Review Article

Magnesium, a drug of diverse use

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Abstract

Magnesium has evolved as a drug with diverse clinical applications. Mg++ is an important caution and its homeostasis is very important for normal body functioning. The physiological role of Mg is due to its calcium channel blocking properties at smooth muscle, skeletal muscle and conduction system levels. The analgesic properties are due to NMDA receptor blocking action. Mg++ is beneficial in acute Myocardial Infarction, protection during open heart surgery and treatment and prevention of heart rhythm disturbances. Mg has an established role in the management of preeclampsia and eclampsia. Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the release of acetylcholine at the motor nerve terminals. The use of MgSo4 in treating tetanus and acute asthma is established.

In conclusion, Mg is a cost effective, widely used drug with multidisciplinary applications. Its majority of physiological effects are attributed to calcium channel blocking properties.

Keywords: Magnesium, Homeostasis, Calcium channel, Conduction system, Acute Myocardial Infarction.

Introduction

Magnesium is a drug with multiple clinical applications .Its role in anaesthesia, ICU and obstetrics is well established. The purpose of writing this review article is to give a holistic view about the clinical importance of magnesium.

We performed a literature review with the purpose of finding the recent evidence based clinical facts about magnesium. In this review, the drug will be discussed with regard to its regulation, physiological role and pharmacological uses. The pharmacological actions are discussed under the heading of cardiovascular, anaesthesia, obstetrics and last but not the least ICU. In intensive care unit, it has applications in the management of acute severe asthma and tetanus.

Magnesium Balance:

Magnesium intake is 20-30 meq/day (240-370 mg/day) in adults. Only 1-2% of total magnesium stores in ECF compartment; 67% is contained in the bone whereas 31% is intracellular. Of the total amount taken, 30-40% is absorbed in the distal small bowel.

Magnesium reabsorption by the kidneys is very efficient; 25% of filtered Mg is reabsorbed in the proximal convoluted tubule, whereas 50-60 % is reabsorbed in the thick ascending limb of the loop of Henle. Factors known to increase Mg reabsorption in the kidneys include hypomagnesaemia, parathyroid hormone, hypocalcaemia, hypovolaemia and metabolic alkalosis. Factors known to increase renal excretion include hypermagnesaemia, acute volume expansion, hyperaldosteronism, hypercalcaemia, ketoacidosis and diuretics.[1] Kidneys are the primary route of elimination which averages 6-12 meq/day.

Plasma Mg is closely regulated between 1.7-2.1 meq/L (.7-1 mmol/l or 1.7-2.4 mg/dl). This regulation of plasma levels involve interaction between gut (absorption), bone (storage) and kidneys (excretion).[1]

Magnesium deficiency is multifactorial. Magnesium deficiency has been demonstrated in 7-11% of hospitalized patients and co-exists with other electrolyte imbalances including potassium and phosphate in 40% of cases and to a lesser extent with sodium and calcium.[2] Absorption of both magnesium and calcium are inter-related ,with concomitant deficiencies of both ions well described. Hypocalcaemia enhances the secretion of parathyroid hormone (PTH). Hypomagnesaemia impairs hypocalcaemia induced PTH release, which is corrected within minutes of magnesium infusion Magnesium is also required for the sensitivity of target tissues to PTH and vitamin D metabolites. In addition to interactions with calcium, magnesium has a major effect on the regulation of transmembrane sodium and potassium movement. [2]

It has been proved by a clinical trial that ionized Mg is a better indicator of magnesium balance in the body than the total Mg concentration.[3] Hence more importance should be given to ionized Mg level than to total Mg comcentration.

Magnesium Toxicity:

Magnesium toxicity is very rare except in certain instances where renal failure prevents urinary excretion (i.e., in the situation where magnesium-containing drugs are given to a patient with renal dysfunction). Symptoms include central nervous system depression, skeletal muscle paralysis, and in extreme cases, coma and death. As plasma magnesium rises above 4 mEq/liter, the deep tendon reflexes are first decreased and then disappear as the plasma level approaches

10 mEq/liter. At this level respiratory paralysis may occur. Heart block can also be caused by the low plasma levels of magnesium. Serum magnesium concentrations in excess of 12 mEq/L may be fatal.

The antidote for magnesium toxicity is calcium gluconate (10mL of 10% solution over 10 minutes) by slow intravenous injection. The patient requires ECG monitoring during and after administration because of the potential for cardiac arrhythmias. Resuscitation and ventilator support should be available during and after dose administration of both magnesium sulphate and calcium gluconate.

Physiological Role:

Magnesium is an important caution that functions as a cofactor in many enzyme pathways.

