Magnesium Sulfate for Severe Acute Asthma in Children

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Magnesium is an abundant intracellular cation that has been used for years in the treatment of hypertension and seizures associated with eclampsia of pregnancy as well as used as a tocolytic agent.¹ Over sixty years ago, Haury showed that magnesium sulfate (MgSO_4) could produce bronchodilation in asthmatics.² However, interest in magnesium sulfate as a potential therapy for acute asthma surfaced in the late 1980s following a series of studies demonstrating that magnesium produced dose-dependent bronchodilation. The precise mechanism by which magnesium produces smooth muscle relaxation is not known, but it is thought to act by enhancing calcium uptake in the sarcoplasmic reticulum³ and/or as a calcium antagonist.⁴ In addition, magnesium is a cofactor regulating a number of enzymatic and cellular activities in the body, including adenylyl cyclase and sodium-potassium ATPase, potentially enhancing the effects of β_2 -agonists.⁵ Other potential beneficial mechanisms in asthma include inhibition of acetylcholine release from cholinergic nerves⁶ and reduction of histamine release from mast cells.⁷

It is not clear whether magnesium acts as a functional antagonist to bronchoconstriction like the β_2 -agonists and theophylline or a specific antagonist like anticholinergics and antihistamines. Studies showing attenuation of the bronchoconstriction from histamine and methacholine would suggest functional antagonism.^{8,9} Some suggest that the response to intravenous magnesium sulfate is dependent upon achieving serum magnesium concentrations of 4–6 mg/dL (1.6–2.4 mmol/L).¹⁰ These values are similar to those that are employed to achieve tocolysis (4–8 mg/dL) and about one half those associated with severe toxicity of respiratory failure, cardiac arrhythmias and death (12–15 mg/dL).¹ It should be pointed out that studies have not reported lower magnesium concentrations in asthmatics than controls although one study reported correlation with bronchial hyperresponsiveness and intracellular magnesium concentrations in asthmatics.^{11–13} Thus, it is unlikely that the bronchodilator response to magnesium is a result of restoring normal homeostasis but most likely a function of its direct antagonistic effects on intracellular calcium activity.

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EVIDENCE FOR EFFICACY IN ACUTE ASTHMA

The National Asthma Education and Prevention Program's Expert Panel Report 2 (EPR 2) listed the use of intravenous MgSO_4 as experimental therapy, as the few available studies were small and inconclusive.¹⁴ However, the recent revision of the Global Initiative for Asthma suggested that either intravenous aminophylline or intravenous MgSO_4 may be considered in pa-

tients with severe exacerbations not responding adequately to standard therapy with inhaled short-acting β_2 -agonists and inhaled anticholinergics.¹⁵ This recommendation is largely based upon a systematic review by the Cochrane Library's Airways Review Group.¹⁶ Although they stated that the routine administration of intravenous MgSO_4 to all patients presenting to the emergency department was not justified, a subset of the most severe patients who responded poorly to initial inhaled β_2 -agonists benefited from MgSO_4 . The conclusion was largely driven by subset analyses from two clinical trials in adults from the same group of authors that found no effect of intravenous MgSO_4 in the overall populations of 135 and 248 patients.^{17,18} The second trial¹⁸ was published as an abstract in 1996,

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but the data was made available to the Cochrane group for their systematic review.¹⁶ In addition, the Cochrane review included two small studies in children (78 patients total) that provided results consistent with the overall results.^{19,20} Based upon risk assessment, the Cochrane review estimated that 8 patients with severe acute asthma would require treatment in order to prevent one hospitalization.

Since the publication of the Cochrane review three randomized controlled trials comparing intravenous MgSO_4 to placebo have been published that appear to confirm their conclusions: one in adults that had been included in the review¹⁸ and two small trials in children.^{21,22} The study by Ciarallo et al.²² is noteworthy in that they used the same study design as their first trial¹⁹ with the exception of a larger dose of intravenous MgSO_4 (40 mg/kg versus 25 mg/kg, both with a 2 gram maximum). Comparing the results of both studies, they suggested there was a dose-response to MgSO_4 and that the larger dose producing almost a doubling of the improvement in peak expiratory flow (PEF) ($P < 0.001$).²² Even more remarkable was their finding that one hospitalization could be prevented for every 2 patients treated with 40 mg/kg of intravenous MgSO_4 , a significantly better rate than suggested by the Cochrane review. The studies by Devi et al.²⁰ and Gurkan et al.²² used doses of 100 mg/kg and 40 mg/kg (both with a maximum of 2 grams) respectively.

