One Drug, Many Uses: A Narrative Review of Magnesium Sulfate for Pharmacists

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Abstract

Background: The purpose of this paper is to review the use of magnesium sulfate (MgSO4) for the treatment of clinical conditions that pharmacists may encounter in an emergency care setting.

Method: A literature search of PubMed and Scopus using the following keywords magnesium sulfate, magnesium, torsades de pontes, torsades, asthma, eclampsia, pre-eclampsia, migraine, hypomagnesaemia and alcohol withdrawal was conducted. There was no exception made to limit the inclusion of relevant clinical trials, and the trials referenced were published between March 2004 and May 2020.

Results: Magnesium is an essential electrolyte regulating a myriad of metabolic processes. Patients may present to emergency care settings with hypomagnesaemia which requires the use of magnesium supplementation. However, patients may also present with a variety of clinical conditions for which magnesium can be used either as first-line therapy or as an add-on therapy.

Conclusion: Given the versatility and low-cost MgSO4 treatment offers in acute emergency settings, pharmacists should be well informed regarding the potential therapeutic role, dosing, and monitoring of the use of MgSO4.

Keywords: Magnesium Sulfate; Torsades De Pointes; Eclampsia; Asthma; Migraine; Alcohol Withdrawal

Introduction

Magnesium (Mg2+) is the second most abundant intracellular cation in the body. Mg2+ promotes enzymatic reactions within the cell during metabolism, assists the production of adenosine triphosphate (ATP), maintains a membrane potential, participates in protein synthesis and plays a vital role in platelet aggregation and coagulation [1]. MgSO4 has been administered as an effective medical therapy in a variety of acute conditions in emergency care settings. MgSO4 has several characteristics that make it an appealing therapeutic option for acute conditions, namely the rapid onset of action, quick renal elimination and low incidence of adverse effects. Thus, the use of MgSO4 has been explored as a treatment option in several disease states such as cardiac arrhythmias, migraine, eclampsia and acute asthma exacerbation [2]. As a member of the patient-centered care team, pharmacists may encounter situations where the use of MgSO4 is warranted. This review provides an update on the therapeutic uses of MgSO4 in emergency care settings for practicing pharmacists and serves as a quick therapeutic reference for the appropriate use of magnesium.

Methods

English language original research or published reviews on the pharmacotherapy use of MgSO₄ were identified through a search of two bibliographic databases (PubMed and Scopus). The publication period was from March 2004 and March 2020 using the keywords: magnesium sulfate, magnesium, torsades, torsades de pointes, arrhythmias, QT prolongation, asthma, eclampsia, pre-eclampsia, migraine, children, clinical trials and alcohol withdrawal.

References from relevant articles were reviewed for additional information (may not be published within the publication period from March 2004 to May 2020).

Administration and preparation

MgSO₄ can be administered orally (PO), intramuscular (IM), intraosseous (IO) or intravenous (IV). One vial of MgSO₄ contains 8.1 mEq of Mg²⁺. The solutions can be made using 0.9% saline solution or in 5% dextrose with pH between 5.5 - 7.0 with an osmolarity of 811 mOsm/L. These solutions can be stored at room temperature [2,3].

Torsades de pointes and malignant arrhythmias

Torsades de pointes (Tdp) is a specific variant of polymorphic ventricular tachycardia associated with prolongation of the QT interval. The electrocardiogram (ECG) of Tdp is characterized by the “points” of the QRS complex twisting around the isoelectric baseline and a short-long-short RR interval pattern immediately preceding the onset of the arrhythmia [4]. Tdp can cause an increase in heart rate from 120 to 240 beats per min. The risk of Tdp markedly increases when the QTc interval is prolonged to over 500 ms or when the interval is prolonged greater than 60 ms from pretreatment value [5]. QT interval prolongation and Tdp may be congenital or acquired. The reason behind acquired QT interval prolongation and Tdp is usually the administration of medications associated with increased QT prolongation risk. Risk factors for drug-induced Tdp include age > 65, female sex, renal insufficiency, electrolyte disorders, arrhythmias with long pauses, genetic disposition and concomitant use of drugs known to increase QT [6]. Medication classes that may cause Tdp to include anti-arrhythmic agents, antibiotics and other anti-infective, antipsychotics and antidepressants. A good resource for up-to-date causative drugs can be found on the website crediblemeds.org, which is maintained by the Arizona Center for Education and Research on Therapeutics. Table 1 provides a list of common medications that can increase the risk of Tdp and QT prolongation. The symptoms of Tdp include palpitations, dizziness, and lightheadedness with syncope. In some cases, Tdp results in ventricular fibrillation, which can be fatal. Hence, reducing the risk factors associated with Tdp is vital.