Mg modulates and controls cell calcium entry and calcium release from sarcoplasmic and endoplasmic reticular membranes. This calcium transportation control is responsible for its numerous physiological roles among which are control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vasomotor tone, blood pressure and peripheral blood flow.

The physiological role of Mg is due to its calcium channel blocking properties at smooth muscle, skeletal muscle and conduction system levels. The analgesic properties are due to NMDA receptor blocking action.

Its physiological clinical applications are discussed below.

Cardiovascular Role of Magnesium:

Magnesium is an oligo-element which has an important effect on the myocardial function and peripheral vascular system. Magnesium influences blood pressure by modulating vascular tone and structure through its effects on myriad biochemical reactions that control vascular contraction/dilation, growth/apoptosis, differentiation and inflammation. Magnesium acts as a calcium channel antagonist, it stimulates production of vasodilator prostacyclins and nitric oxide and it alters vascular responses to vasoconstrictor agents.[4]

Changes in serum Mg concentration occur intraoperatively as evident from the study conducted at Med University of Poland.

Twenty male patients, aged 50-69, undergoing on pump CABG under general anaesthesia, were included in the study. All of them were operated on due to coronary disease . The blood concentrations of Mg were examined in five stages: 1) before the induction of anaesthesia; 2) during extracorporeal circulation; 3) after surgery; 4) in the morning of the first postoperative day; 5) in the morning of the second postoperative day. The blood Mg concentrations were determined by spectrophotometric methods. The blood concentration of Mg decreased during extracorporeal circulation and immediately after surgery and increased in the morning of the first and second postoperative days. The CABG with extracorporeal circulation resulted in a significant decrease in blood Mg concentration.[5]

Various rhythm disturbances, particularly Torsade de points are related to hypomagnesaemia. Intravenous magnesium has been used to prevent and treat many different types of cardiac arrhythmia. It has diverse electrophysiological actions on the conduction system of the heart; including prolonging sinus node recovery time, and reducing automaticity, atrioventricular nodal conduction, antegrade and retrograde conduction over an accessory pathway, and His-ventricular conduction. Intravenous magnesium can also homogenise transmural ventricular repolarisation. Because of its unique and diverse electrophysiological actions, intravenous magnesium has been reported to be useful in preventing atrial fibrillation and ventricular arrhythmias after cardiac and thoracic surgery; in reducing the ventricular response in acute onset atrial fibrillation, including for patients with Wolff-Parkinson-White syndrome; in the treatment of digoxin induced supraventricular and ventricular arrhythmias, multifocal atrial tachycardia, and polymorphic ventricular tachycardia (Torsade de points) or ventricular fibrillation from drug overdoses. Intravenous magnesium is, however, not useful in monomorphic ventricular tachycardia and shock-resistant ventricular fibrillation. Large randomised controlled studies are needed to confirm whether intravenous magnesium can improve patient centre outcomes in different cardiac arrhythmias.[6]

Magnesium is recommended for pulseless ventricular tachycardia or fibrillation that resembles torsades de pointes. The mechanism of action for magnesium for torsades de pointes is not clearly established but thought to shorten the action potential through myocardial potassium channels. A dosage of 1 to 2g diluted in 10mL of 5% dextrose in water given over 5 to 20 minutes is recommended. Rapid administration is associated with hypotension, which is frequently reversible by administration of calcium

The antihypertensive properties are attributed to its calcium channel blocking properties Magnesium status has a direct effect upon the relaxation capability of vascular smooth muscle cells and the regulation of the cellular placement of other cations important to blood pressure - cellular sodium:potassium (Na:K) ratio and intracellular calcium (iCa(2+)). As a result, nutritional magnesium has both direct and indirect impacts on the regulation of blood pressure and therefore on the occurrence of hypertension.[7]

It has been proved that magnesium supplementation in paediatric patients undergoing cardiac surgery prevent the occurance of junctional ectopic tachycardia.[8]

Pulmonary Hypertension and MG:

PH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest and > 30 mmHg during exercise.[9]

Magnesium is a potent vasodilator and hence has the potential to reduce the high pulmonary arterial pressures associated with persistent pulmonary hypertension (PPHN).To see the effects of magnesium in newborn with persistent pulmonary hypertension of newborn (PPHN) who did not respond to mechanical hyperventilation and are candidates for Extra Corporeal Membrane Oxygenation (ECMO), ten newborns who were admitted to Neonatal Intensive Care Unit (NICU) with profound hypoxia and respiratory failure due to PPHN were treated with conventional mechanical ventilation and then mechanical hyperventilation. The newborns who did not respond to mechanical hyperventilation were treated with magnesium sulphate infusion. Nine out of ten babies survived and one of them died. The differences between the mean AaDo2, oxygenation index, and PH after mechanical hyperventilation and magnesium sulphate administration was significant.Magnesium has a role in the treatment of PPHN patients who do not respond to hyperventilation.[10]

