgery is required, and muscle relaxants should be applied accordingly. However, clinicians should not hesitate to use magnesium as a perioperative treatment option when indicated.

Magnesium and Analgesia

Several animal and human studies report antinociceptive effects of magnesium when administered intravenously or intrathecally.

Mechanisms of Action

Suggested mechanisms underlying these antinociceptive effects include the inhibition of calcium influx (calcium channel blockers augment morphine-induced analgesia and decrease total opioid consumption), antagonism of NMDA receptors, and the prevention of enhanced ligand-induced NMDA signaling in a state of hypomagnesemia.^{53–56} In addition, magnesium seems to attenuate or even prevent central sensitization after peripheral tissue injury or inflammation because of inhibition of dorsal horn NMDA receptors.^{50,57–60}

Experimental Data

In a model of postoperative pain, a single bolus of MgSO₄ (281–375 μg) coadministered with intrathecal morphine potentiated the opioid-induced antinociceptive effects in response to noxious thermal stimulation in opioid-naive rats and in those experiencing mechanical allodynia after surgical incision.⁶¹ In contrast, intrathecal MgSO₄ alone was not associated with antinociceptive effects in rat models of acute pain (hot plate and mechanical stimulation), and when using the formalin test to better mimic human pain conditions, MgSO₄ depressed only the late phase of the response.⁶²

However, most animal studies focused on the effects of magnesium in neuropathic pain. In a model of mechanical hyperalgesia in mononeuropathic (sciatic nerve ligation) and neuropathic diabetic rats, intraperitoneal MgSO₄ produced significant antihyperalgesia and amplified the analgesic effect of low-dose intravenous morphine. The latter effect also was observed for the phase 2 response in the formalin test, although MgSO₄ alone had no effect.⁶³ These effects are thought to result from interference with spinal NMDA receptors.^{64,65} Pain and pain-related altered behavior of animals with neuropathic pain can be positively affected by concomitant administration of magnesium and morphine.⁶⁶ When coadministered with morphine, intrathecal MgSO₄ potentiated antinociception to thermal stimulation and delayed morphine tolerance in rats compared with control animals.⁶⁷ However, studies in a rat model of spinal nerve ligation suggested magnesium homeostasis between serum and cerebrospinal fluid is actively maintained through the blood–brain barrier, even when NMDA receptor-gated ion channels were activated.⁶⁸

Clinical Data

Since the early 1990s the effects of magnesium on postoperative pain and opioid consumption have been studied intensively. However, study results are varied. Whereas most studies describe decreased intra- and postoperative analgesic requirements after magnesium supplementation, a few report no or insignificant beneficial effects.^{57,69,70} A systematic review in 2007 that included 14 randomized trials failed to provide convincing evidence.⁷¹ Differences in dose and onset of magnesium administration; type of magnesium salt and pain scores used, as well as choice of patient population; standard baseline pain medication; and anesthesia may con-

tribute to these inconsistencies in the literature. For instance, MgSO_4 was most recently shown to significantly decrease visual analog scale scores as well as total patient-controlled analgesia drug (morphine and ketorolac) consumption in patients undergoing total hip arthroplasty at 4–48 h after surgery.⁷² Intravenous MgSO_4 was given as a bolus (50 mg/kg) 15 min before induction of spinal anesthesia, followed by a continuous infusion ($15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) until the end of surgery.⁷² However, Zarauza *et al.* found no beneficial effects of MgSO_4 on postoperative pain, as assessed by visual analog scale and morphine consumption, when given as an adjunct to general anesthesia in colorectal surgery patients.⁷³ An initial bolus of 30 mg/kg given 20 min after induction of anesthesia was followed by a continuous MgSO_4 drip for 20 h. Intraoperative anesthesia was maintained using continuous infusion of fentanyl, whereas postoperative analgesia was provided by a morphine patient-controlled analgesia device.⁷³ Explanations for these discrepancies in study outcome, in addition to the reasons already given, may include confounding factors, such as age, preoperative pain level and perception, and comedication, that are hard to control. Table 3 summarizes important clinical trials with respect to study design and outcome.

Magnesium and Preventive Analgesia

Preventive analgesia aims to attenuate central sensitization in response to noxious stimuli in the perioperative period.⁷⁴ Drugs considered to induce preventive analgesia were shown to decrease pain intensities and analgesic requirements far beyond their clinical duration of action. However, McCartney *et al.*, in a systematic review (including four studies and a total of 216 patients) on the effects of magnesium on preventive analgesia, failed to show any beneficial effects.⁷⁵

Summary

The current literature of analgesic effects of magnesium is conflicting, and additional major clinical trials using well-defined dose regimens and pain scores are required to achieve more data on possible antinociceptive effects. In this respect, it might be of interest to look for potential pharmacologic interactions with other analgesics, such as the NMDA antagonist ketamine.

Magnesium and Obstetrics

Preeclampsia

Preeclampsia is a multisystem disorder of unknown origin. It complicates 3–10% of pregnancies and is a major cause of maternal and fetal morbidity and mortality.⁷⁶ Preeclampsia is defined as new-onset hypertension and proteinuria developing after the 20th week of gestation up to several weeks after delivery, and it may be aggravated by seizures or coma (eclampsia). Underlying mechanisms include an abnormal vascular response to placentation with increased systemic vascular resistance, enhanced platelet aggregation, stimula-

tion of inflammation and coagulation, and endothelial dysfunction.⁷⁷

Mechanisms of Action

Magnesium seems to improve clinical symptoms of preeclampsia and eclampsia primarily by systemic, cerebral, and uterine vasodilation. In addition to having a direct effect on the vessels, magnesium was shown to increase concentrations of the two endogenous potent vasodilators endothelium-derived relaxing factor and calcitonin gene-related peptide and attenuate circulating concentrations of endothelin-1, an endogenous vasoconstrictor.^{78–80}

Experimental Data

By inhibition of thromboxane synthesis and calcium channel antagonism, magnesium attenuated peroxide-induced vasoconstriction in isolated human placental cotyledons.⁸¹ In gravid ewes, it decreased maternal blood pressure, although uterine blood flow and fetal oxygenation remained unchanged.⁸²

Clinical Data

Evaluation of potential risks and benefits of magnesium in preeclampsia and eclampsia requires differentiation of its administration in mild to severe forms of preeclampsia, in prevention of eclampsia or its progression, and in treatment of eclamptic convulsions.

