pharmaniaga®

Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion

COMPOSITION

Each ampoule contains 2.465g of magnesium sulfate heptahydrate (493mg/mL) with strength of 49.3%.

Each mL of injections contains 2mmol (4mEq) of magnesium ions and 2mmol (4mEq) of sulfate ions.

Excipients: Sodium Hydroxide, Sulfuric Acid (q.s. pH 5.5 to 7.0) and Water for Injection to 5mL.

DESCRIPTION

Clear, colourless sterile solution.

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion is compatible with the following infusion solutions:

- 0.9% sodium chloride solution
- 5% dextrose solution
- Lactated Ringer's solution
- 5% dextrose in 0.9% sodium chloride solution

The solution should be clear, colourless when diluted.

After preparation, the solution must be used within 24 hours and stored below 30°C.

PHARMACODYNAMICS

Pharmacotherapeutic group: Electrolyte solutions

ATC code: B05XA05 – magnesium sulfate

Magnesium is the second most abundant cation in intracellular fluid. It is an essential cation in over 300 enzymatic processes, and is necessary for several steps in glycolysis, the Krebs cycle and in protein and nucleic acid synthesis. It is thus vital for normal energy storage and transfer. Magnesium plays an important role in neurochemical transmission, and is essential for proper neurochemical functioning.

Magnesium has an anticonvulsant effect. Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the amount of acetylcholine liberated at the endplate by the motor nerve impulse. Magnesium is said to have a depressant effect on the central nervous system (CNS), but it does not adversely affect the woman, foetus or neonate when used as directed in eclampsia or pre-eclampsia. Normal plasma magnesium level ranges from 1.5 to 2.5 mEq/L.

It possibly has antiarrhythmic effects and a role in calcium homeostasis and bone mineralisation. There is conflicting evidence that the routine use of intravenous magnesium sulfate is the setting of acute myocardial infarction is beneficial. Deficiency of magnesium is closely associated with other electrolyte disturbances, particularly hypocalcaemia and hypokalaemia. The specific symptoms of hypomagnesaemia are therefore difficult to determine, but may include nausea, vomiting, muscle weakness, neuromuscular dysfunction such as paraesthesia, tremor and cramp, tachycardia and cardiac arrythmia.

Magnesium acts peripherally to produce vasodilation. With low doses only flushing and sweating occur, but larger doses cause lowering of blood pressure. The central and peripheral effects of magnesium poisoning are antagonized to some extent by IV administration of calcium.

Cardiac Electrophysiology: Slows rate of SA node impulse formation in myocardium and prolongs conduction time. Promotes movement of calcium, potassium, and sodium in and out of cells and stabilizes excitable membranes. Hypermagnesaemia can cause the following ECG changes: prolonged PR, QRS and QT intervals.

PHARMACOKINETICS

Approximately 50% of magnesium in the body is found in bone, with the majority of the remainder stored in muscle and soft tissue. 1% or less is contained in the extracellular compartment, of which approximately 33% is protein-bound, with a further 12% bound to anions.

Magnesium is primarily excreted in the urine, with small amounts excreted to faeces, saliva and breast milk. Over 90% of magnesium filtered by the kidneys is reabsorbed, mainly in the ascending limb of the Loop of Henle, with significant amounts also absorbed in the proximal and distal tubules. The clearance is proportional to the plasma magnesium concentration and the glomerular filtration rate. The onset of action after intramuscular injection is about 1 hour and after intravenous injection is nearly immediate. The duration of action after intramuscular injection 3 to 4 hours, and after intravenous injections is about 30 minutes.

Upon intramuscular administration, the plasma concentration of magnesium sulfate shows a slow increase that reaches a plateau within 1 to 2 hours and is followed by a slow decline back to baseline within the next 6 to 8 hours. At the end of 4 hours, after another intramuscular injection of magnesium sulphate, the plasma concentration remains constant.

Plasma protein binding of injected magnesium is comparable to endogenous magnesium.

The unbound magnesium ions diffuse into the extravascular-extracellular space, bones, cross the placenta and are rapidly taken up by foetal tissues and thus magnesium in amniotic fluid, the foetus and in neonates of mothers treated with magnesium sulfate show increased concentrations as compared to untreated mothers.