The standard search strategy of the Cochrane Neonatal Review Group (CNRG) was used for this role of Mg. The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006) and MEDLINE (1966 to April 20, 2007) were searched for relevant randomized and quasi-randomized trials.Magnesium sulfate is able to dilate constricted muscles of the type in the pulmonary arteries. However, its action is not specific and when given via an intravenous infusion, it will act on other muscles in the body including other arteries. This means that even if it were found to be effective in pulmonary hypertension, unwanted actions in other parts of the body might be a problem.

This review found that the use of magnesium sulfate for persistent pulmonary hypertension of the newborn has not been tested by randomized controlled trials. In order to establish a potential benefit, randomized controlled trials are recommended.

Role in Obstetrics:

Mg has an established role in the management of preeclampsia and eclampsia. Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the release of acetylcholine at the motor nerve terminals. Its antihypertensive action is attributed to its calcium channel blocking action.

Eclampsia and pre-eclampsia are important causes of morbidity and mortality during pregnancy childbirth and puerperium.[11] The prevention of seizure activity in pre-eclampsia and recurrent seizures in eclampsia is an essential aspect of management. A number of different anticonvulsants are used to control eclamptic fits and to prevent future seizures. In North America, parenteral magnesium sulphate is the drug of choice for the prevention and treatment of eclamptic convulsions.[12] Magnesium sulphate appears to act as a cerebral vasodilator (particularly on the small diameter vessels) in patients with pre eclampsia. With its potential to relieve cerebral ischaemia this vasodilatation may help explain why magnesium sulphate has anti seizure activity in pre-eclampsia.[13] Its dosing schedules and effectiveness however is empiric, because no randomized trials have demonstrated whether it works and what is the therapeutic level that might prevent seizure, but a value of 3-6mg% is taken as therapeutic .

Magnesium administration to obstetric patients at increased risk of preterm birh provide neuroprotection to preterm babies as evident from multiple studies.[14,15]

Use of magnesium for the treatment of preterm labour is an unlabeled use of the medicine. Magnesium sulfate is sometimes used as a tocolytic medicine to slow uterine contractions during preterm labour. But studies show it does not stop preterm labour and it may cause complications for both mother and baby.[16]

Since magnesium sulfate relaxes most muscles, babies who have been exposed to magnesium for an extended period of time may be listless or floppy at birth. This effect typically goes away as the drug clears from the baby's system.

Women with medical conditions that could be made worse by the side effects described above should not be given magnesium sulfate or similar drugs. This includes women with myasthenia gravis (a muscle disorder) or muscular dystrophy.

Role in Intensive Care Unit:

Magnesium (Mg) deficiency commonly occurs in critical illness and correlates with a higher mortality and worse clinical outcome in the intensive care unit (ICU).[17]

A retrospective study was done on 100 patients ≥ 16 years age, admitted to the medical-surgical intensive care unit (ICU) at the University Hospital over a 2 years period. Observations were made on admission total serum magnesium level, a variety of lab tests related to magnesium, need for ventilator, duration of mechanical ventilation, hospital/ICU lengths of stay, and general patient

demographics. It was concluded that development of hypomagnesaemia during an ICU stay is associated with a guarded prognosis. Monitoring of serum magnesium levels may have prognostic, and perhaps therapeutic, implications.[18]

A-Magnesium and Tetanus:

The most common cause of death in individuals with severe tetanus in the absence of mechanical ventilation is spasm-related respiratory failure, whereas in ventilated patients it is tetanus-associated autonomic dysfunction. A randomized double blinded placebo controlled study was conducted to find whether continuous magnesium sulphate infusion reduces the need for mechanical ventilation and improves control of muscle spasms and autonomic instability. There was no difference in requirement for mechanical ventilation between individuals treated with magnesium and those receiving placebo (odds ratio 0.71, 95% CI 0.36-1.40; p=0.324); survival was also much the same in the two groups. However, compared with the placebo group, patients receiving magnesium required significantly less midazolam (7.1 mg/kg per day [0.1-47.9] vs 1.4 mg/kg per day [0.0-17.3]; p=0.026) and pipecuronium (2.3 mg/kg per day [0.0-33.0] vs 0.0 mg/kg per day [0.0-14.8]; p=0.005) to control muscle spasms and associated tachycardia. Individuals receiving magnesium were 4.7 (1.4-15.9) times less likely to require verapamil to treat cardiovascular instability than those in the placebo group. The incidence of adverse events was not different between the groups.It was concluded that Magnesium infusion does not reduce the need for mechanical ventilation in adults with severe tetanus but does reduce the requirement for other drugs to control muscle spasms and cardiovascular instability.[19]

B-Magnesium and Asthma:

In allergic asthma there is an increase IgE stimulation leading to histamine release. Histamine causes bronchospasm by calcium mediated smooth muscle contraction. Magnesium antagonizes the bronchospasm by its calcium blocking properties.