Mild Preeclampsia. A total of 357 patients with well-defined mild preeclampsia were randomized during labor or the postpartum period in two different double-blind and placebo-controlled trials. No difference in rate of seizures (none in both groups) or in the progression to severe preeclampsia between women receiving placebo or magnesium (12.5 and 13.8%, respectively) could be observed. One study reported higher rates of postpartum hemorrhage and adverse effects in two cases after magnesium treatment.⁸³ However, other studies reported a beneficial effect of magnesium in this particular stage of disease. In a prospective observational study, Alexander *et al.* compared the effects of magnesium prophylaxis for all women with gestational hypertension or preeclampsia to administration of MgSO_4 , only if mild preeclampsia progressed to severe disease.⁸⁴ They observed a 50% overall increase in the prevalence of eclampsia and a subsequent increase in maternal and neonatal morbidity when MgSO_4 was applied only to women with disease progression. Intravenous magnesium (1 g/h) given over 24 h substantially improved disease-mediated erythrocyte deformability and uterine perfusion, thereby increasing blood supply to the fetus in 25 women with mild preeclampsia or intrauterine growth restriction and pathologic uterine blood flow.⁸⁵ A decision analysis of whether magnesium should be used for seizure prophylaxis in patients with mild preeclampsia indicated that both clinical strategies are acceptable and should be selected based on values and preferences of the patient and clinician. Both approaches were considered essentially equiva-

Table 3. Magnesium & Analgesia

Reference & Study Type	Study–Population	Anesthesia & Analgesia	Study Drug	Results	Favors MgSO ₄
Buvanendran <i>et al.</i> ²²⁵ PRCT, n = 52	Labor pain	CSE (fenta, lido, bupi)	50 mg MgSO ₄ i.t. (with opioids)	Duration of analgesia (MgSO ₄)	+
Ko <i>et al.</i> ²²⁶ PRCT, db n = 60	abd. HE	Thiopental, isoflurane, vecuronium, succi, no intraop. analgesia, postop. PCEA (fenta, bupi)	MgSO ₄ bolus (50 mg/kg) after induction, followed by cont. inf. for 6h (15 mg kg ⁻¹ h ⁻¹)	No effect on postop. pain	-
Levaux <i>et al.</i> ²²⁷ PRCT, db n = 24	Lumbar arthrodesis	Propofol, rocuronium, sevoflurane, N ₂ O remifentanil, piritramid (intraop.), piritramid-PCA (postop.)	Single-dose MgSO ₄ (50 mg/kg) over 30 min before induction	Sign. lower piritramid consumption postop., sign. lower VAS scores and higher global satisfaction scores (MgSO ₄)	+
O’Flaherty <i>et al.</i> ²²⁸ PRCT, db n = 80 (3–12 y/o)	TE	Sevoflurane, N ₂ O fenta (periop.) paracetamol, codeine (postop.)	MgSO ₄ bolus (30 mg/kg) preop.	No effect on postop. pain or analgesic consumption	-
Seyhan <i>et al.</i> ²²⁹ PRCT, db n = 80	HE ± salpingo-oophorectomy	Propofol, atracurium, fenta (intraop.), morphine-PCA (postop.)	MgSO ₄ bolus before induction I: 40 mg/kg II: + cont. inf. (10 mg/kg) for 4 h III: + cont. inf. (20 mg/kg) for 4 h	Dose-dependent reduction of intraop. propofol requirements and postop. morphine consumption (40%) (MgSO ₄)	+
Tramer <i>et al.</i> ⁵⁶ PRCT, db n = 42	abd. HE	Thiopental, vecuronium, isoflurane, N ₂ O, fenta (intraop.), morphine-PCA (postop.)	MgSO ₄ bolus (15 ml 20%, 3 g) preop., followed by cont. inf. (2,5 ml/h) for 20 h total dose: 13 g	Sign. less morphine consumption and discomfort postop. (MgSO ₄)	+
Turan <i>et al.</i> ²³⁰ PRCT, db n = 30	Hand surgery	IVRA (lido), if required i.v. fenta (1μg/kg) & diclo (postop.)	MgSO ₄ (10 ml 15%) as diluent for IVRA	Sign. accelerated onset & prolonged duration of sensory/motor block; lower VAS-scores, less fenta/diclo consumption (MgSO ₄)	+
Tauzin–Fin <i>et al.</i> ²³¹ PRCT, db n = 30	Radical retropubic prostatectomy	Propofol, sevoflurane, cisatracurium, sufentanil, paracetamol, tramadol-PCA (postop.)	MgSO ₄ (50 mg/kg) over 20 min after induction; ropi (w.i.)	Sign. decreased total tramadol consumption (MgSO ₄)	+
Bilir <i>et al.</i> ²³² PRCT, db n = 50	Hip replacement	CSE (hyperbaric bupi)	PCEA (fenta ± MgSO ₄ 50 mg & cont. inf. 100 mg/24 h)	Sign. smaller doses & total consumption of epidural fenta (MgSO ₄)	+

(continued)

Table 3. Continued

Reference & Study Type	Study–Population	Anesthesia & Analgesia	Study Drug	Results	Favors MgSO ₄
Kaya <i>et al.</i> ²³³ PRCT, db n = 40	abd. HE	Thiopental, cisatracurium, remifentanyl, sevoflurane morphine-PCA (postop.)	30 mg/kg MgSO ₄ 15 min before induction, cont. inf. 500 mg/h	Sign. decreased total morphine consumption (MgSO ₄)	+
Mentes <i>et al.</i> ²³⁴ PRCT, db n = 83	Lap. CCE	Fenta, propofol, cisatracurium, sevoflurane/N ₂ O tramadol-PCA (postop.)	50 mg/kg MgSO ₄ intraop	Sign. lower pain scores no difference in total tramadol consumption	+/-
Ozcan <i>et al.</i> ²³⁵ PRCT, db n = 24	Thoracotomy	Propofol, fenta, vecuronium, morphine-PCA (postop.)	MgSO ₄ , 30 mg/kg cont. inf. 10 mg kg ⁻¹ h ⁻¹ (postop.)	Significant decreased morphine consumption, no difference in pain scores	+/-
Steinlechner <i>et al.</i> ²³⁶ PRCT, db n = 40	Cardiac surgery	Eto, fenta, cisatracurium, sevoflurane, piritramide (postop.)	86.5 mg/kg Mg gluconate after induction, cont. inf. 13 mg kg ⁻¹ h ⁻¹ for 12 h postop.	Decreased remifentanyl requirement postop, time to extubation was not prolonged	+
Tramer <i>et al.</i> ²³⁷ PRCT, db n = 200	Ambulatory ilioinguinal hernia repair or varicosis surgery	Propofol, fenta, isoflurane/N ₂ O diclo (ilio-inguinal-ilio- hypogastric nerve block)	4 g MgSO ₄ after induction	No difference in time to first rescue analgesic or pain intensities	-

abd. = abdominal; bupi = bupivacaine; CCE = cholecystectomy; cont. = continuous; CSE = combined spinal epidural; db = double-blind; diclo = diclofenac; eto = etomidate; fenta = fentanyl; HE = hysterectomy; inf. = infusion; intraop. = intraoperative; i.t. = intrathecal; i.v. = intravenous; IVRA = intravenous regional anesthesia; lido = lidocaine; MgSO₄ = magnesium sulfate; N₂O = nitrous oxide; PCA = patient controlled analgesia; PCEA = patient controlled epidural analgesia; periop. = perioperative; postop. = postoperative; PRCT = prospective randomized placebo-controlled trial; ropi = ropivacaine; sign. = significant; succi = succinylcholine; TE = tonsillectomy; VAS = visual analog scale; w.i. = wound infiltration.

