Review

Intravenous Magnesium Therapy Treatment of Severe Asthma in Adults

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Prepared specifically for the AMSJ

Keywords: asthma, severe, intravenous, magnesium, adults

This article systematically analyses the evidence behind the use of intravenous magnesium sulphate in adults with severe acute exacerbations of asthma.

Two Tables

Word count: 2020

Abstract

Background: Acute exacerbations of asthma may present as severe life-threatening illness that accounts for as many as 37,500 hospitalisations and 394 deaths each year in Australia. The current cornerstone of therapy in acute asthma includes short acting beta-2 agonists, short acting anti-muscarinic agents and corticosteroids. This systematic review aims to assess the current evidence for the use of intravenous magnesium and its efficacy in acute severe asthma.

Materials and Methods: An online literature review of databases including OVID Medline, The Cochrane Database of Systematic Reviews, and PubMed was undertaken, including articles published between 1980 and 2017. Articles were analysed based on evidence regarding respiratory function, hospital admissions, biochemical effects, and adverse effects.

Results: Although IV magnesium sulphate did not show statistically significant benefits in all asthma groups, there appeared to be some evidence of its efficacy in a subset of patients with severe asthma that had failed other first-line therapies. The treatment can reduce hospital admission rates with little evidence of adverse effects.

Conclusion: The role of IV magnesium sulphate in asthma remains unclear; however, IV magnesium sulphate appears to be efficacious in severe asthma exacerbations when used synergistically with standard therapy.

Introduction

Asthma is a serious medical condition with potentially life-threatening consequences for all age groups. In Australia, acute asthma attacks account for some 37,500 hospitalisations and 394 deaths per year [1]. Although not completely understood, airway hyper-responsiveness is caused by acute and chronic inflammation in the lungs. The sum of these inflammatory reactions causes bronchoconstriction, bronchial oedema, and increased mucus production. Subsequently, patients suffer from recurrent episodic wheezing, dyspnoea, chest tightness, and persistent cough [1,2].

Asthma can be categorised into mild, moderate, severe, or life-threatening (Table 1). A feared complication is status asthmaticus (SA). This is a severe subset of acute asthma that is unresponsive to first line therapies [3]. SA carries a mortality of 10-25% in patients intubated in Intensive Care Units (ICU). During SA, hypoxaemia develops due to lung hyperinflation, alveolar hypoventilation, and regional ventilation/perfusion (V/Q) mismatch, leading to acute type II (hypercapnic) respiratory failure. Death results from cardiopulmonary arrest [4,5].

[Table 1]

Current Australian guidelines highlight three fundamental medication classes to treat moderate-to-severe acute exacerbations: short-acting beta-2 agonists (SABA), short-acting muscarinic antagonists (SAMA), and corticosteroids [7]. The dilemma arises when a patient with SA responds poorly to these established measures. Thus, research into novel or alternative approaches is important. Methylxanthine derivatives, such as theophylline, were initially promising but later failed to show additional benefit over established therapies [8]. One proposed alternative is intravenous magnesium sulphate (IVMS).

Use of magnesium for the treatment of asthma exacerbations was first proposed by Rosello *et al*. in 1936 [9]. While its exact mechanism of action remains unknown, magnesium is hypothesised to mediate bronchodilation via three mechanisms. Firstly, magnesium competes with calcium for entry into cells through voltage- and receptor-operated calcium channels. This causes inhibition of intracellular calcium release from the sarcoplasmic reticulum and inhibits smooth muscle contraction [10]. Secondly, it inhibits acetylcholine release and prevents mast cells from releasing histamine [11]. Thirdly, it has anti-inflammatory properties against T-lymphocytes, neutrophils, and pro-inflammatory cytokines [12].

Worldwide, there are discrepancies in the adoption of IVMS into clinical practice. In the United Kingdom (UK), utilisation of IVMS is extensive, with up to 93% of severe asthma presentations to the emergency department given IVMS [13]. In contrast, IVMS for severe asthma is used sparingly in the United States, given only in 2.5% of emergency department presentations [14]. This disparity is likely due to conflicting data concerning the effects of magnesium on bronchial hyperreactivity [15]. This article aims to examine the effect of IVMS in severe asthma and SA in the emergency department in the three main areas of respiratory function, hospital admissions, and its biochemical and adverse effects.