Asthma exacerbations can be frequent and range in severity from relatively mild to status asthmaticus. The use of magnesium sulphate (MgSO4) is one of numerous treatment options available during acute exacerbations. While the efficacy of intravenous MgSO4 has been demonstrated, little is known about inhaled MgSO4. Randomised controlled trials were identified from the Cochrane Airways Group "Asthma and Wheeze" register. These trials were supplemented with trials found in the reference list of published studies. These studies were found using extensive electronic search techniques, as well as a review of the gray literature and conference proceedings. Six trials involving 296 patients were included. Four studies compared nebulised MgSO4 with beta2-agonist to beta2-agonist and two studies compared MgSO4 to beta2-agonist alone. Three studies enrolled only adults and 2 enrolled exclusively paediatric patients. Three of the studies enrolled severe asthmatics. Overall, there was a significant difference in pulmonary function between patients whose treatments included nebulised MgSO4 in addition to beta2-agonist however, hospitalisations were similar between the groups. Subgroup analyses did not demonstrate significant differences in lung function improvement between adults and children, or between severe and mild to moderate asthmatics. Conclusions regarding treatment with nebulised MgSO4 alone are difficult to draw due to lack of studies in this area. Nebulised inhaled magnesium sulphate in addition to beta2-agonist in the treatment of an acute asthma exacerbation, appears to have benefits with respect to improved pulmonary function and there is a trend towards benefit in hospital admission. Heterogeneity between trials included in this review precludes a more definitive conclusion.[20]

Five randomised placebo controlled trials involving a total of 182 patients were identified. They compared intravenous magnesium sulphate to placebo in treating paediatric patients with moderate to severe asthmatic attacks in the emergency department, with co-therapies of inhaled beta2 agonists and systemic steroids. Intravenous magnesium sulphate probably provides additional benefit in moderate to severe acute asthma in children treated with bronchodilators and steroids.[21]

Magnesium and Laryngoscopic Intubation Response:

The role of magnesium in blunting the intubation response is evolving. Magnesium has direct vasodilating properties on coronary arteries and inhibits catecholamine release, thus attenuating the haemodynamic effects during endotracheal intubation.[22] Magnesium is also a physiological antagonist of calcium, which plays an important role in catecholamine release in respose to sympathetic stimulation. Puri et al found magnesium to be better in blunting the pressor response to endotracheal intubation as well as producing less ST changes in coronary artery disease patients coming for CABG surgery.[23]

A study was conducted to to find optimal dose of magnesium that causes decreased cardiovascular responses after laryngoscopy and endotracheal intubation.

In a double-blind, randomized, clinical trial, 120 ASA-1 patients with ages between 15-50 years, who were candidates for elective surgery, were selected and classified in 6 groups (20 patients in each). The pulse rate and arterial blood pressure were measured and recorded at 5 minutes before taking any drug then, according to different groups,

patients took magnesium sulphate was same in all groups and the pulse rate and arterial blood pressure were measured and recorded just before intubation and also at 1, 3, and 5 minutes after intubation (before surgical incision). There were no statistically significant differences in blood pressure, pulse rate, Train Of Four (TOF), and complications between groups who received magnesium but the significant differences in these parameters were seen between magnesium and Lidocaine groups.

It was concluded that pretreatment with different doses of magnesium have a safe decreasing effect on cardiovascular responses that is more effective than pretreatment with Lidocaine.[24]

Magnesium in Reducing Analgesic Requirements:

Effective treatment of peri- and post-operative pain represents an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. It has become common practice to employ a polypharmacological approach to the treatment of postoperative pain, because no agent has yet been identified that specifically inhibits nociception without associated side effects.

Magnesium is a calcium channel blocker and non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with antinociceptive effects.[25] Magnesium sulphate has been investigated as a possible adjuvant for intra- and postoperative analgesia in different kind of surgeries including gynaecological, orthopaedic and thoracic etc . The majority of the studies suggest that perioperative magnesium sulphate reduces anaesthetic requirements and improves postoperative analgesia. However, some studies have concluded that magnesium sulphate has limited or no effect.

