**MAGNESIUM SULFATE (Systemic)**

Category

Anticonvulsant; electrolyte replenisher; tocolytic; antiarrhythmic.

**Indications**

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Seizures, in toxemia of pregnancy (prophylaxis and treatment) 3, 4, 5, 6, 13¾Intravenous magnesium sulfate is indicated for the prevention and immediate control of life-threatening seizures in the treatment of severe toxemias (pre-eclampsia and eclampsia) of pregnancy. 13, 33, 34

Hypomagnesemia (prophylaxis and treatment) 3, 4, 13¾Magnesium sulfate is indicated for replacement therapy in magnesium deficiency, especially in acute hypomagnesemia accompanied by signs of tetany similar to those of hypocalcemia.
In patients receiving total parenteral nutrition, magnesium sulfate is added to the nutrient admixture to prevent or treat magnesium deficiency. 5, 6, 13

[Premature labor (treatment)] *¾Magnesium sulfate may be used as a tocolytic agent in the management of premature labor. 26, 27, 28, 29, 30, 31, 32, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79

[Tachycardia, ventricular, polymorphous (treatment)] *¾Magnesium sulfate is used in the treatment of torsades de pointes. 7, 8, 9, 10, 11 It is not effective in congenital QT interval prolongation syndromes. 12

Acceptance not established

Early studies seemed to show that intravenous magnesium sulfate administered in the setting of acute myocardial infarction reduced the mortality rate. 14, 15, 16, 22, 23, 24, 25 Pooled data from eight randomized controlled trials showed that intravenous magnesium administered within 24 to 48 hours after onset of symptoms decreased ventricular tachycardia and fibrillation by 49% and the incidence of cardiac arrest by 58% in patients who had not been treated with thrombolytic agents. 23 Intravenous magnesium also reduced the early mortality rate in patients with suspected myocardial infarction in the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). 14 Magnesium"s efficacy appeared to be independent of that of thrombolytic or antiplatelet therapy. 14 In this study, little effect was seen on arrhythmic events, but the incidence of left ventricular failure was reduced in the treatment group. 14, 64

However, recent data from the large randomized controlled trial, the Fourth International Study of Infarct Survival (ISIS-4), seem to challenge these earlier studies. 63, 64 ISIS-4 showed that intravenous magnesium was ineffective in significantly reducing mortality, independent of thrombolytic or antiplatelet therapy, in patients with suspected acute myocardial infarction. 63 There was no significant

evidence that magnesium had any effect on 5-week mortality, and follow-up at one year did not indicate any beneficial effect. 63 In direct contrast to the results of some earlier studies, administration of intravenous magnesium was associated with small but significant increases in heart failure, cardiogenic shock, and in deaths attributed to cardiogenic shock. 63

Differences in study design, particularly between ISIS-4 and LIMIT-2, may explain the conflicting results. Intravenous magnesium was administered later in the course of myocardial infarction in ISIS-4, as compared to LIMIT-2. The ISIS-4 study was not designed to detect a highly time-dependent effect of magnesium on reperfusion injury. Therefore, because of conflicting evidence from these studies, it remains controversial whether the routine use of intravenous magnesium sulfate in the setting of acute myocardial infarction is beneficial. 63, 64

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Anticonvulsant¾

Exact mechanism is not clearly understood. 33, 34 Magnesium may decrease the amount of acetylcholine released at the myoneuronal junction, resulting in depression of neuromuscular transmission. Magnesium also may have a direct depressant effect on smooth muscle and may cause central nervous system (CNS) depression. 13, 33, 34, 35

Antiarrhythmic¾

The exact mechanism of magnesium's antiarrhythmic effect is not clear. Magnesium may decrease myocardial cell excitability by contributing to the re-establishment of ionic equilibrium and stabilizing cell membranes. 21 Magnesium also appears to modulate the sodium current, the slow inward calcium current, and at least one potassium current. 8

Myocardial infarction¾

Possible mechanisms include antiarrhythmic action or direct cardioprotection. 21, 22, 25 Magnesium's cardioprotective action may involve coronary vasodilation, reduction in peripheral vascular resistance, platelet aggregation inhibition, and an effect on the calcium current. 21, 22, 25