When the mother receives 1 to 2 g/h magnesium infusions, foetal serum magnesium concentrations are twice as high as control concentrations, the highest concentrations observed in umbilical and venous and arterial blood. Foetal magnesium plasma concentrations equalise with the maternal within 2 hours, while the increase in amniotic fluid occurs more slowly. The mean baseline cerebrospinal fluid (CSF) magnesium level in preeclamptic women was 1.1 ± 0.05 mmol/L.

Intrapartum magnesium sulfate treatment increased breast milk/colostrum magnesium levels significantly only for 24 hours. After 24 hours magnesium levels in breast milk comes back to normal. Breast milk/colostrum calcium levels were not affected by magnesium sulfate therapy.

Biotransformation and Elimination

Magnesium sulfate is not metabolised and is excreted solely by the kidney.

Urinary excretion is very rapid with a 20-fold increase during magnesium sulfate infusion. About 38 to 53% of the total injected magnesium is excreted 4 hours after the end of the infusion and >90% are eliminated within 24 hours after the infusion.

In patients with normal renal function, the increase in magnesium clearance is linear to the serum magnesium concentrations and the half-life of magnesium is 4 hours. Half-life increases with decrease in glomerular filtration rate.

Urinary calcium concentration increases 4.5-fold during infusion of magnesium sulfate and there is a 3-fold increase in urinary calcium excretion rate which is likely due to competition for common reabsorption sites.

INDICATIONS

Parenteral administration of magnesium is indicated in:
- treatment and prophylaxis of acute hypomagnesaemia.
- prevent hypomagnesaemia in patients receiving total parenteral nutrition.
- prevention and treatment of life-threatening seizures in the treatment of toxaemias of pregnancy (pre-eclampsia and eclampsia).

RECOMMENDED DOSAGE

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion is administered intravenously or intramuscularly.

For Intravenous doses: Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion should be diluted to concentration of 20% magnesium or less. For Intravenous dosing, each 5mL ampoule should be diluted by adding at least 7.5mL of a compatible solution.

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusionis compatible with the following infusion solutions:

- 0.9% sodium chloride solution
- 5% dextrose solution
- Lactated Ringer's solution
- 5% dextrose in 0.9% sodium chloride solution

For Intramuscular doses: A concentration of 25% to 50 % is satisfactory for adults, while a concentration of 20% should be used for infants or children. For adult intramuscular administration dilution is not required, but each 5mL ampoule could be diluted by adding up to 5mL of compatible solution.

The dose of magnesium should be adjusted according to the patient's individual requirements and response.

The total adult daily dose should not exceed 30 to 40 g of magnesium sulfate per day.

Mild Hypomagnesaemia: Adult: A dose of 1g magnesium sulfate (8 mEq) intramuscularly every 6 hours for 4 doses is recommended.

Severe Hypomagnesaemia: Adult: A dose of 0.25 g/kg magnesium sulfate intramuscularly over 4 hours is recommended. Alternatively, a dose of 5 g may be given by slow intravenous infusion over 3 hours.

For Total Parenteral Nutrition use:

Adults: A dose of 0.5 to 3.0 g magnesium sulfate (4 to 24 mEq) daily may be administered.

Infants: A dose of 0.25 to 1.25 g magnesium sulfate (2 to 10mEq) daily may be administered.

Toxaemia of Pregnancy

An initial intravenous dose of 4 g magnesium sulfate is recommended. This is followed by an intramuscular dose of 4 to 5 g into each buttock. This may be followed by a dose of 4 to 5 g into alternate buttocks every four hours as needed. Alternatively, the initial IV dose may be followed by an infusion of 1 to 2 g/hr.

Geriatrics

Geriatric patients often require reduced dosage because of impaired renal function. In patients with severe impairment, dosage should not exceed 20 g in 48 hours. Serum magnesium should be monitored in such patients.

ROUTE OF ADMINISTRATION

Magnesium sulfate is administered intravenously or intramuscularly.

