

## Review of the role of magnesium sulphate in the management of asthma patient at A&E setting

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Controversial views exist with regards to the use of intravenous magnesium sulphate in patient with severe asthmatic attack. The benefit of intravenous magnesium sulphate may be masked by the pooling of patients with different pathophysiology. The subsets of patients with severe asthmatic attack who have not responded to nebulised bronchodilator therapy and intravenous steroid therapy may benefit from intravenous magnesium sulphate therapy. (*Hong Kong j.emerg.med.* 2003;10:37-42)

**Keywords:** Asthma, intravenous, magnesium sulphate, severe attack

### Introduction

Asthma is a common disease encountered in emergency department and its symptoms range from chronic cough to life threatening bronchospasm. Patients with mild attack can be discharged after nebulised broncho-dilator therapy but those with severe attack may need aggressive respiratory support. On the other hand, patients who complain of severe dyspnoea may respond well to standard treatment, i.e. beta agonist bronchodilator, but some may show little response and require ventilatory support in intensive care. With this multidimensional clinical presentation, various clinical parameters have been developed to assess the severity of asthmatic attack and to discover effective medication and treatment modalities to effectively treat and reduce mortality.

The definition of severe asthma varies. It usually depends on the clinical presentation e.g. ability to speak, use of accessory muscle, respiratory rate, presence or absence of rhonchi and ancillary investigations, e.g. peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV<sub>1</sub>) and pulse oximetry SpO<sub>2</sub>.

The common practice of treating severe asthma uses a combination of medications aimed at bronchodilation and antiinflammation, antagonizing the triad of increased airway secretions, inflammation and reversible bronchoconstriction of asthma. However, some patients do not have significant improvement despite treatment with beta-adrenergic agonist e.g. salbutamol, anticholinergic e.g. ipratropium and steroid. Various innovations were developed to try to help this group of patients avoid invasive treatment such as endotracheal intubation. Magnesium was first considered useful in treating asthma about 60 years ago, and several case reports commented on its usefulness in decreasing admission and endotracheal intubation. However, various randomized controlled studies did not support the routine use of intravenous magnesium sulphate in treating patient with relapse

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of asthma. In this article, we are going to review the role of magnesium sulphate in the management of severe asthmatic patients.

## Pharmacology

Magnesium is the second most abundant intracellular cation and is an important coenzyme for various enzyme activities. The homeostasis of magnesium is closely related to that of potassium and hypokalaemia is usually accompanied by hypomagnesemia. The depletion of magnesium will cause refractory hypokalaemia despite potassium supplement.<sup>1</sup> The hypothesis that intravenous magnesium can relieve asthmatic attack was based on the fact that magnesium is useful as a tocolytic in early labour. Hence it may cause airway smooth muscle relaxation. Magnesium also exerts anti-inflammatory effect by decreasing the release of leukotriene and histamine; therefore it may be useful in controlling inflammation in asthma exacerbations.

The smooth muscle relaxing and anti-inflammatory effect of magnesium was due to competitive inhibition with calcium ion during influx into the cell, and calcium influx is a key factor in smooth muscle contraction and the release of inflammatory chemical. Other actions of magnesium include sedation and decrease in the release of acetylcholine, which was considered beneficial as it decreases dyspnoea and bronchoconstriction respectively.

The therapeutic form is magnesium sulphate and the dose used in treating preeclampsia is 4-6 gm intravenous (i.v.) over 15 minutes and maintenance infusion at 1-2 gm/hr. Toxic effect include central nervous system depression and heart block, which appear when the serum concentration exceeds 8 mg/dl. There is no routine monitoring of serum magnesium level during magnesium therapy. Toxicity is usually detected clinically with the loss of ankle jerks, and if signs of toxicity occur, i.v. calcium gluconate can be used as an antidote.

Magnesium is excreted by the kidneys and it should not be used in patients with renal failure.