Tocolytic¾

The exact mechanism is not known. 38 It is speculated that magnesium may decrease myometrial contractility by altering calcium uptake, binding, and distribution in smooth muscle cells. 38 Magnesium has been shown to increase uterine blood flow secondary to vasodilation of uterine vessels. 37, 39

Precautions to Consider

Pregnancy/Reproduction

Pregnancy¾Parenteral magnesium sulfate has been administered to pregnant women in the treatment of pre-eclampsia and eclampsia (toxemia) of pregnancy and as a tocolytic agent. 13, 27, 33, 38 It readily crosses the placenta and rapidly attains fetal serum concentrations that approximate those in

the mother. 38 Magnesium's effects in the neonate may be similar to those in the mother and may include hypotonia, drowsiness, and respiratory depression. 38 Bony abnormalities 40, 45 and congenital rickets have been reported in neonates born to mothers treated with parenteral magnesium sulfate for prolonged periods of time (4 to 13 weeks' duration). 40

FDA Pregnancy Category A. 13

Breast-feeding

Magnesium sulfate is distributed into breast milk. 41 Milk concentrations are approximately twice those in maternal serum. 41

Pediatrics

Appropriate studies on the relationship of age to the effects of magnesium sulfate have not been performed in the pediatric population. However, no pediatrics-specific problems have been documented to date.

Geriatrics

Appropriate studies on the relationship of age to the effects of magnesium sulfate have not been performed in the geriatric population. However, elderly patients are more likely to have age-related renal function impairment, which may require dosage reduction in patients receiving magnesium sulfate. 13

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Calcium (intravenous salts)

(concurrent use may neutralize effects of parenteral magnesium sulfate; calcium gluconate and calcium gluceptate are used to antagonize the toxic effects of hypermagnesemia; also, calcium sulfate may precipitate when a calcium salt is admixed with magnesium sulfate in the same intravenous solution; however, calcium salts and magnesium sulfate may be administered concurrently through separate intravenous lines if required in post-parathyroidectomy "hungry bones" syndrome or tetany associated with hypocalcemia and hypomagnesemia)

CNS depression-producing medications, other 3, 4, 6, 13 (see Appendix II )

(CNS depressant effects may be potentiated when these medications are used concurrently with parenteral magnesium sulfate)

Digitalis glycosides 6, 13

(parenteral magnesium sulfate must be administered with extreme caution in digitalized patients, especially if intravenous calcium salts are also employed; cardiac conduction changes and heart block may occur)

Neuromuscular blocking agents 4, 6, 13, 43

(concurrent use with parenteral magnesium sulfate may result in severe and unpredictable potentiation of neuromuscular blockade)

Nifedipine 46

(concurrent use of parenteral magnesium sulfate with nifedipine may produce an exaggerated hypotensive response 57, 58 )

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Reticuloendothelial cell imaging

(parenteral magnesium sulfate may impair reticuloendothelial cell imaging with technetium Tc 99m sulfur colloid by causing clumping of colloidal particles with subsequent entrapment in the vasculature of the lungs rather than in the liver, spleen, and bone marrow)

**Medical considerations/Contraindications**

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Heart block 3, 4, 6, 13

(magnesium may exacerbate this condition)

>> Renal failure 5 (creatinine clearance < 20 mL per minute)

(clearance of magnesium decreased; risk of magnesium toxicity 13 )

Risk-benefit should be considered when the following medical problems exist

Myasthenia gravis

(magnesium sulfate may precipitate an acute myasthenic crisis by decreasing the sensitivity of the motor endplate to acetylcholine 59, 60, 61, 62 )

>> Renal function impairment, severe 3, 4, 5, 6, 13, 38

(risk of developing hypermagnesemia and magnesium toxicity; patients with severely impaired renal function should receive no more than 20 grams of magnesium sulfate [162 mEq of magnesium] within a 48-hour period; caution is recommended against administering intravenous magnesium too rapidly in patients with oliguria or severe renal failure; 49 close monitoring of serum magnesium concentration is recommended 4, 6 )