Methods

A literature search was conducted in 2016 and 2017. Online databases that were used to evaluate the evidence surrounding the use of intravenous magnesium sulphate include: OVID Medline, The Cochrane Database of Systematic Reviews, and PubMed. Articles were found using the following terms: intravenous, magnesium, adult, exacerbation, asthma, and critical

care. Manual reference searching was also employed during this research period. The literature search was limited to trials from 1980 to 2017 (totalling 37 years).

Initially, articles were screened for relevant search terms in their title and abstract, and the availability of full-text original research. Included in the analysis were full text papers of randomised control trials of intravenous magnesium sulphate compared with placebo in asthma exacerbations in adults. Only papers published in English were included. Studies were excluded if the focus was nebulised magnesium sulphate, the studies involved child subjects (less than 18 years of age), the language of publication was not English, or if the research was unpublished. A total of 504 articles were found using the search terms ‘magnesium’ and ‘asthma’. 113 search results were found using ‘intravenous magnesium AND Asthma’, and these articles were subsequently screened for relevance. Meta-analyses were included if they addressed the key research question and were applicable to adults. Randomised control trials were included if they met the above criteria. A total of 18 randomised control trials and three meta-analyses were included for review.

Results:

Table 2 – lists the articles meeting inclusion criteria in this review, the type of study and the summarised findings of each.

Discussion:

Respiratory function

Several studies have demonstrated IVMS to have positive bronchodilatory effects, showing improvements in spirometry values such as forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow rate (PEFR) after IVMS administration [12-19]. Okayama and Aikawa [12] noted dose-dependent improvements in FVC (117±3%) and FEV_1 (118±1%) after administration of IVMS infusion, which persisted for up to ten minutes after conclusion of the infusion. Although this study was of patients with mild asthma, Okayama and Aikawa [12] noted improved dyspnoea and piping rales in three of these patients who had severe attacks. Noppen and Vanmaele [13] and Skobeloff and Spivey [14] both investigated IVMS in severe asthma and found improvements in FEV_1 (0.94±0.39 L to 1.3±0.44 L) and PEFR (208-216 L/min to 225-297 L/min) respectively that persisted up to 20 minutes after infusion cessation. In both studies, however, there was concomitant administration of SABAs, methylprednisolone, and methylxanthines, which may have had adjunct effects on the IVMS therapy and increased the duration of its efficacy [14]. Additionally, the limited power of these three studies may have contributed to the pronounced pulmonary effects.

Silverman and Osborn [18] conducted a multi-centre randomised double-blinded controlled trial of 248 patients with severe asthma ($FEV_1 \leq 30\%$ predicted). With administration of IVMS therapy, there was a statistically significant improvement in FEV_1 compared to placebo (48.2% versus 43.5%; $p<0.05$). Bloch and Silverman [16] conducted a similar trial with 135 subjects. 35 patients were classified as severe asthmatics, compared to 94 who were classified as moderately-ill based on initial PEFR measurements. Although this study found no benefit in the moderately-ill group, there were improvements in the severely-ill group. The authors hypothesised that patients in the severely asthmatic group were relatively refractory to SABA medication, and that magnesium mediated bronchodilation through alternate pathways [16].

The 3Mg Trial, perhaps the largest trial, enrolled 1109 patients [20]. The authors concluded that there was weak evidence of improvement in patients with severe asthma exacerbations but, interestingly, placed more emphasis on a visual analogue scale (VAS) for assessment of dyspnoea. They showed an improvement in PEFR at 1 hour with IVMS (11.4% in IVMS compared to 10.2% in the control group) and no differences between groups at 2 hours post-therapy (14.4% in both groups). However, the authors did not comment on these findings [20].

Some studies found that IVMS had no benefit in acute severe asthma [21-24]. Although most of these studies were randomised trials, they failed to reach statistical significance in their findings, and also excluded certain subsets of severe acute asthma such intubated patients, which may underrepresent patients with life-threatening asthma [21,23]. Furthermore, one study administered 1.2 g IVMS compared to other studies that used 2 g IVMS. Noting the earlier finding of the dose-dependent effect of IVMS, this may have contributed to the

negative findings in this study [22]. Furthermore, a large trial by Hirashima and Yamana [24] found IVMS had no beneficial impact on 28-day mortality compared to placebo. Here, 619 patients received IVMS and 14,122 received a placebo. However, the authors concluded that further studies are required to clarify the effects of IVMS on severe asthma-related mortality [24].