CONTRAINDICATIONS

Magnesium sulfate is contraindicated in patients with:
- Known hypersensitivity to magnesium and its salts
- Heart block or myocardial damage since magnesium may exacerbate this condition
- Renal failure (creatinine clearance <20 mL/min), since there is an increased risk of hypermagnesaemia in these patients.
- Hepatic encephalopathy
- Hepatic failure
- Myasthenia gravis

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion should not be administered to pregnant women in the two hours prior to delivery, unless it is the only therapy available to prevent eclamptic seizures. There is a risk that the neonate will be born with hypermagnesaemia and depressed breathing.

WARNINGS AND PRECAUTIONS

Magnesium should be administered with caution in patients with impaired renal function, since the risk of hypermagnesaemia is increased in these patients.

Magnesium sulfate should not be used in hepatic coma if there is a risk of renal failure.

Monitoring serum magnesium levels and the patient's clinical status is essential to avoid the consequences of overdosage in toxaemia. Clinical indications of a safe dosage regimen include the presence of the patellar reflex (knee jerk) and absence of respiratory depression (approximately 16 breaths or more/min). When repeated doses of the drug are given parenterally, knee jerk reflexes should be tested before each dose and if they are absent, no additional magnesium should be given until they return. Serum magnesium levels usually sufficient to control convulsions range from 3 to 6 mg/100 mL (2.5 to 5 mEq/L). The strength of the deep tendon reflexes begins to diminish when magnesium levels exceed 4 mEq/L. Reflexes may be absent at 10 mEq magnesium/L, where respiratory paralysis is a potential hazard. An injectable calcium salt should be immediately available to counteract the potential hazards of magnesium intoxication in eclampsia.

Magnesium sulfate may precipitate an acute myasthenic crisis. Sensitivity to parenteral magnesium has been reported.

An intravenous preparation of a calcium salt (e.g. calcium gluconate) should be readily available for use when magnesium sulfate is given intravenously.

Administer with caution if flushing and sweating occurs. When barbiturates, narcotics or other hypnotics (or systemic anaesthetics) are to be given in conjunction with magnesium, their dosage should be adjusted with caution because of additive CNS depressant effects of magnesium.

Serum calcium levels should be routinely monitored in patients receiving magnesium sulfate.

Laboratory Tests: Monitoring of serum magnesium levels is advised at periodic intervals during therapy to ensure that normal serum magnesium levels are not exceeded.

The patellar reflex should be tested prior to administering repeat doses of magnesium sulfate.

Suppression of the reflex is an indication of magnesium intoxication.

Respiration rate should be determined and should be at least 16 per minute prior to each dose of magnesium sulfate, as respiratory depression is the most critical side effect of the medication.

Urine output should be monitored and should be at least 100 mL during the four hours preceding dosing, to ensure adequate excretion of magnesium.

INTERACTION WITH OTHER MEDICAMENT

Aminoglycoside: Streptomycin sulfate and tetramycin sulfate activity is inhibited by magnesium ions.

Cardiac glycosides/ digitalis: Magnesium salts should be administered with caution in patients treated with cardiac glycosides, since heart block may occur if calcium salts are required to treat magnesium toxicity. (See OVERDOSAGE)

Calcium channel blockers: Potentially increases the risk of hypotension when given with calcium channel blockers (amlodipine, clevidipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, verapamil) in pregnant women. Concomitant use of calcium channel blockers may rarely lead to a calcium ion imbalance and could result in abnormal muscle function.

CNS depressants: Concurrent use of magnesium salts and CNS depressant drug may result in an enhanced CNS depressant effect. The action of non-depolarizing muscle relaxants such as tubocurarine is potentiated and prolonged by parenteral magnesium salts. Thus, when CNS depressants are to be given in conjunction with magnesium, their dosage should be adjusted with caution.

Neuromuscular blocking agents: Concurrent use of magnesium salts with neuromuscular blocking agents may result in an excessive neuromuscular blockade.

Nifedipine: Concurrent use of magnesium sulfate and nifedipine may result in an exaggerated hypotensive response.

Suxamethonium: Predicted to increase the effects of suxamethonium.

INCOMPATIBILITIES

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusionis incompatible with calcium salts. Calcium sulfate may precipitate when calcium salts are mixed with magnesium sulfate in the same intravenous solution.

Magnesium salts have also been reported to be incompatible with alkali carbonates and bicarbonates and soluble phosphates.