The treatment of Tdp first involves the discontinuation of drugs inducing Tdp and the correction of any electrolyte imbalance. If the patient is hypokalemic or hypomagnesaemic, serum K⁺ or Mg²⁺ should be corrected immediately. Patients with Tdp who are hemodynamically unstable should undergo asynchronous defibrillation. According to the American Heart Association guidelines, patients who are hemodynamically stable regardless of the patient’s serum Mg²⁺ levels should be administered MgSO₄ 2g intravenous (IV) push over 1 - 2 minute (with 10 - 20 mL of 0.9% normal saline flush to ensure systemic delivery). If the patient is unresponsive to the first dose of MgSO₄, a second IV bolus of 2g can be administered within 5 minutes [7]. In patients who are unresponsive to MgSO₄ IV isoproterenol or a rapid overdrive pacemaker maybe used in the case of bradycardia and drug-induced QT prolongation. For pediatric patients, the recommended dose of MgSO₄ is 25 - 50 mg/kg (IV/IO) upto 2g [8]. The role of MgSO₄ in the treatment of Tdp is primarily based on two observational studies demonstrating its effectiveness [9,10]. Administration of MgSO₄ is thought to help restore the Na⁺ and K⁺ gradients maintained by the Na⁺/K⁺-ATPase pump since Mg²⁺ is an essential co-factor for the sarcolemmal pump function [11]. In addition, Mg²⁺ is also thought to compete with Ca²⁺ influx mediated by the voltage-gated Ca²⁺ channels. These effects reduce the occurrence of early after depolarizations (EADs), thereby stabilizing the membrane to reduce QT prolongation [6]. Although the use of MgSO₄ is not effective in terminating polymorphic ventricular tachycardia in patients with normal QT interval, it is the drug of choice for the management of Tdp in patients with hemodynamic stability [12,13].
### Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Generic Name</th>
<th>Classification of Risk</th>
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</thead>
<tbody>
<tr>
<td>Anesthetics</td>
<td>Propofol</td>
<td>×</td>
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<td></td>
<td>Sevoflurane</td>
<td>×</td>
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<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone</td>
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<tr>
<td></td>
<td>Disopyramide</td>
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<td></td>
<td>Dronedarone</td>
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<td></td>
<td>Dofetilide</td>
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<td></td>
<td>Flecaïnide</td>
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<td></td>
<td>Ibutilide</td>
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<td></td>
<td>Procaïnamide</td>
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<tr>
<td></td>
<td>Quinidine</td>
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<td></td>
<td>Sotalol</td>
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<tr>
<td>Antibiotics</td>
<td>Azithromycin</td>
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<tr>
<td></td>
<td>Ciprofloxacine</td>
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<td></td>
<td>Clarithromycin</td>
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<td></td>
<td>Erythromycin</td>
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<tr>
<td></td>
<td>Levofloxacine</td>
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<td></td>
<td>Moxifloxacine</td>
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<td>Telavancine</td>
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<td></td>
<td>Telithromycin</td>
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<tr>
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<td>Arsenic trioxide</td>
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<td></td>
<td>Vandetanib</td>
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<td></td>
<td>Bendamustine</td>
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<tr>
<td>Antidepressants</td>
<td>Citalopram</td>
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<td></td>
<td>Escitalopram</td>
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<td></td>
<td>Mirtazapine</td>
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<td></td>
<td>Venlafaxine</td>
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<tr>
<td>Antiemetics</td>
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<td></td>
<td>Dolasetron</td>
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<tr>
<td>Antifungals</td>
<td>Fluconazole</td>
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<td>Pentamidine</td>
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Acute asthma exacerbation

