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Review

Stating the obvious: intravenous magnesium sulphate should be the first parenteral bronchodilator in paediatric asthma exacerbations unresponsive to first-line therapy

What is the most appropriate second-line intravenous bronchodilator treatment when a child with a severe asthma attack is not responsive to initial inhaled therapy? The second-line treatment options for acute asthma include parenteral β_2-agonists, methylxanthine and magnesium sulphate ($MgSO_4$). There is a poor evidence-base to inform this decision. This review argues that intravenous $MgSO_4$ is the obvious treatment of choice for this situation as the initial treatment based on current knowledge. We describe the mode of action, scope and limitations of $MgSO_4$, safety profile, economic impact, comparisons of the alternatives, and finally, what the guidelines say. This review explores the suitability of intravenous $MgSO_4$ as a pragmatic and safe initial second-line therapy for children unresponsive to initial asthma management.

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Introduction

Acute exacerbation or "attacks" of asthma pose a significant burden to paediatric healthcare facilities and to patients and their families. Despite a consensus on the fundamental principles underpinning the management of an acute asthma exacerbation, considerable variations exist in the "second-line approach" recommendations in guidelines once initial inhaled bronchodilators and corticosteroids have not worked [1–4]. Most second-line treatment options for acute asthma include parenteral β_2-agonists, methylxanthine and magnesium sulphate ($MgSO_4$) [5–8]. There are few clinical trials comparing their relative efficacy and safety profiles [9]. This paucity of evidence can potentially lead to a clinical dilemma for the treating physician on selecting a safe and effective initial second-line agent in children unresponsive to the initial conventional approach.

With ever-increasing pressures on healthcare facilities, an ideal step-up treatment should be safe and effective with minimal resource implications. The traditional agents used in asthma escalation, such as parenteral β_2-agonists and aminophylline, are known to require complex calculations for rate and dilution and the need for high-dependency monitoring [1–4].

$MgSO_4$ has a distinct mechanism of action in acute asthma, and has been a subject of interest in research for well over half a century. $MgSO_4$ can be administered through inhalational and intravenous

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routes. Inhaled $MgSO_4$ has been shown to be effective as an adjuvant therapy to standard management [10], although more recent data suggest it has little effect on length of stay and admission [11]. On its own, however, it has a limited utility in improving lung function and reducing hospital admissions [12]. Intravenous administration of $MgSO_4$ can improve clinical outcomes without significant safety concerns and resource implications. This review explores the suitability of intravenous $MgSO_4$ as a pragmatic and safe initial second-line therapy for children unresponsive to initial asthma management.

$MgSO_4$ in acute asthma: mechanism of action

Acute asthma exacerbation is associated with reversible obstruction of the airways through a complex interplay of bronchoconstriction, inflammation of the airways and increased mucus production. $MgSO_4$ exerts its beneficial effects at multiple levels in the inflammatory cascade of acute asthma. The bronchodilator effects of $MgSO_4$ are attributed to the blockade of calcium channels in the airway smooth muscles and a reduction in airway excitability. Furthermore, $MgSO_4$ exerts an anti-inflammatory effect through several mechanisms, including the obliteration of the release of oxygen free radicals, stabilisation of T-cells and mast cells, and facilitating the release of endogenous nitric oxide and prostacyclins. A synergistic bronchodilator action, when used simultaneously with salbutamol, has also been proposed [13, 14].

The usual recommended bolus dose of intravenous $MgSO_4$ is 25–50 $mg \cdot kg^{-1}$ (maximum 2 g) [15], but higher doses of 50–75 $mg \cdot kg^{-1}$ have also been proposed to achieve therapeutic drug levels [16].

$MgSO_4$ as the first parenteral bronchodilator: scope and limitations

There is a scarcity of adequately designed and powered trials that compare the efficacy and safety of intravenous $MgSO_4$ with other parenteral bronchodilators in acute asthma. The available evidence is further marred by a lack of uniformity in the use of clinical rating scales and other outcome parameters [17]. The bulk of evidence on intravenous $MgSO_4$ hence stems from observational studies and a limited number of placebo-controlled studies.