lent with regard to outcome because the no-magnesium strategy was associated with a reduction of neonatal mortality and maternal side effects but also an increased risk of maternal death and neurologically compromised neonates.⁸⁶

Severe Preeclampsia. In addition to several case reports and smaller studies, four large trials evaluated the effects of intravenous magnesium on prevention of eclamptic convulsions in 12,673 patients with severe preeclampsia.^{87–90} The main study is the Magnesium Sulfate for Prevention of Eclampsia (Magpie) Trial: a multicenter study, conducted at 175 hospitals in 33 countries that included 10,110 women (42.5% defined as having severe or imminent preeclampsia in each group). Although a significant risk reduction was found for seizures in women assigned to magnesium administration, results were criticized because of heterogeneous clinical characteristics and poorly defined aspects of patient care.⁸⁸ However, as demonstrated in an extensive review by Sibai, the overall results of these trials indicate a significantly smaller incidence of eclampsia (relative risk [RR] 0.39; 95% CI, 0.28–0.55; *P* value not reported).⁹¹ Moreover, no adverse

effects on maternal or fetal/neonatal morbidity were observed, although respiratory depression (RR 2.06; 95% CI, 1.33–3.88) was significantly higher after magnesium prophylaxis in severely preeclamptic women. A Cochrane review including nine trials evaluating the effects of magnesium in the progression of preeclampsia to eclampsia found a more than 50% risk reduction compared with placebo. No difference in neonatal and maternal mortality was observed. Approximately 25% of magnesium-treated women experienced side effects, mainly flushing.⁹²

Eclampsia. The Collaborative Eclampsia Trial compared the efficacy of magnesium with other anticonvulsants in eclamptic women. Similar to various smaller randomized studies, this multicenter trial, including 1,687 patients, showed a clear benefit of magnesium on seizure recurrence (52% and 67% lower risk for additional convulsions compared with diazepam and phenytoin, respectively), but found no differences in maternal morbidity and mortality.⁹³ Cochrane systematic reviews confirmed that MgSO₄ is more effective than diazepam, phenytoin, or a “lytic cocktail” (usually a mixture

of chlorpromazine, promethazine, and pethidine) for treatment of eclampsia.^{94–96}

Preterm Birth and Fetal Neuroprotection. Preterm birth is defined as birth before 37 weeks of gestation and is associated with a significant risk of neurologic morbidity and early neonatal mortality. Its exact pathophysiology remains unknown, but different maternal and fetal factors, such as poly- or oligohydramnios, intrauterine infection, or uterine overdistension resulting in premature rupture of membranes, fetal endocrine activation, etc. seem to play a significant role in preterm labor and birth.⁹⁷ Magnesium is widely used as a tocolytic agent in different parts of the world and has been shown to attenuate uterine contractility *in vitro* and *in vivo*. Underlying mechanisms include a decrease in intracellular calcium concentration and a subsequent inhibition of myosin light-chain kinase.⁹⁸ However, results of clinical trials have not been convincing. Large clinical trials have not shown any benefit of magnesium over placebo or nifedipine in the delay of delivery.^{99,100} A meta-analysis of nine trials studying the effects of magnesium on prevention of preterm birth demonstrated no benefit in delaying birth compared with control.¹⁰¹ Cerebral palsy is characterized by motor and postural dysfunction caused by nonprogressive damage to the developing fetal or infant brain. Preterm birth is a risk factor for cerebral palsy, and the incidence increases with decreasing birth weight and gestational age. The multicenter, placebo-controlled and double-blind Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) Trial showed no beneficial effect of antenatal MgSO₄ on the combined risk of moderate or severe cerebral palsy or death when given to women at imminent risk for delivery at 24 through 31 weeks of gestation (n = 2,241). However, MgSO₄ significantly decreased the risk of moderate or severe cerebral palsy among surviving children (1.9% vs. 3.5%; RR 0.55; 95% CI, 0.32–0.95; P = 0.03).¹⁰² This finding was recently confirmed by a Cochrane database review evaluating five trials with a total of 6,145 neonates.¹⁰³ Antenatal magnesium given to women at risk for preterm birth substantially reduced the risk of cerebral palsy, with the number of women needed to treat of 63. There was also a significant reduction in the rate of substantial gross motor dysfunction, but pediatric mortality or other neurologic impairments were not affected.¹⁰³

Summary

Since its approval for treatment of preeclampsia and eclampsia in the early 1990s, magnesium remains the most commonly used drug for these indications in the United States.¹⁰⁴ Based on available literature, there is a clear Class I, Level of Evidence A Recommendation (American Heart Association [AHA]) for the use of magnesium as an anticonvulsant in severe preeclamptic or eclamptic women. The evidence for its routine use in mild forms of preeclampsia remains uncertain, and large multicenter studies are needed to validate conclusions with respect to safety and efficacy. As recommended, MgSO₄ should be applied intravenously, us-

ing a loading dose of 4–6 g over 20–30 min and a subsequent maintenance dose of 1–2 g/h. The infusion should be continued for at least 24 h after delivery.⁹¹ To avoid serious adverse effects, respiration, the presence of tendon reflexes, and urine output should be closely monitored during treatment.¹⁰⁵ There is no evidence supporting the use of magnesium for tocolysis in women at risk for preterm birth. However, antenatal administration may be considered because there is Level A Evidence (AHA) showing its neuroprotective effects in preterm neonates.¹⁰³

Magnesium and Pheochromocytoma

Pheochromocytoma is a catecholamine-producing and secreting neoplasm arising primarily from the adrenal medulla with an estimated incidence of 500–1,100 cases in the United States each year.¹⁰⁶ The care of patients during surgical removal of pheochromocytoma poses a significant anesthetic challenge because of the well-described hemodynamic disturbances occurring when a tumor is manipulated and finally resected.

Standard preoperative treatment includes pharmacologic stabilization by α - and β -adrenergic antagonists. Several case reports have described the successful use of magnesium during pheochromocytoma crisis.^{107,108}

Mechanisms of Action

Magnesium may stabilize hemodynamics by inhibition of catecholamine release from the adrenal medulla and peripheral adrenergic nerve endings, direct blockade of catecholamine receptors and vasodilation, and antiarrhythmic properties related to L-type calcium channel antagonism.¹⁰⁹

Experimental Data

Magnesium has potent antiarrhythmic and α -adrenergic effects in baboons treated with continuous adrenaline infusion, leading to an increase of cardiac output and stroke volume. It appears to dilate arterial, rather than venous, vessels but did not depress myocardial function.^{110,111} Zheng *et al.* studied the acute cardiovascular effects of a 30-mmol bolus in chronically instrumented awake sheep.¹¹² Magnesium reduced systemic vascular resistance, thereby decreasing mean arterial blood pressure by 23%, and increased cardiac output and heart rate by 38%. It had little effect on contractility and primarily increased myocardial blood flow because of direct myocardial vasodilation.