Asthma is a significant contributor to morbidity and mortality internationally and has a considerable impact on healthcare costs. The overall economic impact in the United States of America is reportedly 56 billion dollars annually [14]. Severe asthma exacerbations that can progress to a life-threatening medical emergency are mostly managed in acute care settings such as the emergency department (ED). Several factors may trigger severe exacerbations including medication noncompliance, upper respiratory infection and pneumonia, allergens, exercise, severe stress, comorbidities, patients who require greater than two canisters of short-acting β-agonist (SABA) per month and patients with two or more hospitalizations or three or more ED visits in the past year [15]. In addition, the GINA 2019 strategy report concludes the use of ≥ 3 canisters of SABA markedly increases the risk of asthma exacerbations, and ≥ 12 canisters of SABA increases the risk of death [14]. Among these triggers, medication non-compliance due to the educational gap, lack of access to medications, and patient adherence is the leading cause of acute exacerbation. Moreover, severe acute asthma exacerbation can occur with the use of certain medications. For example, the use of both non-steroidal anti-inflammatory agents (particularly aspirin) and steroid tapers may disrupt airway patency and increase airway resistance, while β-adrenergic blockers are thought to trigger bronchospasms [16].

The main treatments for a severe asthma exacerbation are to correct significant hypoxemia using supplemental oxygen and to rapidly reverse airway flow obstruction with the administration of inhaled SABAs and systemic steroids [17]. In patients with severe and life-threatening asthma exacerbations, use of IV MgSO₄ may be considered. Life-threatening asthma exacerbation is characterized by an inability to speak, a reduced peak expiratory flow of less than 25% of a patient’s personal best, and a failed response to frequent bronchodilator and IV steroid therapies [18,19]. Two meta-analysis studies examining the role of IV MgSO₄ as an adjunctive therapy with

**Table 1:** List of drugs that are associated with known or possible risk of QT prolongation and torsades de pointes 6, Woosley [61].

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Risk of QT Prolongation</th>
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<tbody>
<tr>
<td>Antimalarial</td>
<td>Chloroquine</td>
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<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine</td>
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<td></td>
<td>Droperidol</td>
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<td></td>
<td>Haloperidol</td>
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<td></td>
<td>Thoridazine</td>
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<td></td>
<td>Aripiprazole</td>
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<td>Clozapine</td>
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<td></td>
<td>Paliperidone</td>
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<td></td>
<td>Promethazine</td>
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<tr>
<td>Muscle Relaxant</td>
<td>Tizanidine</td>
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</tr>
<tr>
<td>Opioid Agonist</td>
<td>Methadone</td>
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<tr>
<td>Phosphodiesterase</td>
<td>Cilostazol</td>
<td>×</td>
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<tr>
<td>Inhibitors</td>
<td>Anagrelide</td>
<td>×</td>
</tr>
<tr>
<td>Tyrosine Kinase</td>
<td>Sorafenib</td>
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</table>

β2-agonists and systemic steroids concluded that the use of MgSO4 aided in avoiding hospitalization (OR: 0.290, 95%; CI: 0.143 to 0.589) [20,21]. Studies have shown that MgSO4 causes relaxation of smooth muscle by attenuating Ca2+ influx and the subsequent inactivation of myosin phosphorylation. The inhibition in Ca2+ influx also decreases mast cell degranulation and acetylcholine release. These processes lead to the relaxation of bronchial smooth muscle contributing to the reduced airflow obstruction associated with acute asthma exacerbations. Moreover, the use of MgSO4 has also been shown to enhance histamine-induced bronchodilation and augment the effects of albuterol [22]. In cases of acute asthma exacerbations, a single infusion of 1 - 2g of IV MgSO4 over 15 - 30 minutes has been shown to improve lung function.