Intravenous Regional Anaesthesia (IVRA) Using Lidocaine and Magnesium:

IV regional anaesthesia (IVRA) is one of the simplest forms of regional anaesthesia and has the most frequent success. However, IVRA has been limited by tourniquet pain and its inability to provide postoperative analgesia.[26] To improve block quality, prolong postdeflation analgesia, and decrease tourniquet pain, different additives have been combined with local anaesthetics, with limited success.

The mechanism of action of magnesium as an adjunct to IVRA is obviously multifactorial. The different possible mechanisms of action of magnesium (other than those mentioned in the introduction) have been discussed. Studies have reported that magnesium has an endothelium-derived nitric oxide-induced vasodilatory effect. Nitric oxide causes an activation of guanyl cyclase and an increase in cyclic guanine monophosphate, which mediates the relaxation of vascular smooth muscles. Nitric oxide is also a potent inhibitor of neutrophil adhesion to vascular endothelium.

A study was conducted at Department of Anaesthesiology and Reanimation, Medical Faculty, Trakya University, Edirne, Turkey to evaluate the effects of magnesium, when added to lidocaine for IV regional anaesthesia (IVRA), on tourniquet pain. Thirty patients undergoing elective hand surgery during IVRA were randomly assigned to two groups. IVRA was achieved with 10 mL of saline plus 3 mg/kg lidocaine 0.5% diluted with saline to a total of 40 mL in group C or with 10 mL of 15% magnesium sulphate (12.4 mmol) plus 3 mg/kg lidocaine 0.5% diluted with saline to a total of 40 mL in group M. Anaesthesia quality, as determined by the anaesthesiologist and surgeon, was better in group M ($P < 0.05$). Time to the first postoperative analgesic request in group C was 95 ± 29 min and in group M was 155 ± 38 min ($P < 0.05$). Diclofenac consumption was significantly less in group M (50 ± 35 mg) when compared with group C ($130 + 55$ mg) ($P < 0.05$). It was concluded that magnesium as an adjunct to lidocaine improves the quality of anaesthesia and analgesia in IVRA.[27]

Magnesium and Shivering:

Hypothermia may be an effective treatment for stroke or acute myocardial infarction; however, it provokes vigorous shivering, which causes potentially dangerous haemodynamic responses and prevents further hypothermia. Magnesium is an attractive anti-shivering agent because it is used for treatment of postoperative shivering and provides protection against ischaemic injury in animal models. We tested the hypothesis that magnesium reduces the threshold (triggering core temperature) and gain of shivering without substantial sedation or muscle weakness.

Magnesium significantly reduced the shivering threshold. However, in view of the modest absolute reduction, this finding is considered to be clinically unimportant for induction of therapeutic hypothermia.[28]

The Role of Magnesium in Pheochromocytoma:

Magnesium has got anti- adrenergic actions. These anti- adrenergic actions are secondary to multiple mechanisms of which calcium antagonism is one mechanism Calcium is responsible for stimulus response coupling increase in catecholamine release from adrenal medulla and adrenergic nerve terminals These anti-adrenergic actions along with antiarrythmic and vasodilator properties have led to the role of Mg in surgery for pheochromocytoma.[29-32]

In one of the clinical trial, the study group was given intravenous Magnesium sulphate 60mg/kg before intubation.

The study group showed markedly less increase in catecholamine surge after intubation and less change in heart rate and systolic blood pressure in comparison with the control group.

Conclusion

On the basis of literature review it is concluded that Magnesium can contribute in reducing the intraoperative anaesthetic requirement. MgSO4 reduces analgesic and muscle relaxant requirement and hence reduces the anaesthetic cost. The serum concentration of magnesium ions after administration of MgSO4 remains significantly higher in patients pretreated with MgSO4 according to dosage. The incidence of both postoperative arrhythmias and postoperative low cardiac index (<2.5l/min/m2) was statistically significantly more frequent in hypomagnesaemic patients ($p<0.05$) after cardiopulmonary bypass. Magnesium has a positive effect on neuromuscular block, provides a better quality of anaesthesia while hastening functional recovery. MgSO4 also acts as an adjunct to lidocaine and improves the quality of anaesthesia and analgesia in IVRA. Its role in the prophylaxis of eclampsia is also well proven. The use of MgSo4 in treating tetanus and acute asthma is under trial. It has an established role in blunting the laryngoscopic intubation response. It has a questionable role in offsetting the shivering.

In a nutshell, Mg is a cost effective, widely used drug with multidisciplinary applications. Majority of its physiological effects are attributed to calcium channel blocking properties.

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