Clinical Data

Adults. Several concepts for the anesthetic care of patients undergoing surgical removal of pheochromocytoma have been described.¹¹³ However, because of the tumor's low incidence, large prospective clinical trials are missing, and conclusions have to be drawn from a few small studies and case reports. In 1989, James published a series of 16 patients undergoing elective pheochromocytoma surgery, who had been given α - and β -adrenergic antagonists before surgery

and received a loading dose of MgSO_4 (40–60 mg/kg), followed by a continuous perioperative infusion of 2 g/h.¹¹⁴ Additional boli of 20 mg/kg were used to keep blood pressure within ± 30 mmHg of baseline values. A total of 8–18 g MgSO_4 was administered during surgery (60–150 min). In 11 of 16 patients, magnesium was highly effective in providing hemodynamic stability, although 4 patients required additional sodium nitroprusside during manipulation of the tumor.

Children. Because 20% of all pheochromocytomas occur in children, magnesium may be a treatment option.¹¹⁵ In a 5-yr-old boy undergoing laparoscopic tumor resection, intraoperative hemodynamic stability was successfully achieved with a loading dose of 40 mg/kg, followed by continuous infusion of $15\text{--}30 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ MgSO_4 . Additional administration of nicardipine was required only twice, during pneumoperitoneum and tumor manipulation.¹¹⁶

Pheochromocytoma Crisis

Hypertensive crisis caused by pheochromocytoma may be an additional indication for magnesium. Magnesium was shown to improve severe hypertension and hypertensive encephalopathy in three patients with pheochromocytoma.¹¹⁷ Based on magnesium's arteriolar-dilating properties, its use might be advantageous to that of sodium nitroprusside, which dilates both arterioles and venules and may thus worsen hemodynamics, especially in hypovolemic patients. Because magnesium was shown to inhibit catecholamine receptors, it may be superior to other competitive adrenergic antagonists, such as phentolamine and doxazosin, because excessive catecholamine concentrations may be present.¹¹⁷

Summary

Magnesium may be an effective drug in adults and children for providing hemodynamic stability during pheochromocytoma surgery in addition to standard therapy. To achieve maximal effect, serum concentrations of 2–4 mM should be maintained.¹¹⁶

Magnesium and Asthma or Chronic Obstructive Pulmonary Disease

Asthma

Asthma is a common disorder affecting more than 12 million people in the United States, with an estimated 1.8 million visits to emergency departments for acute asthma each year.¹¹⁸

Mechanisms of Action. A variety of experimental data suggest that magnesium-induced bronchodilation may be mediated by several pathways: attenuation of calcium-induced muscle contractions, inhibition of cholinergic neuromuscular transmission, antiinflammatory activity, potentiation of β -agonists on adenylyl cyclase, and reversal of magnesium depletion after β -adrenergic treatment.^{119–122} Evidence also exists that prostaglandin-mediated vascular smooth muscle

relaxation may be magnesium-dependent, and magnesium possesses mild sedative effects that are valuable to achieving anxiolysis and relaxation in acute bronchoconstriction.¹

Experimental Data. Magnesium was shown to relax rabbit bronchial smooth muscle at rest and during stimulation with histamine, bethanechol, or electrical impulse in a dose-dependent manner.¹¹⁹ Likewise, MgSO_4 concentration-dependently relaxed histamine-induced contraction of guinea pig tracheal strips *in vitro* and increased the percentage of the bronchial cross-sectional area in dogs after histamine-elicited bronchoconstriction *in vivo*.¹²³

Clinical Data

Intravenous Magnesium. In 2000, a Cochrane systematic review evaluated seven trials (five adult, two pediatric) with a total of 665 patients for the efficacy of intravenous magnesium as an adjunct to standard therapy (β -agonists and systemic corticosteroids) in the treatment of severe asthma.¹²⁴ The pooled results failed to show a significant benefit for magnesium with respect to pulmonary function and hospital admission. However, subgroup analysis of patients with acute severe asthma showed an improvement of peak expiratory flow rate by 52.3 l/min (95% CI, 27–77.5) and forced expiratory volume in 1 s by a mean of 9.8% of the predicted value (95% CI, 3.8–15.8), as well as a marked decrease in hospital admissions when treated with a single dose of MgSO_4 (2 g in adults and 25–100 mg/kg in children given over 20–35 min). The authors concluded that there is no evidence for the routine use of intravenous magnesium in all asthmatic patients but that it appears beneficial in patients presenting with acute severe asthma.¹²⁴ These data are supported by a recently published review combining new evidence of six trials (three adult, three pediatric) with the original Cochrane article now including a total of 965 patients.¹²⁵

Magnesium seems less beneficial in chronic stable asthma. A daily dose of 450 mg magnesium chelate did not benefit chronic asthmatic adults.¹²⁶ Despite the lack of effect in chronic asthma, magnesium may be advantageous in patients with bronchial hyperreactivity. A randomized, controlled, and double-blind study demonstrated a significant improvement in methacholine-provoked bronchial hyperreactivity in 30 patients after intravenous MgSO_4 ($0.3 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$).¹²⁷ Several case reports support these findings, one of which describes continuous magnesium infusion to facilitate rapid extubation and recovery in a ventilated patient not responding to standard bronchodilating therapy.¹²⁸

Inhaled Magnesium. A Cochrane review including six trials (three adult, two pediatric, one mixed) and a total of 296 patients failed to provide convincing evidence that the addition of nebulized MgSO_4 (95–385 mg or 250–280 mmol) to standard bronchodilator therapy (inhaled β -agonists) improves the outcome of patients presenting with acute asthma.¹²⁹ Compared with β -agonist treatment alone, pulmonary function was improved, and those with severe asthma had a significant difference when analyzed separately;

however, there was considerable between-study heterogeneity. The total MgSO_4 dose applied varied, dependent on the number of nebulizations and cointerventions, such as additional administration of corticosteroids, which further impairs comparisons between studies. Inhaled MgSO_4 alone did not have any benefit on pulmonary function compared with β -agonists and did not influence the rate of hospital admission.¹²⁹ Aggarwal *et al.* studied the effects of nebulized MgSO_4 and salbutamol compared with salbutamol alone in 100 patients with acute asthma classified as severe or life-threatening. Despite nebulization three times at intervals of 20 min and increasing doses, there was no difference in spirometric or laboratory values or hospital admission between the two groups.¹³⁰

Children. Subgroup analysis of the Cochrane review evaluating the effects of intravenous magnesium on patients with acute asthma revealed a benefit for magnesium in pediatric patients.¹²⁴ A recent meta-analysis recommended the use of magnesium in children with moderate to severe acute asthma.¹³¹ Five randomized, placebo-controlled trials including 182 children were evaluated. Intravenous magnesium was associated with a significant absolute risk reduction for hospitalization (number needed to treat = 4), a significantly smaller risk for persistent bronchoconstriction and a significant improvement of the asthma symptom score. Because different dose regimens were used (25 mg/kg, 40 mg/kg, 75 mg/kg), and the dose-response relation differed among studies, future research should focus on the optimal dose regimen for children. In this regard, Glover *et al.* showed that a loading dose of 29.6 mg/kg MgSO_4 followed by a continuous infusion dose of $18 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for the treatment of refractory wheezing in children in an ICU was a safe mode of drug application.