Impact of the use of intravenous $MgSO_4$ on patient outcome and organisational burden

Trials using intravenous $MgSO_4$ as a second-line agent in acute asthma generally favour its early use. Pooled results from randomised controlled trials with a total of 425 children comparing $MgSO_4$ with placebo or other parenteral agents demonstrated that the use of parenteral $MgSO_4$ resulted in significant benefits with clinical improvement, need for hospitalisation or mechanical ventilation, and discharge from the emergency department [18]. Notable caveats in interpreting these trials were smaller sample sizes and variable outcome parameters. This finding is consistent with an earlier meta-analysis on $MgSO_4$ treatment in emergency department settings [19], where concurrent use of $MgSO_4$ intravenously with inhaled bronchodilators and systemic corticosteroids resulted in an improvement in clinical scores. Thus, it appears that early use of intravenous $MgSO_4$ could compliment the bronchodilator response to the first-line agents.

Two systematic reviews illustrated the unequivocal benefit of intravenous $MgSO_4$ in improving spirometry parameters and hospital admission rates in the paediatric age group [12, 20], but not with nebulised $MgSO_4$. A Cochrane review by Griffiths *et al*. [21] investigating the effect of intravenous $MgSO_4$ on hospitalisation rates as the primary outcome serves as a further testament, with a reduced odds for admission of 68% with intravenous $MgSO_4$.

Mechanical ventilation in *status asthmaticus* is challenging and is reserved for patients who fail to respond to optimal medical management and develop respiratory failure. Torres *et al*. [22] reported a marked reduction in mechanical ventilation requirements for children with acute asthma exacerbation who received intravenous $MgSO_4$ within the first hour of treatment in the emergency department compared with those who only received standard care (nebulisation with β_2-agonists and corticosteroids). This study is interesting but has potential flaws. It was an open study and thus not blinded and in the control group there was a 33% intubation rate, which is extremely high. Considering the significant impact that mechanical ventilation has on the patient and hospital resources, these results could imply a potential significant saving of resources and reduced impact on the child.

A recent open intervention study with intravenous $MgSO_4$ alone given to all the subjects presenting with acute asthma exacerbation before receiving nebulised bronchodilators or steroids demonstrated a significant improvement in lung function parameters [23]. These findings indicate that intravenous $MgSO_4$ has bronchodilator properties even when used as a sole agent in the initial management of asthma.

High-dose continuous infusions of $MgSO_4$ have been used in the emergency department. This approach appears to have an effect on earlier discharge from the emergency department. In an open label, randomised, prospective study of 38 children (aged 6–16 years) in a single centre study from Paraguay, 50 $mg \cdot kg^{-1}$ over 1 h (bolus) was compared with high-dose prolonged $MgSO_4$

infusion of 50 mg·kg^{-1}·h^{-1} for 4 h (maximum of 8000 mg per 4 h) [24]. 47% in high-dose prolonged $MgSO_4$ infusion group (nine out of 19) *versus* 10% (two out of 21) in the bolus group (p=0.032) were discharged at 24 h, with an absolute risk reduction of 37% (95% CI 10–63) and a number needed to treat of 2.7 (95% CI 1.6–9.5) to facilitate a discharge at or before 24 h. The length of stay was shorter in the high-dose prolonged $MgSO_4$ infusion group (mean±SD: high-dose prolonged $MgSO_4$ infusion, 34.13±19.54 h; bolus, 48.05±18.72 h; p=0.013; 95% CI, 1.3–26.5) [24]. This is interesting data but has not been compared head-to-head with other regimens and so the exact role of high-dose continuous infusions of $MgSO_4$ in the emergency department is unclear.

Does the early use of intravenous $MgSO_4$ in the emergency department reduce the chances of hospitalisation?

An analysis of the Cochrane reviews on randomised controlled trials looking at the efficacy and safety of second-line agents used in acute asthma escalation regimes covering 67 trials unequivocally established that the use of intravenous $MgSO_4$ reduced chances, as well as the duration, of hospitalisation (high certainty evidence) [9]. The review did not identify any second-line interventions that could reduce the chances of critical care admission. Another systematic review [25] also inferred that a dose of intravenous $MgSO_4$ at 50–75 mg·kg^{-1} in emergency departments reduced the chance of hospital admission, with one hospitalisation prevented for every five children receiving the dose. A meta-analysis [19] of five randomised placebo-controlled trials also demonstrated that administration of intravenous $MgSO_4$ reduced the hospitalisation rates with a number needed to treat of four patients.