USE IN PREGNACY AND LACTATION

Pregnancy

Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusionmay be administered to pregnant women to treat seizures associated with severe pre-eclampsia. Magnesium sulfate readily crosses the placenta. Foetal serum concentrations approximate those of the mother. When used in pregnant women, foetal heart rate should be monitored. If magnesium sulfate is administered in the two hours preceding delivery, the neonate may be born with signs of hypermagnesaemia, including respiratory depression, and therefore magnesium sulfate should not be given in the two hours preceding delivery unless it is the only therapy available to prevent or treat eclamptic seizures.

Bony abnormalities and congenital rickets have been reported in neonates born to mothers treated with parenteral magnesium sulfate for prolonged periods of time (5 to 7 days duration).

When used for hypomagnesaemia or arrhythmias or prevention of seizures in pre-eclampsia or treatment of seizures and prevention of seizures recurrence in eclampsia or severe acute asthma, it is not known to be harmful for short-term intravenous administration of eclampsia, but excessive doses in third trimester cause neonatal respiratory depression.

Lactation

After intravenous administration, magnesium is distributed into breast milk, and the concentration of magnesium in the breast milk is approximately twice that in the maternal serum. Magnesium salts should therefore be used with caution in lactating patients. However, magnesium is cleared from the breast milk within 24 hours of the cessation of the infusion.

Labour and Delivery

Continuous administration of magnesium sulfate is an unapproved treatment for preterm labour. The safety and efficacy of such use have not been established. The administration of magnesium sulfate outside of its approved indication in pregnant women should be by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.

ADVERSE EFFECTS

Excessive administration of magnesium sulfate may result in hypermagnesaemia. The signs of hypermagnesaemia may include: nausea, vomiting, flushing, hypotension, muscle weakness, muscle paralysis, blurred or double vision, CNS depression and loss of reflexes. More severe hypermagnesaemia may result in respiratory depression, respiratory paralysis, renal failure, coma, cardiac arrhythmias and cardiac arrest. Hypocalcaemia with tetany, secondary to hypermagnesaemia, has been reported.

Hypersensitivity reactions may occur in some patients receiving the treatment.

After intramuscular injection, irritation and pain at the injection site may occur.

SYMPTOMS AND TREATMENT OF OVERDOSE

Clinical Features

Hypermagnesaemia may occur when large doses of magnesium are given, especially in patients with renal failure. Signs of hypermagnesaemia include: nausea, vomiting, flushing, hypotension, muscle weakness, muscle paralysis, blurred or double vision, CNS depression and loss of reflexes. More severe hypermagnesaemia may result in respiratory depression respiratory paralysis, renal failure, coma, cardiac arrhythmias and cardiac arrest.

Treatment of Overdose

In the treatment of hypermagnesaemia, the following measures may be required:

- Blood pressure and respiratory support.
- Intravenous administration of 2.5 to 10 mmol calcium salts (such as calcium gluconate) reverse the effects of magnesium toxicity.
- Dialysis may be required, particularly if renal function is impaired.
- If renal function is normal, adequate fluids should be given so that urine output is at least 60 mL/hr to assist removal of magnesium from the body.
- Physostigmine (0.5 to 1.0 mg subcutaneously) may be helpful, but routine use is not recommended due to the potential toxicity.

EFFECTS ON ABILITY TO DRIVE AND USE OF MACHINE

No studies on the effects on the ability to drive and use machines have been performed.

INSTRUCTIONS FOR USE

Once used, discard any remaining solution.

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STORAGE CONDITIONS

Store below 30°C.

Infusion solution	Period of stability (hours)
5% dextrose infusion	24 hours
0.9% sodium chloride solution	
Lactated Ringer's solution	
5% dextrose in 0.9% sodium chloride solution	

SHELF LIFE:

The injection can be used within 36 months from the date of manufacture if kept as recommended.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not longer than 24 hours at temperature below 30°C.

DOSAGE FORM AND PACKAGING AVAILABLE

10 x 5mL ampoule (clear glass ampoule) of Pharmaniaga Magnesium Sulfate Concentrate 49.3% w/v Solution for Injection or Infusion.

10 ampoules per unit PVC tray were packed in carton.

PRODUCT REGISTRATION HOLDER/ MANUFACTURER

PHARMANIAGA LIFESCIENCE SDN BHD (198201002939)

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