Chronic Obstructive Pulmonary Disease

Only a small number of studies addressed the effects of magnesium on chronic obstructive pulmonary disease. In a randomized, placebo-controlled, double-blind clinical trial, Skorodin *et al.* studied the effects of intravenous MgSO_4 (1.2 g) after nebulized albuterol treatment in 72 patients presenting with acute exacerbation of chronic obstructive pulmonary disease.¹³² After 30–40 min, the peak expiratory flow rate was significantly improved in the magnesium group, although there was no difference with regard to dyspnea. Administration of intravenous MgSO_4 (2 g) in 22 patients with stable chronic obstructive pulmonary disease was associated with a reduction of lung hyperinflation and improved muscle strength.¹³³

Summary. In the absence of straightforward evidence, one can rely on the 2008 revised National Asthma Education and Prevention Program guidelines for managing exacerbations of asthma.¹³⁴ In patients with life-threatening exacerbations of asthma and in those in whom exacerbations remain in the severe category after 1 h of intensive conventional therapy, the administration of magnesium sulfate can be considered

(Class II, Level of Evidence A, AHA). It is also suggested that nebulized salbutamol be administered in isotonic MgSO_4 because it provides greater benefit than when delivered in normal saline. There is little evidence to recommend the routine use of magnesium in patients with chronic obstructive pulmonary disease.

Magnesium and Neuroprotection

Because of its diverse roles in various cellular functions, magnesium has been suggested to have beneficial effects in several neurologic disorders.

Mechanisms of Action

In addition to NMDA antagonism and especially important for the ischemic penumbra, magnesium was shown to protect neurons and glia cells by numerous other modes of action.¹³⁵ By inhibiting ischemia-induced glutamate release and calcium-dependent enzymes, magnesium exerted anti-excitotoxic properties in different animal models and prevented cellular apoptosis in hippocampal slices of newborn piglets.^{136–139} In a rat model of cerebral ischemia, cortical spreading depression and anoxic depolarization were shown to be attenuated.¹⁴⁰ Of particular interest in subarachnoid hemorrhage, magnesium is a cerebral vasodilator, shown to increase blood flow in rat brain, as desired.¹⁴¹

Experimental Data

In a rat model of middle cerebral artery occlusion, magnesium consistently reduced cerebral infarct volume by 25–61%. This effect seemed to be dose-dependent and could be elicited in a time window of as long as 6 h after onset of ischemia.^{142,143} Using the same model, Lee *et al.* demonstrated significantly improved electrophysiologic and neurobehavioral recovery, as well as reduced brain infarction after intracarotid infusion of magnesium at the beginning of reperfusion (90–120 min after onset of ischemia).¹⁴⁴ Administration of 250 $\mu\text{mol/kg}$ MgSO_4 significantly attenuated motor and cognitive deficits after 4 weeks of traumatic brain injury in rats, when given 30 min after injury.¹⁴⁵ In a rabbit model of spinal cord ischemia, 3 mg/kg intrathecal MgSO_4 significantly decreased glutamate concentrations in the cerebrospinal fluid, diminished acute neuronal loss, and improved lower extremity hind limb function.¹⁴⁶ Szr *et al.* observed a dose-dependent decrease of lipid peroxidation and improved spinal somatosensory evoked potentials after 300–600 mg/kg subcutaneous MgSO_4 was administered to 30 rats after spinal cord injury.¹⁴⁷ However, one study reported that 3 mg/kg intrathecal MgSO_4 induced severe but reversible motor dysfunction after spinal cord ischemia after aortic occlusion in rabbits.¹⁴⁸

Stroke

The large multicenter Intravenous Magnesium Efficacy in Stroke (IMAGES) Trial evaluated the benefit of magnesium in the treatment of acute stroke. A total of 2,589 patients was

randomized to receive either intravenous MgSO_4 (16 mmol over 15 min, then 65 mmol over 24 h) or placebo after acute stroke.¹⁴⁹ No difference in mortality or (permanent) disability could be observed after 90 days. Another large phase 3 clinical trial, the Field Administration of Stroke Therapy—Magnesium (FAST-MAG) Trial, currently is evaluating the benefit of field-initiated (within the first 2 h after onset of symptoms) magnesium in improving long-term functional outcome of patients with cerebral infarction and intracerebral hemorrhage. The researchers will study 1,298 patients by June 2011 (International Standard Randomized Controlled Trial Number NCT00059332).¹⁵⁰ A nonrandomized, open-label pilot trial in 2004 preceding the FAST-MAG Trial demonstrated dramatic early recovery in 42% of patients and good 90-day global functional outcome in 75% of patients treated with intravenous MgSO_4 (4-g loading dose followed by 16 g as maintenance dose) within 2 h after stroke onset.¹⁵⁰ Although there is little evidence for a time frame facilitating maximal neuroprotective efficacy of magnesium in stroke, the most promising window is assumed to cover the first 3 h after onset of ischemia. Thus, the lack of effect seen in the IMAGES Trial may result in part from a delay in treatment because only 3% of patients received intravenous magnesium within the first 3 h after onset of symptoms, whereas the initiation of magnesium administration averaged 12 h. Additional limitations include the lack of a reliable measure of initial stroke severity as an important predictor of outcome and verification of sufficient magnesium concentrations in ischemic tissue. An increase of blood pressure is known to improve recovery after stroke. However, magnesium did induce mild hypotension. Thus, it remains open to debate whether the net effect observed results from a mixture of neuroprotection and injury caused by decreased perfusion of ischemic tissue. Subgroup analysis revealed a potential benefit of magnesium in patients with subcortical stroke lacunar syndromes, although *post hoc* analyses need to be interpreted carefully.

Carotid Surgery

Patients undergoing carotid endarterectomy are at particular risk for postoperative cognitive deficits caused by cortical ischemia after intraoperative hypotension or embolic events. A single randomized, double-blind, placebo-controlled trial analyzed data of 92 patients with asymptomatic or symptomatic carotid artery stenosis with $\geq 60\%$ scheduled for carotid endarterectomy. MgSO_4 given as a 2-g loading dose over 25 min and a maintenance dose of either 8 g or 16 g over 24 h significantly improved neurocognitive function on postoperative day 1 compared with placebo or higher-dose MgSO_4 (4-g loading dose, 16 g as maintenance dose).¹⁵¹ The same group showed that the dose of MgSO_4 did not influence the requirement, duration, or amount of postoperative pressor support.¹⁵² However, a truly neuroprotective effect of magnesium during carotid endarterectomy is difficult to claim because potential confounders such as residual effects of an-

esthetics cannot be completely ruled out considering an observation period of only 24 h after surgery in that study.