The use of IV MgSO4 was shown to reduce the hospital admission rates compared to placebo (Odds ratio (OR) 0.75, 95%CI, 0.6 - 0.92) for patients who have failed to respond to oxygen and/or first-line agents [23]. Silverman, et al. reported that the use of IV MgSO4 resulted in significant improvement in patients with low force expiratory volume 1 (FEV1) [24]. While Silverman, et al. did not report any significant adverse effects with the use of IV MgSO4, a review of randomized controlled trials by Kew, et al. reported flushing, fatigue, and burning at the injection site were some of the common adverse effects associated with the use of IV MgSO4 [23]. Hypotension was reported in 8% of the patients on IV MgSO4 versus 6% placebo group [25]. In pediatric populations, the recommended dose is 25 - 50 mg/kg IV MgSO4 over 20 minutes. Systematic reviews describing the use of MgSO4 in acute asthma exacerbations have shown that MgSO4 can not only improve lung function but can also reduce hospitalization rates [23,26]. MgSO4 was shown to reduce the odds of hospital admissions; for every five children treated in the ED, one hospital admission could be prevented [27]. Pharmacists may play an active role in the management of acute asthma exacerbation patients by monitoring patient response to conventional treatments such as SABAs or corticosteroids; however, if unresponsive, pharmacists may recommend the use of MgSO4 as an add-on therapy.

**Eclampsia**

Preeclampsia is a multisystem hypertensive disease that affects 5 to 8% of pregnancies. It is defined as the new onset of hypertension and proteinuria after 20 weeks of gestation [28]. Eclampsia is a manifestation of damage from severe preeclampsia and should be suspected in any pregnant woman who develops seizures in the setting of hypertension, edema and proteinuria. Clinicians should pay attention to signs and symptoms associated with eclampsia such as a headache, blurred vision, confusion, hyperreflexia and epigastric pain. Eclampsia may also occur during the postpartum period, usually over the first few days [29].

The management of eclampsia includes the treatment of seizures, hypertension and the delivery of the fetus. Although not an anticonvulsant per se, MgSO4 has long been used for the treatment of eclampsia seizures with good results [30]. The vasodilatory action MgSO4 is thought to be due to the decrease in the concentration of potent vasoconstrictor endothelin (ET)-1. Additionally, Mg2+ has been shown to increase circulating concentrations of endothelium-derived-relaxing-factor and calcitonin gene-related peptide [31,32]. However, the antagonistic action of MgSO4 on N-methyl-D-aspartate (NMDA) and Ca2+ leads to a decrease in convulsing activity. A study conducted by the Magpie Trial Collaborative group demonstrated that the use of Mg2+ lowered the risk of eclampsia by 58% (95%CI, 40 - 70%). Furthermore, the use of MgSO4 was also shown to decrease maternal mortality instead of morbidity (Relative Risk (RR) = 0.5%, 99%CI, 0.26 - 1.14) [33]. The dosing for IV MgSO4 is 4 to 6g followed by an infusion of 1 to 2g per hour. A serum Mg level of 4 - 7 mEq/L is considered to be therapeutic, although more clinical trials need to be conducted to validate the target therapeutic levels [34]. MgSO4 can also cross the placental barrier to provide a neuroprotective effect to the neonate. The adverse effects associated with the MgSO4 include chest pain, nausea, vomiting, and sedation. In 1% of women, respiratory arrest was also reported [35]. When Mg2+ levels are approaching toxicity, patellar reflexes diminish and respiratory rate slows. Pharmacists should actively monitor patients receiving MgSO4 for these signs and symptoms of toxicity. In addition, sustained hypertension is more likely to cause eclampsia resulting in cerebral hyperperfusion and edema. If significant elevations in blood pressure persist despite the administration of MgSO4, management of hypertension should be initiated. The following antihypertensive options are available for use: 1) hydralazine 5 mg IV, repeat at 20-min intervals; consider another drug if no response at a maximum of 20 mg; 2) labetalol 20 mg IV, then 40-80 mg IV every 10 min (maximum, 220 mg); IV infusion
1 - 2 mg/min titrated to response; 3) nifedipine 10 mg PO, repeat in 30 min as often as necessary; and 4) nitroprusside 0.25 mcg/kg/min infusion to a maximum dose of 5 mcg/kg/min [36].