Respiratory disease

(increased risk of respiratory depression)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Blood pressure monitoring 49

(recommended at periodic intervals)

Cardiac function monitoring (ECG) and

Magnesium concentrations, serum 13

(recommended at periodic intervals during therapy as indicated by the clinical situation; normal average serum magnesium concentrations are 1.6 to 2.6 mEq per L [0.8 to 1.2 mmol per L] 42 )

Deep tendon reflexes, especially patellar reflex or knee jerk determinations 4, 5, 6, 13

(used as an indication of CNS depression prior to administration of repeated doses; suppression of reflex may be related to impending respiratory arrest. The patellar reflex should be tested before each dose and, if the reflex is absent, no additional doses should be given until a positive response is obtained. The disappearance of the reflex is a useful sign for detecting excessive magnesium serum concentrations 34 )

Renal function determinations, especially urine output 13, 34

(recommended at periodic intervals; urine output should be at least 100 mL per 4 hours 13, 34 )

Respiration rate determination 4, 5, 6, 13

(rate should be at least 16 breaths per minute prior to each parenteral dose of magnesium sulfate, since respiratory depression is the most critical side effect of this medication, rapidly proceeding to fatal respiratory paralysis)

**Side/Adverse Effects**

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Note: Although the side/adverse effects are stratified according to serum magnesium concentrations and early signs and symptoms of hypermagnesemia, these effects may occur early or late in the course of hypermagnesemia and may not always correlate with serum magnesium concentrations. 49, 51

Those indicating need for prompt medical attention

Signs of hypermagnesemia

¾in order of increasing serum magnesium concentrations 3, 5, 6, 34, 35 :

| Effect | Serum magnesium concentration (mEq per L) |
|---|---|
| Deep tendon reflexes present, but possibly hypoactive | 4 to 7 |
| Prolonged PQ interval; widened QRS interval on ECG | 5 to 10 |
| Loss of deep tendon reflexes | 8 to 10 |
| Respiratory paralysis | 10 to 13 |
| Altered cardiac conduction | 15 |
| Cardiac arrest | 25 |

Early signs and symptoms of hypermagnesemia

Bradycardia 48; diplopia 33, 38; flushing 13, 33; headache 38; hypotension 47, 48; nausea 33, 38; shortness of breath 38; slurred speech 33; vomiting 38, 48; weakness 33, 38

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing ).

Clinical effects of overdose

For clinical effects of overdose, see signs of hypermagnesemia in Side/Adverse Effects section.

Treatment of overdose

Blood pressure and respiratory support; 13, 34 artificial respiration is often required. 3, 4, 5, 6, 13, 47

Slow injection of intravenous calcium 3, 4, 5, 6, 13, 47 gluconate, 5 to 10 mEq of calcium or 10 to 20 mL of a 10% solution 5 (diluted if desirable with 0.9% sodium chloride injection) 13 to reverse heart block or respiratory depression.
Subcutaneous administration of physostigmine (0.5 to l mg) may be helpful; 13 however, routine use is not recommended because of its toxicity.
Dialysis may be required to remove magnesium sulfate if renal function is reduced. 3, 4, 5

General Dosing Information

Magnesium sulfate injection 50% must be diluted to a concentration of 20% or less prior to intravenous infusion. 13

The rate of intravenous injection should generally not exceed 150 mg per minute, except in severe eclampsia with seizures. 13

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

MAGNESIUM SULFATE INJECTION USP

Usual adult and adolescent dose

Seizures, in toxemia of pregnancy¾
Intravenous, 4 to 5 grams (32 to 40 mEq [16 to 20 mmol] of magnesium) in 250 mL of 5% dextrose injection USP or 0.9% sodium chloride infused over thirty minutes 13, 52.