Subarachnoid Hemorrhage

Delayed cerebral ischemia is one of the main causes of death and disability after subarachnoid hemorrhage and usually occurs 4–10 days after the initial bleeding event. The placebo-controlled Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage (MASH) Trial suggested that intravenous MgSO_4 as an adjuvant to nimodipine may reduce delayed cerebral ischemia by 34% (hazard ratio 0.66; 95% CI, 0.38–1.14) and subsequent poor outcome, defined as Rankin score more than 4 after 3 months, by 23% (RR 0.77; 95% CI, 0.54–1.09; numbers needed to treat = 12).¹⁵³ Administration of 64 mm/day MgSO_4 was started within 4 days after subarachnoid hemorrhage until 2 weeks after aneurysm occlusion.¹⁵³ Likewise, a systematic review analyzed three trials ($n = 379$) that compared MgSO_4 with placebo in addition to nimodipine, and reported borderline statistical significance for the RR of poor outcome after subarachnoid hemorrhage (RR 0.75; 95% CI, 0.57–1.00).¹⁵⁴ However, the most recently published Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage [iMASH]-Trial could not demonstrate any benefit of intravenous magnesium, given within the first 48 hours after the initial bleeding event for up to 14 days, over placebo with respect to neurological outcome (Extended Glasgow Outcome Scale 5 to 8) at 6 months in 327 patients with aneurysmal subarachnoid hemorrhage. One current clinical trial (Magnesium in Aneurysmal Subarachnoid Hemorrhage [MASH] II European Union Drug Regulating Authorities Clinical Trial [EudraCT] 2006-003523-36 including a total of 1200 patients is under way to confirm these data in a large patient population.

Traumatic Brain Injury

Traumatic brain injury is a major cause of death and disability worldwide. Its pathophysiology involves a primary event, characterized by neuronal cell death, ischemia, brain edema, and others, followed by secondary insults of multifactorial nature, which are believed to exacerbate the neurologic damage.¹⁵⁶ Despite considerable experimental evidence regarding the neuroprotective effects of magnesium in traumatic brain injury, clinical trials provide conflicting results. Temkin *et al.* randomized 499 patients with moderate or severe traumatic head injury to either placebo or MgSO_4 within 8 h after injury continuing for 5 days and targeting serum concentrations of 1.0–1.85 mM or 1.25–2.5 mM.¹⁵⁷ Magnesium did not have any benefit on the primary outcome measure based on mortality, seizures, functional measures, or neuropsychologic tests when assessed 6 months after injury. Patient outcome seemed to be affected rather negatively.¹⁵⁷ In contrast, Dhandapani *et al.* reported a favorable outcome in 30 patients with closed traumatic brain injury randomized to MgSO_4 within 12 h after injury (odds ratio 4.13; 95% CI, 1.39–12.27; $P = 0.009$).¹⁵⁸ Outcome was evaluated using

the Glasgow Outcome Scale 3 months after injury. Patients received 4 g intravenous MgSO₄ and 10 g intramuscular MgSO₄ as a loading dose, followed by an intramuscular maintenance dose of 5 g every 4 h for 24 h. No significant side effects were observed. Because the number of patients included in that study is rather small, data should be interpreted carefully. Secondary brain insults or differences in study design with respect to inclusion/exclusion criteria and magnesium regimen may have contributed to inconsistent study results, and larger trials for definite evaluation of magnesium's effect in traumatic brain injury are certainly required.

Spinal Cord Injury

Once primary injury to the spinal cord has occurred, reduction of secondary injury and ongoing ischemia by stabilizing hemodynamics and spinal perfusion pressure is most important. Magnesium has proven its neuroprotective potential in experimental spinal cord injury. Whether these effects translate to the clinical setting remains to be evaluated in large clinical trials.

Low bioavailability has to be considered as a limiting factor of magnesium's potential positive effects on neurologic disorders, such as delayed cerebral ischemia or traumatic brain injury, and thus outcome.¹³⁵ Parenteral application of magnesium was shown to increase magnesium concentrations in the cerebrospinal fluid of animals and humans by 20–25% in some studies.^{159,160} This increase was significantly smaller (15% for total magnesium and 11% for ionized magnesium, respectively) in patients with brain injury treated with intravenous magnesium for 24 h.¹⁶¹ However, other studies suggest there is no correlation between plasma and cerebrospinal fluid magnesium.¹⁵⁶ In addition, permeability of the blood–brain barrier may differ based on types and degrees of neuronal disease.¹⁶²

Summary

Animal and human studies investigating the neuroprotective character of magnesium show conflicting results. Onset of treatment, dosing, and duration of administration remain to be characterized. Current guidelines of the American Stroke Association do not recommend magnesium as a neuroprotective agent in the early management of ischemic stroke (Class III, Level of Evidence A, AHA).¹⁶³ This is also reflected in the 2009 guidelines for the management of aneurysmal subarachnoid hemorrhage, in which the value of calcium antagonists other than nimodipine is referred to as uncertain.¹⁶⁴

Magnesium and Myocardial Infarction

Acute myocardial infarction and related arrhythmias are still one of the major causes of death in the United States and most Western countries.¹⁶⁵

Mechanisms of Action

Magnesium was found to induce coronary and systemic vasodilation, to improve metabolism of cardiomyocytes, and to attenuate ischemia–reperfusion injury of myocardial tissue.^{166–169} Many of these protective effects have been ascribed to calcium antagonism because calcium overload is the leading cause of myocardial cell death.⁵⁵ Na⁺/K⁺ adenosine 5'-triphosphatase and Ca²⁺ adenosine 5'-triphosphatase are important regulators of myocardial membrane stability. Magnesium is a cofactor of both enzymes, and additional substitution was shown to decrease membrane excitability.¹⁷⁰ In addition, magnesium prolongs the absolute refractory period and shortens the relative refractory period, thereby reducing the incidence of infarction-related arrhythmias.¹⁷¹

Experimental Data

Different *in vivo* experimental animal models of coronary occlusion and reperfusion demonstrated an increased infarct size and exacerbation of myocardial stunning when magnesium deficiency was present at the time of injury.^{172,173} Underlying mechanisms may include increased lipid peroxidation, as shown for bovine aortic endothelial cells under magnesium-deficient conditions.¹⁷⁴ A protective effect of 8 mM MgSO₄ on cardiac function and infarct size could be demonstrated in a globally ischemic–reperfused isolated rat heart model, when magnesium was administered for 5 min starting 10 min before onset of ischemia.¹⁷⁵ Attenuation of up-regulated P-selectin expression and decreased myocardial necrosis may be involved.¹⁷⁶ Infarct size could also be limited when magnesium was administered within 15–45 min after reperfusion of the coronaries.^{168,169,177}

Clinical Data

In humans, hypomagnesemia is associated with a higher incidence of lethal arrhythmias after acute myocardial infarction, whereas intravenous administration of magnesium reduced early mortality.^{178,179} MgSO₄ (50 ml for the first 24 h and 12 mmol for the second 24 h) decreased 30-day mortality to 6.7% (17% for control patients) when given within 3 h after hospital admission.¹⁷⁹

Major Clinical Trials

Because reperfusion injury after myocardial ischemia was shown to crucially affect patients' outcome, major clinical studies on the role of magnesium on ischemia–reperfusion injury have been conducted. However, inconsistent data were obtained.