CONCERNS WITH THE EVIDENCE

As reviewed above, the use of intravenous MgSO_4 as adjunctive therapy in severe acute asthma, particularly in children, would appear to provide the potential for high benefit with very few risks outside of the need for intravenous access. Of note, the results of the Cochrane review stimulated an NIH workshop in September 2000 co-sponsored by the National Center for Complementary and Alternative Medicine and the NHLBI to assess the science and make recommendations regarding research on MgSO_4 for acute asthma. The workshop resulted in a Request for Proposals for a definitive study of intravenous MgSO_4 in severe acute asthma.²³ Meta-analyses do not provide definitive conclusions but are a tool to assess disparate findings from a body of clinical trials. They primarily grade the

evidence using Jadad quality scores that focus on randomization, blinding and allocation concealment.²⁴

However, factors such as adequacy of dosing, effect of co-interventions, and/or similar severity of illness across studies may result in significant differences in outcomes. In addition, use of subsets from post hoc analyses without prior stratification of enrollment is fraught with problems as the randomization is no longer present, particularly if the subset numbers are low. For example, the study by Bloch et al. had an original population of 135 but only 35 in the severe group, and two thirds of those were in the group receiving MgSO_4 .¹⁷ The study by Silverman et al. with 248 initial patients found a significant difference in the group presenting with a forced expiratory volume in 1 second (FEV_1) $< 20\%$ of predicted missing word that included 63 patients with 52% more in the placebo group.¹⁸ The primary function of both meta-analyses and post hoc subset analyses of large clinical trials is exploratory in order to determine and facilitate design of prospective randomized clinical trials and to determine the feasibility of such trials.

Standardization of asthma severity and lack of control of co-interventions was problematic, both within and across all the studies, and could very well have biased the results. Some of the studies used baseline lung function while others used failure to respond to initial standard therapy. However, the initial standard therapy ranged from one to three doses of inhaled β_2 -agonist.¹⁶ The later study by Ciarallo also allowed use of ipratropium bromide as part of initial therapy.²¹ However, Strauss et al. reported that even in the more mild patients with a good response to inhaled β_2 -agonists, a significant variation in response with up to 36% required only a single 2.5 mg nebulized dose of albuterol with an additional 20% requiring two doses and the rest, required a third dose to a cumulative total of 7.5 mg to achieve the optimal response.²⁵ This 3-fold variation in response combined with the potentially 3-4 fold differences in lung delivery from patient to patient is likely to result in a more heterogeneous group included in studies if at least 3 doses of standard therapy are not used.

Those studies that used response to inhaled β_2 -agonists as entry criteria had variable lung function criteria, ranging from failure, to double

their PEF, to < 60% - 75% predicted FEV1. In addition, intrastudy variation in baseline severity has been reported. The baseline FEV1 % predicted values in the first Ciarallo study were significantly different with the control baseline of 45% and the treatment group 33% ($P=0.01$).¹⁹ The Cochrane review tried to overcome this disparity of baseline severity by using the percentage of hospital admissions in the placebo group as a measure of severity, classifying the patients as severe if the control group admission rate was > 70%.¹⁶ However, using an outcome variable as a criteria for entry level severity assessment is circular reasoning and, as discussed below, can be affected by co-interventions or lack thereof. The lack of adequate control of baseline therapy was not considered by the Cochrane systematic review as many of the studies left co-interventions to the discretion of the treating (non-research) physicians, thereby providing a wide variance.¹⁶ For example, Ciarallo et al.²¹ reported patients received on average 1.6 nebulization treatment (no dose provided) over the 110 minutes following $MgSO_4$ administration, where recommended therapy would be to continue to administer one treatment every 20 minutes (5 treatments) or a minimum of 1 treatment per hour (at least 2-3 treatments). On the otherhand, in the study by Bloch et al., all patients received nebulized albuterol at the time of $MgSO_4$ and at 30, 60, 120 and 180 minutes following administration.¹⁷

COMPARISONS WITH OTHER BRONCHODILATORS

No studies have compared the administration of $MgSO_4$ to other interventions shown to improve outcomes over standard doses of inhaled β_2 -agonists. Compared to inhaled β_2 -agonists, intravenous $MgSO_4$ is only a moderately potent bronchodilator.^{26,27} Okayama et al. compared 2.46 grams of intravenous $MgSO_4$ to 0.67 mg nebulized albuterol in ambulatory patients and demonstrated a 15% mean incremental improvement in FEV1 that was not significantly different to the low dose of albuterol.²⁶ Noppen et al.²⁷ studied patients during the first 2 days of hospitalization for acute asthma and noted a 12% mean incremental improvement in FEV1 following 3 grams of intravenous $MgSO_4$ that was significantly less than that produced by 2.5 mg of nebulized albuterol. Most of the studies in acute

severe asthma confirm the relatively modest improvement in lung function, with the Cochrane review reporting a 10% improvement in FEV1 % predicted over control therapy. Of interest are the two studies in children by Ciarallo that reported mean maximum incremental improvements in the FEV1 of 24%.^{19,21} In the first trial all values were reported as percentage increase over baseline; thus, the low baseline for the $MgSO_4$ group of 33% predicted magnified the incremental change.¹⁹ The authors suggested that children may be more sensitive to the effects of $MgSO_4$ than adults. However, there is no direct evidence to support an age-dependent responsiveness, and the small differences noted could be explained by study design differences.