Overall, three meta-analyses of a total of 21 studies suggested that pooled results failed to demonstrate statistically significant evidence for benefit across all asthma severity groups [25-27]. Kew *et al*. [28] examined 14 studies with 2313 patients who were randomised to receive 1.2-2 g IVMS or placebo. Patients that were given a beta-2 agonist, corticosteroids, and oxygen were included in the study. The authors concluded that the evidence supported use of magnesium, in combination with standard therapy, to reduce hospital admissions and improve spirometric indices of lung function. However, the authors commented that differences in the trial designs of the reviewed papers — whether the concomitant use of medications or asthma severity — altered the treatment effect of IVMS. Moreover, the research suggests that IVMS should be used as adjunct therapy or reserved for patients who fail to respond to initial therapies [25,27].

Hospital admissions

There are conflicting results regarding the effects of IVMS on hospital admissions in the setting of acute asthma. Many studies have noted reduced admission rates [14,16,19,20]. The 3Mg Trial highlighted that 72% of patients given IVMS were admitted to hospital within seven days from presentation compared to 78% of controls [20]. However, other studies found little to no differences in admission rates [18,21]. In the study by Silverman and Osborn [18], admissions were counted at four hours post-presentation to the emergency department. This may not be representative of admissions since, for instance, some patients may require a longer emergency department stay to be stabilised before being admitted. Boonyavorakul and Thakkinstian [21] found a lower hospital admission rate in the magnesium group but this failed to achieve statistical significance. Furthermore, the authors noted that the lower study power may have contributed to the non-significant findings. Nevertheless, a meta-analysis reported that, whilst overall there was no difference in hospital admissions, admissions in the subgroup of patients with severe asthma tended to be lower in those treated with IVMS compared with placebo (OR 0.10; 95% CI 0.04-0.27) [26]. Currently, the evidence favours reduced admissions but further robust research is required to elucidate this point, and to see if there have been reductions in length of hospital stay.

Biochemical effects

Research highlights that magnesium is a predominantly intracellular ion, and therefore serum levels may not reflect intracellular concentrations [13]. It is possible to have normal serum levels of magnesium with intracellular depletion [29]. Studies have shown that in asthmatic patients, intracellular magnesium levels are depleted in comparison to their non-asthmatic counterparts. Furthermore, the use of adrenergic stimulation and sympathomimetic medication during an acute asthma exacerbation can decrease magnesium levels through urinary loss and intracellular shift [30]. Noppen and Vanmaele [13] examined serum and intracellular concentrations of magnesium following IVMS infusion and found that the magnesium concentrations in red blood cells did not significantly differ after the magnesium infusion [13]. Dominguez and Barbagallo [31] analysed magnesium levels in erythrocytes

and found that intracellular magnesium concentrations were significantly lower in asthmatic patients. Intracellular magnesium levels appear to correlate with bronchial reactivity to methacholine in atopic subjects with and without asthma, and with and without bronchial hyper-reactivity [31]. In a 2001 study conducted by Schenk and Vonbank [15], 30 patients with known bronchial hyper-reactivity were trialled on either intravenous magnesium or a placebo. Patients who demonstrated bronchoconstriction went on to have a subsequent bronchial provocation test with methacholine. The study concluded that the use of magnesium significantly improved bronchial hyper-reactivity. In the magnesium infusion group, 30% of subjects regained their baseline FEV_1, compared to just 10% in the placebo group. The authors recommended using magnesium as an adjunct to standard therapy [15]. This study did not measure intracellular magnesium levels but hypothesised that subjects may have had some intracellular depletion. While Schenk and Vonbank [15] used methacholine as a source of bronchial provocation, Hill and Britton [32] found that IVMS did not alter airway reactivity when using inhaled histamine for bronchial provocation [32]. This discrepancy remains unclear given that magnesium has anti-inflammatory properties [11].

Adverse effects

Concerns have been raised over the potential side effects of hypermagnesaemia, including arrhythmia, hypotension, and loss of deep tendon reflexes [17]. None of the studies in this review found patients who experienced or demonstrated symptoms of hypermagnesemia after 2 g of magnesium infused over 20 minutes. However, some patients experienced palpitations, tremors, anxiety, dry mouth, and nausea, which authors attributed to salbutamol or other SABA agents [18]. The most commonly recognised symptom of magnesium administration is a cutaneous warmth which is well-tolerated by most patients [28]. The use of magnesium in severe asthma exacerbations has been demonstrated to counteract the tachycardia of sympathomimetic medications. This occurs by inhibiting calcium influx and blocking outward movement of potassium through ion channels in myocytes [33]. Sydow and Crozier [29] utilised high-dose IVMS (10-20 g over 1 hour) in ventilated patients with status asthmaticus, noting that two patients had arterial hypotension as a side effect of the treatment [29]. Nevertheless, this hypotension could be treated with vasopressors [34]. Thus, it appears IVMS administered acutely is safe and well-tolerated with minor adverse effects.