Simultaneously, intramuscular doses of up to 10 grams (5 grams or 10 mL of undiluted 50% solution in each buttock) are given. 13 Alternatively, the initial intravenous dose of 4 grams may be given by diluting the 50% solution to a 10 or 20% concentration; the diluted fluid (40 mL of a 10% solution or 20 mL of a 20% solution) may then be injected intravenously over a period of three to four minutes. 13 Subsequently, 4 to 5 grams are injected intramuscularly into alternate buttocks every four hours as needed. 13 Alternatively, after the initial intravenous dose, some clinicians administer 1 or 2 grams per hour as an intravenous infusion. 13

Hypomagnesemia¾
Severe deficiency¾
Intramuscular, 250 mg (2 mEq [1 mmol] of magnesium) per kg of body weight administered within a four-hour period. 5, 6, 13

Intravenous infusion, 5 grams (40 mEq [20 mmol] of magnesium) in 1 L of 5% dextrose injection or 0.9% sodium chloride injection, administered slowly over a three-hour period. 5, 6, 13

Mild deficiency¾
Intramuscular, 1 gram (8 mEq [4 mmol] of magnesium) as a 50% solution, administered every six hours for four doses (a total of 32.5 mEq of magnesium) per twenty-four hours. 3, 5, 6, 13

Total parenteral nutrition (TPN)¾
Intravenous infusion, 1 to 3 grams (8 to 24 mEq [4 to 12 mmol] of magnesium) a day. 13

Note: Up to 6 grams a day may be necessary in selected patients, such as in patients with short bowel syndrome. 53

[Ventricular tachycardia, polymorphous] *¾
Intravenous, 2 grams (16 mEq [8 mmol] of magnesium) given over one to two minutes; the dose may be repeated if the arrhythmia is not controlled after five to fifteen minutes. Additionally, an intravenous infusion of 3 to 20 mg per minute may be needed. 7, 9, 50

[Premature labor] *¾
Initial: Intravenous, 4 to 6 grams (32 to 48 mEq [16 to 24 mmol] of magnesium) infused over twenty to thirty minutes. 26, 27, 28, 29, 30, 31, 32, 55

Maintenance: Intravenous infusion, 1 to 3 grams (8 to 24 mEq [4 to 12 mmol] of magnesium) per hour until contractions abate. 26, 27, 28, 29, 30, 31, 32, 54, 55, 56

Note: Extreme care must be used in the parenteral administration of magnesium sulfate in order to avoid toxic serum concentrations.
Geriatric patients often require lower dosages because of reduced renal function.
An intravenous preparation of a calcium salt (e.g., 10% calcium gluconate or gluceptate) should be readily available when magnesium sulfate is administered. 3, 4, 5, 6, 13

Usual adult prescribing limits

40 grams (320 mEq [160 mmol] of magnesium) a day. 3, 5, 13

Usual pediatric dose

Total parenteral nutrition (TPN)¾
Intravenous infusion, 0.25 to 1.25 grams (2 to 10 mEq [1 to 5 mmol] of magnesium) a day. 13

Strength(s) usually available

U.S.¾10% w/v (1 gram [8 mEq of magnesium] per 10 mL) (Rx) [Generic]

12.5% w/v (1.25 grams [10 mEq of magnesium] per 10 mL) (Rx) [Generic]

50% w/v (5 grams [40 mEq of magnesium] per 10 mL) (Rx) [Generic]

Canada¾20% w/v (2 grams [16 mEq of magnesium] per 10 mL) (Rx) [Generic] 1

50% w/v (5 grams [40 mEq of magnesium] per 10 mL) (Rx) [Generic] 1

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 3.

Protect from freezing.

Incompatibilities:

Formation of a precipitate may result when magnesium sulfate is mixed with solutions containing: 13

Alcohol (in high concentrations)
Alkali carbonates and bicarbonates
Alkali hydroxides
Arsenates
Barium
Calcium
Clindamycin phosphate
Heavy metals
Hydrocortisone sodium succinate
Phosphates
Polymyxin B sulfate
Procaine hydrochloride
Salicylates
Strontium
TartratesThe potential for incompatibility will often be influenced by changes in the concentration of reactants and the pH of the solutions. 13

Separation of intravenous fat emulsions may occur with concentrations of magnesium greater than 20 mEq per mL in total parenteral nutrition admixtures. 53

It has been reported that magnesium may reduce the antibiotic activity of streptomycin, tetracycline, and tobramycin when given together. 13