Migraine

Patients presenting to the ED with a headache comprises 4.5% of all ED visits [37]. Cluster headaches, migraines with and without aura, and especially menstrual migraines have been associated with low levels of magnesium [38]. Several therapeutic options are available for the treatment of an acute migraine, including triptans, dihydroergotamine, dopamine antagonists (e.g. metoclopramide, prochlorperazine), non-steroidal anti-inflammatory drugs, opioids, and valproic acid [39]. A decrease in serum Mg²⁺ has been associated with cortical spread depression (CSD), which causes aura in a migraine [40]. In fact, a recent matched case-control study from the International Clinical Psychopharmacology found the odds of acute migraine headaches increased 35.3 times when serum magnesium reached below normal level (OR: 12.4 - 95.2, p = 0.001) [41]. Magnesium has been shown to decrease vasoconstriction, decrease neurogenic inflammation, and inhibit the function of the NMDA receptor [42]. The use of MgSO₄ (1g IV) was shown to provide benefit with headache relief at 60 min in comparison to the placebo with migraine with aura (50% vs. 13%; p < 0.05) and was also shown to provide headache freedom (37% vs. 7%; p < 0.05). However, in patients without aura, the use of MgSO₄ did not show any significant difference with headache relief (33% to 17%, p = ns) and headache freedom (23% vs. 10%, p = ns) in comparison to placebo [43,44]. A cross-sectional study in patients (n = 70) with a severe migraine headache treated with 30 mg ketorolac in one hospital was compared to the administration of 1g (IV) MgSO₄ in another hospital. It was observed that there was an improvement in pain score in the group treated with MgSO₄ 1 or 2h following administration [45]. A recent systematic review by Miller et al. reported that while the efficacy of MgSO₄ (IV) in the treatment of acute non-traumatic headaches was inconclusive, however, the use of IV Mg is potentially beneficial in pain control beyond 1 hour, aura duration and the need for rescue analgesia [46].

Status migrainosus (SM) is a severe manifestation of migraine, and due to the severity of the condition, parenteral formulations are recommended for treatment [47]. The use of MgSO₄ along with corticosteroids, anticonvulsants, anti-inflammatory drugs, and antiepileptics, and serotonergic agents are recommended. The dose of MgSO₄ for SM is 500-1000 mg IV. The use of MgSO₄ as a therapeutic tool in migraine management is appealing, given the low cost and lack of serious side effects [48]. Notably, MgSO₄ can also used safely during pregnancy [49]. Although current studies have demonstrated the benefit of MgSO₄ in migraines with aura, large randomized placebo-controlled studies are needed to confirm these findings and to evaluate the treatment efficacy of MgSO₄ in migraine patients without aura.

Alcohol withdrawal

Alcohol dependence and abuse-related medical issues place a burden on ED and hospital operations. Reports indicate that alcohol withdrawal syndrome (AWS) may prevail in up to 8% of hospitalized patients and is a common occurrence in ED [50]. AWS refers to the manifestation of signs and symptoms of withdrawal upon the reduction or cessation of alcoholic intake after heavy or chronic alcohol usage. Depending on the individual, the onset of AWS and presentation of worsening stages may vary. In 3 - 5% of patients, AWS will progress into delirium tremens (a delirium in combination with alcohol withdrawal) with a current mortality rate of 1 - 4%. Hypomagnesaemia occurs in about 30% of patients undergoing AWS via decreased nutritional magnesium intake, increased intracellular Mg²⁺ uptake through coexistent respiratory alkalosis, increased renal losses and increased gastrointestinal Mg²⁺ losses due to diarrhea or steatorrhea [51].

Primary clinical goals of treating AWS include minimizing symptoms, preventing complications, and facilitating continued abstinence from alcohol. Current National Institute for Health and Care Excellence (NICE) guidelines suggest to “monitor and correct fluid and electrolyte abnormalities,” therefore warranting the use of IV magnesium replenishment [52]. The pharmacological basis of Mg²⁺ in AWS is attributed to its’ action on altering Ca²⁺ influx mediated via NMDA receptors. Magnesium binds to and competes with glutamate binding on the NMDA receptors, thereby attenuating the overall neural excitation through decreasing Ca²⁺ influx and reestablishing impulse control.
The use of MgSO₄ is also shown to stabilize hepatocyte membrane, resulting in an overall decrease in hepatocyte mediated enzymatic response and is thought to provide hepato-protective effects [54].

A Cochrane Review meta-analysis of four trials involving 317 participants was conducted to assess the prevention and treatment of AWS in hospitalized patients using MgSO₄. The review showed inconclusive results; however, this was due to the limited number of trials, heterogeneity between trials, and high bias. Hence, the use of MgSO₄ in AWS is primarily for the restoration of electrolyte imbalance, but utility as a treatment option is inconclusive [55]. Future studies are required to further investigate the effectiveness of MgSO₄ in the treatment of AWS.