Leicester Intravenous Magnesium Intervention Trial, 1992.

In the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), 2,316 patients with assumed myocardial infarction were included and received either 8 mmol MgSO₄ for 5 min, followed by 65 mmol for 24 h, or placebo. All-cause mortality at 28 days in the treatment group was significantly ($P = 0.04$) less than that of control patients.¹⁸⁰

Fourth International Study of Infarct Survival, 1995. In the fourth International Study of Infarct Survival (ISIS-4),

58,050 patients with suspected myocardial infarction were included and randomized to either MgSO₄ treatment (8 mmol for 15 min, followed by 72 mmol over 24 h) or standard care. Thrombolytic therapy was administered in both groups as indicated. Thirty-five days after hospital admission, an insignificant increase in mortality (6%) as well as a significantly higher rate of bradycardia, heart failure, and death caused by cardiogenic shock ($P < 0.001$) after magnesium treatment were observed.¹⁸¹ The heart failure and death rates were suggested to result from significant induced hypotension after magnesium administration.¹⁸²

The most probable explanations for the controversial results of LIMIT-2 and ISIS-4 relate to the differences in timing of magnesium administration, dosing, and a low control group mortality rate in ISIS-4. Cardioprotective effects of magnesium were shown to require high serum concentrations at the time of reperfusion. In LIMIT-2, the median time from onset of chest pain to randomization was 3 h compared with 8 h in the ISIS-4 Trial. According to the protocol, patients in LIMIT-2 began receiving magnesium when thrombolytic therapy was initiated, whereas patients in ISIS-4 received magnesium after, rather than before, or with thrombolytic therapy. In 30% of patients who did not undergo thrombolysis, the median time to randomization was 12 h, so a relevant number of patients might have already achieved spontaneous reperfusion.¹⁸³ The dose of magnesium administered also could have played an important role because other trials using less than 75 mM showed a significantly reduced early mortality. In previous trials, the benefit of magnesium correlated well with control group mortality. Control group mortality in ISIS-4 was only 7.2%, suggesting that most patients were at low risk and thus unlikely to benefit from magnesium therapy.

Magnesium in Coronaries Trial. The Magnesium in Coronaries (MAGIC) Trial, a multicenter, double-blind, placebo-controlled trial, was designed to resolve these controversies by evaluating whether administration of intravenous magnesium to high-risk patients, patients older than 65 yr, or those not eligible for reperfusion therapy in the course of myocardial infarction would result in better survival. A total of 6,213 patients, receiving either MgSO₄ (2-g bolus over 15 min, followed by 17 g [~68 mmol] over 24 h) or placebo were included, and the study drug was started within 6 h after onset of clinical symptoms (median time of 3.8 h) and before angioplasty or fibrinolysis. All patients received standard treatment. Magnesium treatment had no beneficial effects on the primary (30-day mortality) or the secondary outcome measures (incidence of heart failure).¹⁸⁴

Several reasons for the lack of effect of magnesium administration were discussed. Publication bias and small sample sizes in previous trials may have overestimated magnesium's potential benefit. The cardioprotective effects of magnesium may have been covered by current therapies for myocardial infarction not being used in previous trials, the doses of

MgSO₄ being used were too high, or magnesium simply being ineffective.

Minor Clinical Trials

Gyamlani *et al.* enrolled 100 patients with diagnosed acute myocardial infarction, who received 15 g MgSO₄ over 48 h starting within 2 h of admission.¹⁷⁰ When thrombolytic agents were applied, MgSO₄ was given within the following 30 min of treatment. Development of arrhythmias (8% *vs.* 34%), cardiac failure (4% *vs.* 14%), and mortality (4% *vs.* 20%) were significantly reduced by magnesium. In 150 patients undergoing angioplasty with low or intermediate risk of acute myocardial infarction, MgSO₄ infusion (7 g over 5 h) significantly decreased aortic systolic pressure ($P = 0.043$) before intervention. However, primary (30-day infarct size) and secondary end points (ventricular arrhythmias, death, and others) were not affected.¹⁸²

Summary

According to the most recent Cochrane database review analyzing 26 trials that studied the effects of intravenous magnesium on acute myocardial infarction, magnesium seems unlikely to reduce mortality after early and late treatment, after thrombolytic therapy, or when used at high doses (more than 75 mM). It may reduce the incidence of ventricular fibrillation or tachycardia or severe arrhythmias but also may increase the incidence of profound hypotension, bradycardia, and flushing.¹⁸⁵ Taken together, there is no evidence for the routine use of magnesium in patients with acute myocardial infarction at any level of risk (Level of Evidence A, AHA).

Magnesium and Cardiac Arrest

Magnesium was reported to have a beneficial effect on the incidence of cardiac arrest after refractory ventricular fibrillation.^{186,187}

Experimental Data

In a porcine model of coronary occlusion, intravenous MgSO₄ (80 mg/min given 10 min before, during, and 15 min after epicardial shocking) attenuated generation of free oxygen radicals and preserved left ventricular function after defibrillation.¹⁸⁸ Magnesium pretreatment (30 mg/kg), calcium, or a combination of both did not affect time until cardiovascular collapse or survival of hyperkalemic cardiac arrest in rats.¹⁸⁹

Clinical Data

In a small prospective and controlled study ($n = 22$), normomagnesemia was directly correlated to successful resuscitation after cardiac arrest after ventricular fibrillation or tachycardia.¹⁹⁰ Evaluating the effects of 2 g MgSO₄ during resuscitation after cardiopulmonary arrest, Hassan *et al.* included 105 patients with refractory or recurrent ventricular fibrillation not responding to initial defibrillation.¹⁹¹ Mag-

nesium did not improve return of spontaneous circulation or discharge from hospital alive. Similarly, magnesium did not improve the rate of successful resuscitation, survival for 24 h, or survival until hospital discharge in a randomized, placebo-controlled trial studying 156 patients with cardiac arrest regardless of their initial rhythm.¹⁹²

Summary

Based on current literature, there is no evidence for the routine use of magnesium in patients with cardiac arrest.

Magnesium and Cardiac Arrhythmias

Although magnesium is not considered a classic antiarrhythmic drug, it may convert some types of malignant arrhythmias. Accordingly, low magnesium serum concentrations were shown to be potentially proarrhythmic.

Mechanisms of Action

Being an endogenous calcium antagonist, magnesium slows electrical activity of the sinoatrial node, prolongs atrioventricular conduction, and finally increases the refractory period of the atrioventricular node.¹⁹³

Clinical Data

Supraventricular Arrhythmias. Primarily studying the effects of milrinone in 1,068 patients with moderate to severe congestive heart failure (New York Heart Association III/IV), this large clinical trial also evaluated the prognostic significance of alterations in serum magnesium.¹⁹⁴ There was no evidence that low serum magnesium is an independent risk factor for sudden death or all-cause death. In a small prospective study, Moran *et al.* reported MgSO₄ to be superior to amiodarone in conversion of acute atrial tachyarrhythmias in critically ill patients.¹⁹⁵ Likewise, a retrospective cohort evaluation of normomagnesemic patients by Coleman *et al.* demonstrated an enhanced ability of dofetilide to successfully convert atrial fibrillation or flutter into sinus rhythm, when MgSO₄ was used in addition.¹⁹⁶ However, most of the studies have moderate quality and small patient numbers, so there is only little evidence supporting the routine use of magnesium for conversion of atrial fibrillation.