The safety profile of intravenous $MgSO_4$

A review of 53 papers on the use of intravenous $MgSO_4$ in asthma in the emergency room did not highlight any safety concerns [25]. Furthermore, the use of $MgSO_4$ did not produce any haemodynamic or neuromuscular problems even at extended dose regimes that included a bolus followed by an infusion over 4 h [26]. The wide therapeutic window and safety profile of intravenous $MgSO_4$ is further affirmed by a retrospective study of children who received prolonged $MgSO_4$ infusions for more than 24 h [27].

Is monitoring of serum levels needed?

The recommended dose of $MgSO_4$ is 25–50 mg·kg^{-1} per dose (maximum 2 g) [15]. After the loading dose, the serum $MgSO_4$ levels have been examined in several studies; adverse effects tend to occur at levels exceeding 9 mg·dL^{-1}. Significant untoward events such as respiratory depression and arrhythmia occur with serum levels exceeding 12 mg·dL^{-1}. The maximum 1-h post-dose serum levels attained after a bolus of up to 20 g in adults have been shown to be three times the normal serum levels (normal range 1.7–2.2 mg·dL^{-1}) [28]. Ionised $MgSO_4$ levels are regarded as superior in ascertaining the correlation with the bronchodilator effects. The exact correlation between the ionised and total serum levels is poorly understood and is likely influenced by the blood pH. Due to this, serum $MgSO_4$ level estimation is not routinely recommended with bolus dose regimes [27].

The financial impact of the addition of intravenous $MgSO_4$

A cost-utility analysis comparing the economic burden of adding intravenous $MgSO_4$ to the standard treatment (salbutamol nebulisation and methylprednisolone) observed the use of the former offered superior cost-efficiency when compared to the latter. The authors recommended the inclusion of $MgSO_4$ in acute asthma management protocols, especially in middle-income countries [29].

Second-line agents in acute asthma management: weighing up the options

Acute asthma protocols use intravenous β_2-agonists, aminophylline or $MgSO_4$ when the response to first-line treatment is suboptimal [1–4]. In a randomised controlled trial that compares these second-line approaches, Singhi *et al*. [30] compared the 1-h post-treatment Clinical Asthma Severity (CAS) scores in 100 children whose clinical condition mandated $MgSO_4$, terbutaline or aminophylline, administered intravenously. The authors observed that intravenous $MgSO_4$, used as an adjuvant to inhaled β_2-agonists and corticosteroids, was more efficacious and safer than terbutaline or aminophylline. No adverse effects were reported in children who received $MgSO_4$, while hypokalaemia and vomiting were reported in some children with terbutaline and aminophylline, respectively. Notwithstanding the possible impacts of a small sample, lack of double-blinding and inter-observer variability in clinical scoring, this trial places intravenous $MgSO_4$ as a reasonable first option when conventional nebulisation and corticosteroids fail. A previous smaller trial [31] compared intravenous $MgSO_4$ and salbutamol in a critical care environment. Both the agents produced discernible improvement in the clinical picture, albeit the latter faring slightly better.

Aminophylline has a narrow therapeutic range, mandating careful balancing of dosing to optimise

the therapeutic benefits while avoiding adverse effects. Attaining serum levels within this desired range can be challenging, as drug elimination rates can vary between individuals [32]. Emesis is a common side-effect, while a reduction in seizure threshold is reported even with therapeutic serum levels [33]. Confusion, neurological depression, dysrhythmias and alteration of hepatic function are known to occur with blood levels exceeding the therapeutic range.

Intravenous salbutamol is preferred by some as the standard escalation agent for acute asthma. There is an absence of standard recommendations on the use of nebulised bronchodilators alongside its intravenous use. Markedly elevated salbutamol concentrations have been reported in children who have received intravenous salbutamol at the currently recommended doses. Common adverse events include anxiety, tremors, lactic acidosis, hypokalaemia, raised blood sugar and sinus tachycardia, which can also be associated with clinical deterioration, thus resulting in a potentially confusing picture for the clinician. In addition, the drug levels that can be associated with these side-effects are not clear [34]. An alternate β_2-agonist often employed parenterally in acute asthma is terbutaline. Its use has been associated with severe sympathomimetic effects such as tachycardia, arrhythmia, and myocardial ischaemia [17].