Hypomagnesaemia

Magnesium is an essential element that regulates numerous biological processes. It plays a primary role in regulating key enzymatic activity such as a Na⁺/K⁺-ATPase pump, hexokinase, creatinine kinase, and adenylate cyclase. Additionally, Mg²⁺ also plays a role in regulating the functions of Ca²⁺ and K⁺ ion channels [1]. In healthy individuals, normal serum Mg²⁺ level is stated to range from 0.76-1.15 mmol/L (1.52 - 2.3 mEq/L) [56]. While hypomagnesaemia (serum Mg²⁺ > 1.15 mmol/L) has lower occurrence and is usually associated with renal insufficiency, hypomagnesaemia (serum Mg²⁺ < 0.76 mmol/L) occurs commonly in the general population [1]. Low levels of Mg²⁺ can lead to loss of appetite, nausea, vomiting and fatigue. The typical presentations of hypomagnesaemia with anorexia, nausea, positive Chvostek and Trousseau signs, hypokalemia and hypocalcemia. Pronounced hypomagnesaemia can present with muscle spasms, tetany, arrhythmias, and neurological symptoms such as reversible altered mental status and seizures [56,57]. Conditions such as chronic alcohol abuse, poorly managed diabetes, gastrointestinal disorders (e.g. Crohn’s disease, Ulcerative colitis, Celiac disease), chronic kidney disease and dialysis, and endocrine dysfunctions such as hyperparathyroidism and hyperthyroidism can lead to a decrease in serum Mg²⁺ levels [1].

Another important cause associated with hypomagnesaemia is the use of certain drugs such as diuretics (long-term use of loops and thiazide-type diuretics), immunosuppressants (cyclosporine), aminoglycosides, antifungals (amphotericin B), bisphosphonates, and proton pump inhibitors (Table 2). In an ED setting, pharmacists can play a critical role in minimizing the risk of hypomagnesaemia by monitoring serum electrolyte concentration and the appropriate use of medications that are more likely to cause a Mg²⁺ deficiency. In patients who are presenting with signs and symptoms of hypomagnesaemia regardless of their serum Mg²⁺ concentration, IV MgSO₄ is administered. However, approximately 50% of the administered dose is excreted in the urine; therefore magnesium replacement should be performed over 3 to 5 days. One widely accepted dosing regimen is to administer 8 to 12g of MgSO₄ in divided doses, in the first 24 hours followed by 4 to 6 g/day for 3 to 5 days [58]. In pediatric patients, the dose is 25 - 50 mg/kg (max 2 gm/dose) every 6 hours for 2 - 3 doses [59]. The administration should be continued until the signs and symptoms have completely resolved. However, in patients with renal insufficiency, the dose may be reduced by 25% to 50% [60].

Adverse effects

MgSO₄ has a large therapeutic index, and at typical doses, there are minimal adverse effects. The most common adverse effects are associated with transient facial warmth and flushing [3]. Transient hypotension may also occur with rapid IV infusion. Changes in cardiac rhythms, absent reflexes, and respiratory depression have occurred at high Mg serum levels (> 12 mg/dl). In patients with Renal failure, the dose of MgSO₄ must be adjusted, and the serum level should be frequently monitored.

Conclusion

MgSO₄ is the first-line therapy in the treatment of torsade de pointes, eclampsia and hypomagnesaemia. In addition to these conditions, the use of MgSO₄ can also be considered in the treatment of acute asthma exacerbations and migraine. Table 3 summarizes the dosage of MgSO₄ used in the treatment of these conditions. The potential use of MgSO₄ in an emergency setting is appealing since it has a lower risk of adverse reactions and extremely cost-effective compared to many other therapeutic interventions. Additionally, MgSO₄ can be readily prepared and stored in the pharmacy and/or ED ready use. Moreover, larger randomized controlled trials to assess the parameters such

Table 2: List of drugs associated with known hypomagnesaemia risk [1,62,63].

Table 3: Commonly used dose of MgSO₄ in various conditions in an emergency setting [2,6,59,64].

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Bibliography


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