Australian Guidelines

Currently, the Australian guidelines recommend a graduated therapy for treatment of severe asthma. This starts with intermittent or continuous nebulisation of bronchodilators. The guidelines recommend repeat nebulisation in patients that respond poorly to initial therapy. After subsequent nebulisation, the guidelines recommend use of 10 mmol magnesium sulphate (equivalent of 2.5 g) over 20 minutes [7].

Despite lack of Australian-specific data involving the therapeutic use of IVMS, the current literature available would support the use of magnesium routinely in adult patients with severe or life-threatening exacerbations of asthma. IVMS would be best utilised in combination with standard therapy including oxygen, inhaled beta-2 agonists, inhaled anti-muscarinic agents, and corticosteroids in severe exacerbations.

Limitations

This paper did not include unpublished research or research that is not published in English, raising the potential for selection bias.

Conclusion

Evidence for the role of IVMS in the treatment of acute exacerbations of asthma remains conflicting. The literature appears to support the use of magnesium in severe exacerbations of asthma, defined as a $FEV_1 \leq 30\%$ of predicted. In reviewing the literature, magnesium has the greatest effect when given with standard therapy to treat exacerbations of asthma. In some studies, IVMS appears to be beneficial in reducing hospital admission rates in severe asthma exacerbations. Current literature suggests that IVMS may be considered as a first-line therapy in conjunction with current standard therapy in Australia.

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Table 1. Classification system for asthma severity based on Forced Expiratory Volume in one second (FEV1) predicted or personal best. Adapted from Albertson et al. [6]

Classification	**Signs and Symptoms**	**FEV_1**
Mild	Dyspnoea only with activity, wheezing	>70%
Moderate	Dyspnoea interferes with or limits usual activity, wheezing	40-69%
Severe	Dyspnoea at rest, interferes with speaking full sentences, decreased breath sounds, reduced wheezing	<40%
Life-threatening	Too dyspnoeic to speak, perspiring, may lack air movement and wheezing (silent chest), cyanosed, lethargic	<25%

Table 2. Studies included in the literature review. N = sample size; RCT = Randomised Controlled Trial; CI = Confidence Interval; AUC = area under curve; PEFR = Peak Expiratory Flow Rate; FVC = Forced Vital Capacity; FEV1 = Forced Vital Capacity in 1 second; SMD = Standardized mean differences.

Study	Design	N	Objectives	Outcome	Statistics
Okayama *et al*. [12] 1987, USA	Crossover	10	IVMS in acute and severe asthma exacerbations	Improved respiratory resistance, $FEV_{1,}$ and FVC	IVMS improvement Respiratory resistance: 71%±3%, FVC: 117%±5%, FEV: 118%±1% compared to baseline $p \leq 0.05$
Noppen *et al*. [13] 1990, USA	Drug response	6	IVMS vs. albuterol on FEV_1	Significant improvement FEV_1 with IVMS	FEV_1 following IVMS administration 0.94±0.39 L to 1.3±0.44 L $p<0.05$
Skobeloff *et al*. [14] 1990, USA	RCT Double blind	38	IVMS in poor responders to first-line therapy	IVMS improved FEV_1 vs. placebo	225-297 L/min IVMS group vs. 208-216 L/min placebo (p-value not stated)
Tiffany *et al*. [23] 1993, USA	RCT Double blind	48	IVMS 2 g loading + infusion vs. loading only vs. placebo on FEV_1 or PEFR	No significant changes in FEV_1 or PEFR	FEV_1=0.036, p=0.96 PEFR=0.51, p= 0.61
Sharma *et al*. [17] 1994, England	Single blind Crossover	18	IVMS vs. normal saline in known asthmatics without exacerbation	IVMS significantly increased FEV_1, FEF 25-75% and V_{50}	FVC pre-treatment 2.75±0.88, after IVMS 2.86±0.87 FEV_1 pre-treatment 1.60±0.63, after IVMS 1.74±0.67 $p<0.05$
Bloch *et al*. [16] 1995, USA	RCT Double blind	135	IVMS + standard therapy effects on pulmonary function test and admission rates	No statistically significant changes in cohort overall, but there were statistically significant improvements in FEV1 and admissions rates in a subgroup of patients with severe exacerbations	Overall cohort: Hospital admission: 35.3% placebo, 25.4% IVMS (p=0.21) Subgroup with severe exacerbations: admission rates 78.6% placebo, 33.3% IVMS (p=0.009) FEV_1 ($p<0.05$)
Hill and Britton [31] 1996, England	RCT Double blind	20	Histamine provocation test IVMS vs. placebo on AUC for change in FEV_1	Weak bronchodilator effect. AUC significantly higher in the magnesium group. No significant difference between IVMS vs. placebo on histamine provocation	AUC, p=0.049 Histamine provocation p=0.7
Alter *et al*. [25] 2000, USA	Meta-analysis of 9 trials	859	IVMS bolus in acute asthma exacerbations	Adjuvant bolus IVMS statistically beneficial in improving spirometric airway function by 16% of a standard deviation	95%CI (0.028-0.297); p=0.02