## Objective

The objective of this article is to review the role of magnesium in the treatment of asthma. Intravenous magnesium sulphate is our main concern but the effect of nebulised magnesium sulphate is another treatment modality we review.

## Method

Medline search was performed for articles using the keywords asthma, magnesium, and only English articles were selected and no time range was specified in this search. One randomized trial was found by hand search of recent journals.

There were 18 relevant articles found using this methods which included meta-analysis, randomized control trials, randomized trials and case reports.

### *Intravenous magnesium sulphate for patient with severe asthma*

Recently published article by Porter and colleagues<sup>2</sup> in the department of emergency medicine, Albert Einstein Medical Center, Philadelphia, reported a randomized double blind study of the effect of i.v. magnesium sulphate in 42 patients, aged between 18 to 55 years old, who presented with moderate to severe asthma, i.e. peak flow rate <100 l/min or <25% peak flow rate. Patients either received 2 gm i.v. magnesium sulphate or placebo after receiving bronchodilator and i.v. steroid. Porter and his colleagues concluded that the use of i.v. magnesium sulphate was not useful in moderate to severe asthma, as 5/18 (28%) of patients who received magnesium versus 5 of 24 (21%) of patient who received placebo were admitted (P=0.72) and at 60 min, patients who received magnesium sulphate had mean peak flow rate of 174 l/min versus 212 l/min of those who received placebo (P=0.04).

In Asia, the study conducted by Boonyavorakul and colleagues<sup>3</sup> in Ramathibodi hospital, Bangkok concluded that magnesium sulphate as an adjunctive therapy did not improve either admission rate or severity score in patients with acute severe asthma.

This study was a randomized, double blinded study of 34 patients aged between 15 to 65 years old and 34 of whom presented with severe asthmatic attack, (severity scores greater than 4). Either magnesium sulphate 2 gm i.v. or sterile water as placebo were given and the admission rate of placebo and MgSO<sub>4</sub> group were 25.00% and 17.65% respectively. The relative risk of hospitalization with MgSO<sub>4</sub> was 0.71 times relative to patients who received placebo (95% CI of RR=0.01-2.67).

Two other randomized studies did not favour the routine use of magnesium in moderate to severe asthma in adult.

Scarfone and colleagues<sup>4</sup> conducted a randomized trial of using magnesium to treat children with moderate to severe asthmatic attack in St. Christopher's hospital for children. In this study, 54 patients between the ages of 1 to 18 years old who presented with severe asthma as defined by the pulmonary index score of 8 to 13, were either given 75 mg/kg of magnesium sulphate (maximum 2.5 gm) or placebo after treatment with methylprednisolone (1 mg/kg) and nebulised albuterol treatment (0.15 mg/kg). They found that mean change in pulmonary index was 2.83 for the magnesium group as compared to 2.66 for the placebo group. Furthermore 11/24 of the magnesium group were hospitalized (46%) while 16/30 of the placebo group were hospitalized (53%) and they concluded that routine high dose of magnesium was not efficacious in moderate and severe asthma in children.

### ***Possible indication for using i.v. magnesium sulphate in treatment of severe asthma***

While some articles do not support the routine use of i.v. magnesium sulphate as a routine adjunctive treatment in severe asthma, others found significant clinical improvement in patient receiving i.v. magnesium sulphate. Bloch and colleague<sup>5</sup> in their randomized double-blind study found that i.v. magnesium sulphate (2 gm) decreased admission rate (33.3% in magnesium treated group vs. 78.6% in placebo group) and resulted in a significant improvement in FEV<sub>1</sub> in the severe group (FEV<sub>1</sub> <25% predicted on presentation) of asthmatic patient.