Atrial Fibrillation after Cardiac Surgery. Arrhythmias, especially atrial fibrillation, are frequently complications after cardiac surgery, with a typical time frame of 24–96 h after surgery and a peak incidence on postoperative day 2.^{197–202} The underlying mechanisms are multifactorial. Hypomagnesemia, caused by cardiopulmonary bypass, high-dose diuretic therapy, surgical stress, and exogenous catecholamines, is one known risk factor for the postoperative development of atrial fibrillation. Clinical trials studying the effects of perioperative magnesium prophylaxis gave conflicting results. In 200 patients undergoing coronary artery bypass grafting, Toraman *et al.* reported that preoperative, intraoperative, and early postoperative administration of 6 mmol MgSO₄ significantly reduced postoperative atrial fi-

brillation (2% *vs.* 21% in the control group).²⁰³ In a meta-analysis on the prophylactic use of magnesium during surgery, Alghamdi *et al.* described a significant risk reduction (RR 0.64; 95% CI, 0.47–0.87; *P* = 0.004, numbers needed to treat = 11) of atrial fibrillation after magnesium administration.²⁰⁴ Eight studies with a total of 1,033 patients were included. MgSO₄ doses ranged from 7.5 to 25 g, administered between 2 and 5 days after surgery. Reviewing 15 randomized controlled trials, Shepherd *et al.* found atrial fibrillation to be less likely the longer prophylaxis lasted and the earlier it was initiated.²⁰⁵ However, one has to be careful in interpreting these data because a statistically significant heterogeneity was present. In recent large clinical trials in which magnesium was used concomitantly with β -blockers as standard therapy, magnesium showed little or no effect.^{206,207} A dose of 5 g intravenous MgSO₄ given in addition to an established oral β -blocker protocol until postoperative day 4 did not reduce the incidence of atrial arrhythmias in 927 nonemergent cardiac surgery patients.²⁰⁷ Considering all of the data, current evidence for beneficial effects of magnesium in the prophylaxis of life-threatening arrhythmias after surgery is controversial. Studies conducted were small, and significant heterogeneity between different trials was present. A definite answer of whether magnesium replacement in a state of hypomagnesemia in that patient population is or is not of potential depends on the results of more large, well-designed clinical trials.

Ventricular Arrhythmias. Current treatment options consist of cardioversion, amiodarone, and normalization of serum electrolytes, including magnesium. Two small studies demonstrated reduced and even suppressed episodes of nonsustained monomorphic ventricular tachycardia after magnesium administration.^{208,209} However, to date there is no solid clinical evidence recommending magnesium in the treatment or prophylaxis of monomorphic ventricular tachycardia.²¹⁰

Torsades de Pointes. Torsades de pointes tachycardias certainly benefit from administration of magnesium. Malfunction of potassium channels results in delayed ventricular repolarization and inactivation of calcium channels.²¹² The late calcium influx combined with the prolonged repolarization causes early after-depolarizations, leading to torsades de pointes and associated long QT intervals.²¹³ Magnesium attenuates these pathologic changes by inhibiting calcium currents, as shown by a variety of experimental and clinical data.^{213–216} As an urgent measure, 2 g MgSO₄ (25–50 mg/kg in children²¹²) should be the drug of choice, followed by electrolyte stabilization and efforts to accelerate the basic heart rate.^{212,217}

Digoxin-induced Arrhythmias. Magnesium is well established in the management of digoxin-induced tachyarrhythmias.²¹⁸ Digoxin antibodies are the basic treatment, but in hypomagnesemic patients, especially those susceptible to digoxin-induced arrhythmias, intravenous administration of magnesium should be part of the immediate standard ther-

Table 4. Drug Interactions

Calcitriol	May increase magnesium serum concentrations
Calcium channel blockers	Magnesium may enhance hypotensive effects
Antibiotics	Magnesium may decrease absorption of quinolone and tetracycline antibiotics as well as nitrofurantoin; aminoglycoside antibiotics may lower magnesium serum concentrations
Digoxin	May increase renal excretion of magnesium; magnesium may decrease effects of digoxin
Neuromuscular blockers	Magnesium enhances the neuromuscular blockade
Antidiabetics	Magnesium may increase absorption of glipizide and glyburide
Prednisone	May lower magnesium serum concentrations
Diuretics	Loop and thiazide diuretics may lower magnesium serum concentrations

apy until Fab antibodies are available (Class IIa, Level of Evidence B, AHA).²¹⁹

Summary

Magnesium has an essential role in normal cardiac electrophysiology, and altered serum concentrations may contribute to a variety of cardiac arrhythmias.

Reflecting the current controversy of existing evidence, the majority of guidelines (American College of Cardiology, AHA, American College of Chest Physicians, European Society of Cardiology) for managing atrial fibrillation or postoperative cardiac arrhythmias does not recommend magnesium for standard therapy, whereas the European Association for Cardio-Thoracic Surgery approves prophylaxis with magnesium for minimizing the incidence of atrial fibrillation in patients undergoing cardiac surgery.^{220–222} However, there is a clear recommendation for MgSO₄ in patients with long QT syndrome and episodes of torsades de pointes (Class IIa, Level of Evidence B, AHA).²¹⁹

Magnesium and Side Effects

Intravenous administration of magnesium generally is associated with minor side effects. It may provoke burning sensation or pain on injection and induce agitation, drowsiness, and nausea. Patients also may experience headache, dizziness, and muscle weakness or report hypotension and bradycardia.⁴⁸ In eclampsia, approximately 25% of women treated with magnesium experience side effects, mainly flushing.²²³ Magnesium may increase the risk of postpartum hemorrhage and respiratory depression.⁹¹ Because magnesium crosses the placenta, it may induce neonatal lethargy, hypotension, and

rarely respiratory depression after prolonged administration (more than 48 h).²²⁴ Several interactions with drugs commonly used in the clinical setting exist. A summary is given in table 4.

Conclusion

Magnesium plays a key role in numerous physiologic processes, and various indications have been proposed for its use as a therapeutic agent. Despite promising experimental data, large clinical trials often have provided conflicting results, questioning the expected efficacy of magnesium in several clinical settings. Additional research is required to complete our understanding of when and how to use magnesium therapeutically. Nevertheless, there are conditions that benefit from magnesium therapy, such as preeclampsia, eclampsia, and torsades de pointes arrhythmias. Maintenance of magnesium serum concentrations within normal physiologic limits is desirable, and with respect to its well-established safety profile, one may consider magnesium an additional alternative for the specific described pathologies when standard therapy fails.

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