The 10% - 20% incremental improvement in FEV1% predicted is similar to that provided by aminophylline administered as monotherapy or ipratropium bromide administered as adjunctive therapy to optimal inhaled β_2 -agonists.²⁸⁻³⁰ Several trials in both emergency departments and hospitalized patients have shown no further benefit to adding aminophylline to optimal inhaled β_2 -agonists.^{28,31} One notable exception is a study that reported greater improvement in lung function in the patients receiving aminophylline when the inhaled β_2 -agonists administration was used as an outcome variable and not administered on a regularly scheduled basis.³² It is interesting that the study by Tiffany et al. failed to demonstrate a significant bronchodilator effect or difference in hospital admissions from intravenous $MgSO_4$.³³ All patients received intravenous aminophylline and regularly scheduled inhaled β_2 -agonists. The Cochrane review suggested that the patients in this study had mixed severity due to the low admission rate in the placebo group (29%), yet they used the same entry criteria as the study by Skobeloff et al.³⁴ whose patient population was considered severe. The principal difference between studies was the control of baseline therapy by Tiffany et al.³³

The studies of the addition of inhaled ipratropium bromide to standard therapy of inhaled β_2 -agonists and systemic corticosteroids are interesting. Early single dose trials suggested a further improvement in lung function but no difference in hospitalization rate, whereas followup trials of frequent multiple doses provided evidence for a decreased hospitalization in the patients presenting with the more severe

airway obstruction.^{29-31,35} A meta-analysis of studies in children suggested that 11 patients would need to be treated to prevent one hospitalization in children presenting with an FEV1 $\leq$ 55% predicted.³⁵ Similar findings were reported for a meta-analysis of adults studies where patients presenting with an FEV1 $<$ 30% predicted had a 38% reduction in admission rate.³⁶ These are the same groups of children and adults that would reportedly benefit from the addition of intravenous MgSO₄.^{16,19-22} One trial in children noted an 83% admission rate in the patients who had severe obstruction and received only albuterol. The admission rate was reduced to 27% with the addition of ipratropium, suggesting the severity of these patients was similar to that in the magnesium trials.²⁹ Two large prospective randomized clinical trials designed to assess hospital admission confirmed these results, reporting that 6 children with severe obstruction (FEV1 $<$ 30% predicted) required treatment to prevent one hospitalization³⁰ and the number of adults requiring treatment was 5.³⁷ The trials of intravenous MgSO₄ did not use or control for the use of ipratropium bromide.¹⁶ The recent trial by Ciarallo allowed ipratropium bromide alone or in combination with nebulized albuterol as initial therapy and continued baseline therapy; however, this was not consistent across all patients in the study.¹⁹

The primary concern with the pediatric studies of intravenous MgSO₄ is the lack of control of baseline therapy. The studies by Ciarallo reported the largest effect in patients who received on average 1.6 nebulization treatments over the next 110 minutes following the administration of MgSO₄.^{19,21} Recommended baseline therapy would be to continue to administer 1 treatment every 20 minutes (5 treatments) or a minimum of 1 treatment per hour (at least 2–3 treatments). Because the baseline therapy was inadequate, one could not determine if MgSO₄ added significantly or whether it was just better than inadequate baseline therapy.

CONCLUSIONS

Intravenous MgSO₄ produces moderate degrees of bronchodilation in pediatric patients with acute severe asthma in whom inhaled β_2 -agonists are withheld or not routinely administered.¹⁹⁻²¹ The administration of magnesium has

not produced added bronchodilation or improved therapeutic outcomes in patients who have continued to receive standard recommended inhaled β_2 -agonist therapy of acute severe asthma.^{17,18,33,38} However, post hoc subset analyses suggests that a definitive, prospective, randomized trial of patients with severe obstruction and an inadequate response to initial therapy is warranted. This trial needs to place close attention to entry criteria and control of baseline therapy. In addition, a trial comparing outcomes with the addition of multiple dose ipratropium bromide versus intravenous MgSO₄ in patients with severe asthma would be important. At this time due to the lack of efficacy except in subset analyses, the use of MgSO₄ should continue to be considered experimental, and less invasive alternatives such as multiple dose inhaled ipratropium should be used.

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