Ciarallo and colleagues<sup>6</sup> did a randomized, double-blind, placebo-controlled clinical trial on the use of i.v. magnesium sulphate (25 mg/kg) for moderate to severe paediatric asthma (PEFR<60%, 6-18 years old) and they showed that children with i.v. MgSO<sub>4</sub> infusion had significantly greater improvement in short-term pulmonary function. Devi and colleagues<sup>7</sup> did a randomized double-blind, placebo-controlled trial on intravenous magnesium in children 1-12 years old with acute severe asthma not responding to conventional therapy, i.e. 3 doses of nebulised salbutamol at 20 min intervals, i.v. aminophylline and corticosteroid and showed that the MgSO<sub>4</sub> group had early and significant improvement as compared to the placebo group in PEFR, SpO<sub>2</sub> and clinical asthma score. Santana and colleagues also found that i.v. magnesium sulphate (50 mg/kg) and i.v. salbutamol (1 microgram/kg/min) improved the degree of acidosis and reduction of PaCO<sub>2</sub>, in their double-blind, placebo-controlled clinical trial including children above 2 years old with severe acute asthma admitted to the observation ward of paediatric intensive care unit.

Furthermore, there are case reports supporting the use of MgSO<sub>4</sub> for patients with severe asthma. One such report<sup>8</sup> was on the use of i.v. magnesium sulphate for the management of refractory bronchospasm in a ventilated young asthmatic male patient. He presented with severe asthmatic attack and inhaled salbutamol, nebulised salbutamol, ipratrobium bromide, hydrocortisone, salbutamol, ketamine and midazolam infusions failed to reduce his peak airway pressure or improve his CO<sub>2</sub> clearance, but showed clinical improvement over the next 24 hours after a loading dose of 1.2 gm of magnesium and 15 gm of magnesium infusion over 24 hours.

The available literature is full of conflicting results. Are these results truly contradictory or just represent two different results in continuous clinical spectrum?

Rowe and colleagues<sup>9</sup> in the systematic review of the literature which included 2 studies in children and 5 studies in adults, found that the pooled results failed to demonstrate any statistically significant evidence

of a beneficial effect of magnesium sulphate in terms of admission rates or pulmonary functions. However, in the subgroup study of severe asthmatic patient, i.e. 25-30% predicted peak expiratory flow rate at presentation (adult), failure to respond to initial treatments (adult and children) and failure to improve beyond 60% predicted after 1 hour of care (children), the use of i.v. magnesium sulphate resulted in lower admission rate than those treated with placebo (OR: 0.10; 95% CI: 0.04-0.27) and improvement in lung function tests were more pronounced.

The meta-analysis by Alter and colleagues<sup>10</sup> after the review of 9 randomized double blind clinical trials involving 859 participants concluded that i.v. bolus magnesium sulphate as an adjunct therapy improved spirometry airway function by 16% in acute bronchospasm.

Therefore, it is likely that selected groups of patients with severe asthma not responding to nebulised bronchodilator therapy may benefit from intravenous magnesium sulphate.

### ***Nebulised magnesium sulphate***

Asthma affects the small airway, and the delivery of medication into the airway will have greatest efficacy and least systemic effect. Nebulised salbutamol and inhaled steroid were well studied. How about nebulised magnesium sulphate?

In a laboratory study on the effect of nebulised magnesium sulphate (3 ml 268 mmol/L) in reversing bronchoconstriction induced by methacholine challenge test in asthmatic subjects, Chande and Skoner<sup>11</sup> found that magnesium sulphate has a minimal bronchodilatory effect. In studying the effect of nebulised magnesium in sodium metabisulfite (MBS) induced bronchoconstriction in subjects, Nannini and colleagues<sup>12</sup> concluded that inhaled magnesium sulphate had protective effect. They studied 10 asthmatic patients with an average age of 38.8 and found that magnesium diminished the bronchoconstrictor response to MBS (p=0.08).

Nannini and colleagues<sup>13</sup> conducted a study on the effect of inhaled magnesium sulphate (3 ml isotonic

solution) in treating acute asthma exacerbation, they found that magnesium sulphate as a vehicle for nebulised salbutamol increase the peak flow response to treatment compared to salbutamol with normal saline. Mangat and colleagues<sup>14</sup> also found that nebulised magnesium sulphate (3 ml 3.2% solution) had significant bronchodilatory effect similar to nebulised salbutamol.