Intravenous $MgSO_4$ in the acute asthma treatment hierarchy: current guidelines and practices

The British Thoracic Society/Scottish Intercollegiate Guidelines Network (UK 2019) recommends $MgSO_4$ as the first-line intravenous agent in children failing to respond to nebulised bronchodilators [1]. A bolus dose of salbutamol may also be considered early. Aminophylline is recommended only when other treatment approaches are exhausted [1]. The Australian Asthma Council also propose intravenous $MgSO_4$ as the preferred intravenous second-line agent in severe/life-threatening asthma, with intravenous salbutamol and aminophylline recommended as third-line agents [2]. The Canadian Paediatric Society position statement also makes similar recommendations on $MgSO_4$ and salbutamol use, with aminophylline reserved for critical care settings [3]. This standpoint on the use of $MgSO_4$ is shared by the Global Initiative for Asthma (GINA), which does not approve the use of aminophylline for safety concerns, and limits the use of terbutaline for very unwell children with respiratory effort inadequate to deliver nebulised bronchodilator [4]. The New Zealand Asthma and Respiratory Foundation guidelines extend the use of intravenous $MgSO_4$ to pre-hospital settings [35].

A recent Paediatric Emergency Care Applied Research Network (PECARN) registry review noted the use of intravenous $MgSO_4$ is in around 10% of children presenting with acute asthma, with the median time from triage to administration around 2.5 h. A discharge from the emergency department after intravenous $MgSO_4$ was deemed safe [36]. The acceptance of intravenous $MgSO_4$ is again reflected in a nationwide survey from the Netherlands, where 96% of the respondents reported its use in children who failed to respond to first-line asthma therapy [37]. Perhaps the most telling evidence of the increasing recognition of intravenous $MgSO_4$ in *status asthmaticus* is that its use has almost doubled across children's units across the USA over the past decade [38]. A concurrent reduction in the length of hospital stay, from 1.6 days in 2010 to 1.4 days in 2017, was also noted in this review.

Conclusion

The choice of the escalation agent in acute asthma management often remains obscure, with a range of options and widespread variability in emergency practice. Evidence pooled in this review indicates that the early use of intravenous $MgSO_4$ in acute asthma management when conventional inhaled bronchodilators fail is beneficial in improving the clinical course and reducing hospitalisation. The lack of special clinical and pharmacokinetic monitoring requirements puts this drug in a uniquely advantageous position over intravenous β_2-agonists or methylxanthine. The safety profile of intravenous $MgSO_4$ also appears to be distinctly superior compared with the other agents. However, there is a distinct shortage of well-powered studies with robust designs comparing the clinical efficacy and impact on hospital resources. The bulk of current evidence is constituted by studies examining the safety and efficacy of individual agents and based on this, the authors conclude that intravenous $MgSO_4$ should be the answer to the "escalation dilemma" in acute asthma management in children.

The final conclusions of the paper by Neame *et al.* [33], on which intravenous bronchodilator to choose, gave simple pragmatic advice: "Decisions about which treatment to use should include risk management considerations such as ease of prescription, preparation and administration factors and availability of high-dependency beds". We would agree with this and argue that $MgSO_4$ should be the initial second-line intravenous medication to use once maximal inhaled therapy has failed. Intravenous $MgSO_4$ is easy to prepare and administer, has the best side-effect protocol (compared to the other intravenous bronchodilator options), does not need serum drug level monitoring, does not require admission to a paediatric high-dependency unit/paediatric

intensive care unit to give [5, 6], and, once the emergency department team are experienced with $MgSO_4$ delivery, is a safe initial intravenous option. Until an adequately powered head-to-head trial shows superiority of any of the other intravenous bronchodilators, $MgSO_4$ is the obvious choice.

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Conflict of interest

G. Erumbala has nothing to disclose. S. Anzar has nothing to disclose. A. Tonbari has nothing to disclose. R. Salem has nothing to disclose. C. Powell is an Assistant Editor of Archives of Disease in Childhood; reports participation on a Data Safety Monitoring Board or Advisory Board for BRACE study (Australia; Chair) and PARROT study (Liverpool and Australia; Chair).

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