Boonyavorakul *et al*. [21] 2000, Australia	RCT Double blind	33	2 g IVMS vs. standard therapy on severity score and admissions	No statistically significant improvement	Admission: 95%CI (0.19-2.67) Severity score: p=0.366
Rowe *et al*. [26] 2000, England	Meta-analysis of 5 adult and 2 paediatric trials	665	Adjuvant IVMS in acute asthma in the emergency department in terms of FEV_1, PEFR, and hospital admissions	Not for routine use in all severities of asthma exacerbations. Severe exacerbations improved FEV_1 and PEFR	Respiratory function: SMD, 0.30; 95% CI (0.05-0.55); p=0.02; Hospital Admission: RR 0.86; 95%CI (0.73-1.01); p=0.06
Schenk *et al*. [15] 2001, USA	RCT Double blind	30	IVMS bronchodilation post-methacholine provocation	Significantly increased FEV_1 approximately 20% vs. placebo	The time to decrease FEV1 by 20% following dosing of methacholine was 0.83±0.54 mg/mL to 1.31±0.66 mg/mL, p=0.0001 in IVMS, compared to no change in the placebo group (0.86±0.52 mg/mL to 0.91±0.54 mg/mL, p=0.83)
Silverman *et al*. [18] 2002, USA	RCT Double blind	248	IVMS vs. placebo in severe asthma (FEV_1 <30%)	Improved FEV_1	IVMS group mean FEV_1 of 48.2% predicted, compared to 43.5% predicted placebo group p=0.045
Singh *et al*. [19] 2008, Iran	RCT Single blind	10	IVMS vs. placebo	Statistically significant improvement FEV_1 6.07%	IVMS: 40.77+9.2% improvement from baseline, Control: 34.7+7.3% improvement
Bradshaw *et al*. [22] 2008, England	RCT Double blind	129	1.2 g IVMS vs. placebo in patients with PEF<75%	No benefit with regards to hospital admission rates or % predicted PEF at 60 min for the whole group, or for subgroups of life-threatening, severe and moderate acute asthma	Hospital admission rate: IVMS 79%, placebo 78% p=0.98 Predicted PEF at endpoint IVMS 63.7%, placebo 61.6 p=0.63
Goodacre *et al*. [20] 2013, England	RCT Double blind	1109	IVMS and nebulised magnesium vs. placebo on admissions and breathlessness	No statistically significant improvement in hospital admissions or breathlessness	Admissions at 4 hours: IVMS 279, placebo 278 (p=0.083) Change in % predicted PEFR at 1 hour: IVMS 11.4%, placebo 10.2%
Shan *et al*. [27] 2013, England	Meta-analysis of 11 adult trials	1754	IVMS and nebulised magnesium in adults and children with acute asthma	Significant improvement in respiratory function but weak evidence on admission rates	Respiratory function: SMD, 0.30; 95%CI (0.05-0.55); p=0.02 Admission: RR 0.86; 95%CI (0.73-1.01); p=0.06
Kew *et al*. [28] 2014, USA	Meta-analysis of 14 adult trials	2313	Most studies were double-blinded trials comparing a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes versus a matching placebo.	Single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute	Hospital admission: 0.75; 95%CI (0.60-0.92) favours magnesium

				asthma who have not responded sufficiently to oxygen, beta$_2$-agonists and IV corticosteroids.	PEF: 4.78 95%CI (2.14-7.430 favours magnesium