Though the initial results of nebulised magnesium sulphate is appealing, further clinical studies to assess the efficacy of nebulised magnesium sulphate in various clinical setting (e.g. children vs. adult, moderate vs. severe asthma, low vs. high dose of nebulised magnesium sulphate) is necessary before we can apply it in clinical use.

### ***Role of magnesium sulphate in chronic asthma***

Magnesium sulphate do not appear to be effective in patients with chronic asthma. The study by Hill and Britton<sup>15</sup> showed that neither i.v. nor inhaled magnesium was useful in patients with chronic asthma and Bernstein and colleagues<sup>16</sup> concluded that 2 gm i.v. magnesium was not effective as a bronchodilator in chronic stable asthmatic.

## **Discussion**

Intravenous magnesium sulphate is useful in some patients with severe asthmatic attack. The difference in response may be related to the definition of severity. All studies above were randomized, double blind studies. All studies claimed only patients with 'severe attack' were selected, but the definition of severity differed in different studies, the severity being defined on initial presentation by PEFr,<sup>2</sup> pulmonary index scores,<sup>4</sup> or failed response to nebulised salbutamol.<sup>6,7</sup> Apart from the differences in definition of severe asthma exacerbation in different studies, all patients received similar adjunctive treatment; standard dose of nebulised beta-adrenergic agonist, steroid, and magnesium sulphate in doses of 2 to 2.5 gm or 75 mg/kg (paediatric dose) being given after randomization and consent. All studies showed no severe toxicity i.e. CNS sedation or cardiovascular side effect.

Clinical presentation of severe asthmatic attack is multidimensional. In the study by Rodrigo,<sup>17</sup> he proposed that the definition of severe asthma should be based on PEFr on initial presentation and 30 min later after treatment, as some patients with low PEFr initially had dramatic improvement after inhaled salbutamol. Hence if all patients with severe exacerbation on initial presentation were enrolled, the effect of magnesium might be masked. If only patients who had severe asthma exacerbation not responding to nebulised salbutamol were selected, they would benefit from i.v. magnesium sulphate (Number Need to Treat=2).<sup>18</sup>

The dose of intravenous magnesium sulphate studied was 2 gm or 75 mg/kg. The dose was conservative, compared with the dose for treatment of eclampsia which is two to three times higher i.e. 4-6 gm. Li<sup>19</sup> suggested that patient might be treated with an intravenous bolus dose of 10 to 24.6 gm! To define the dose response relationship in severe asthmatic attack, further studies by using higher doses of magnesium sulphate are necessary.

Magnesium is contraindicated in patient with renal failure, and systemic toxicity due to high dose of magnesium limits the application in certain circumstances. Nebulised magnesium sulphate may be a solution in such a condition, as high concentration of magnesium may be delivered locally without causing systemic side effect. Further studies should be performed to investigate the clinical efficacy and systemic response to nebulised magnesium.

## Conclusion

I.V. magnesium sulphate is useful as an adjunctive treatment in severe asthma with failed response to nebulised salbutamol. It is a safe drug at 2 gm in patient with normal renal function, and the side effect can be monitored clinically. Calcium gluconate i.v. should be readily available when magnesium sulphate is being given to the patient. The routine use of magnesium sulphate for acute asthma is not recommended.

Further studies<sup>9</sup> including: 1) the effect of higher dose magnesium sulphate; 2) the effect of nebulised magnesium sulphate; 3) the clinical use of magnesium sulphate in extremely severe asthmatic attack; 4) optimal dose and duration of magnesium sulphate; 5) studies involving very young children; 6) the effect of magnesium sulphate based on prior inhaled steroid use; 7) the study on severity which is clearly defined (pulmonary function result AND response to initial beta-agonist therapy) are necessary before a comprehensive understanding of magnesium in the management of asthma will be available.

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