Magnesium Bolus or Infusion Fails to Improve Expiratory Flow in Acute Asthma Exacerbations*

Brian R. Tiffany, M.D.; William A. Berk, M.D.; Iain Keir Todd, PA-C, M.Ed.; and Suzanne R. White, M.D.

Objective: Intravenous magnesium sulfate improves objective measures of expiratory flow in patients with acute severe exacerbations of asthma.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Urban emergency department.

Participants: Forty-eight asthmatic patients aged 18 to 60 years with initial peak expiratory flow rate (PEFR) <200 L/min who failed to double their initial PEFR after two standardized albuterol treatments.

Interventions: Subjects were randomized to three groups: a loading dose of magnesium sulfate, 2 g IV over 20 min followed by 2 g/h over 4 h (infusion), magnesium sulfate, 2 g over 20 min followed by placebo infusion (bolus), or placebo loading dose and infusion (placebo). All subjects received standardized aminophylline and steroid therapy.

Measurements: The PEFR and FEV₁ were measured at the start of the loading dose, and 20, 50, 80, 140, 200, and 260 min later using a water-displacement spirometer. Changes from baseline were compared by one-way analysis of variance for repeated measures.

Results: Magnesium sulfate administration did not at any time significantly improve either FEV₁ (F = 0.036, p = 0.96) or PEFR (F = 0.51, p = 0.61). This study had the power to detect a PEFR difference of 26 L/min and a FEV₁ difference of 0.19 L between groups (β = 0.20, α = 0.05 two-tailed significance).

Conclusion: Use of IV magnesium sulfate in addition to standard therapy does not provide clinically meaningful improvement of objective measures of expiratory flow in patients with moderate to severe asthma exacerbations.

(Chest 1993; 104:831-34)

**Materials and Methods**

A convenience sample of patients between the ages of 18 and 60 years presenting to our emergency department with acute asthma as defined by the American Thoracic Society guidelines, and able to give informed consent, were eligible for the study. Patients were excluded for first episode of wheezing, history of chronic bronchitis or emphysema, oral temperature >38.2°C; history of renal failure, history of congestive heart failure, or requiring tracheal intubation. On arrival, peak expiratory flow rates (PEFRs) were measured with a hand-held spirometer (Wright) and the best of three efforts was recorded. Patients with an initial PEFR more than 200 L/min were excluded. All others were given two treatments with aerosolized albuterol, 2.5 mg 30 min apart. Patients whose PEFR either failed to increase by more than 100 percent or remained below 200 L/min and gave informed consent were entered in the study. The PEFR criteria were designed to select a subset of patients with severe attacks who were not responding well to aerosolized therapy.

Intravenous (IV) lines were established, and blood samples were collected to determine initial theophylline and magnesium levels. Subjects then received methylprednisolone, 125 mg IV, a third albuterol aerosol treatment, and an aminophylline loading dose and infusion sufficient to maintain serum theophylline levels at approximately 15 µg/L. Subjects were randomized to one of the following three treatment groups: an infusion group that received magnesium sulfate, 2 g IV over 20 min followed by a continuous magnesium infusion of 2 g/h over 4 h; a bolus group that received magnesium sulfate, 2 g IV over 20 min followed by a placebo infusion; or a placebo group that received a saline placebo bolus and infusion. Patients were assigned to a treatment group by computerized random number generation under the control of the hospital pharmacy. Investigators and patients were blinded to patient assignment to the study groups. Pulmonary function was measured by a water-displacement spirometer (Warren-Collins). Pulmonary function was tested at 0, 20 (end of bolus), 50, 80, 140, 200, and

---

*From the Department of Emergency Medicine, Detroit Receiving Hospital and University Health Center, Wayne State University, Detroit. Manuscript received November 2, 1992; revision accepted January 28, 1993.

Reprint requests: Dr. Tiffany, Department of Emergency Medicine, 4201 St Antoine, Detroit 48201

---

ANOVA = analysis of variance; PEFR = peak expiratory flow rate

---

Standard therapy of acute exacerbations of asthma includes treatment with β-adrenergic agents, methylxanthines, and parenteral steroids.1,2 Despite the efficacy of these agents, a considerable proportion of patients fail to respond and require hospitalization and/or intubation. Other patients relapse after discharge from emergency departments and require further treatment. Several recent reports have suggested that magnesium administered as an intravenous bolus produces bronchodilation in asthmatics.5-7 Its low cost, widespread availability, and low incidence of side effects make magnesium an attractive addition to bronchodilator therapy. However, to our knowledge, no study has addressed whether magnesium provides a clinically meaningful additional benefit over the use of standard bronchodilator therapy alone and some reports suggest that the beneficial effect of magnesium is short lived.5,8 We conducted a randomized, double-blind, placebo-controlled trial to address the following hypothesis: when used in combination with standard bronchodilator therapy, magnesium sulfate provides additional improvement in objective measures of expiratory flow.

---

Downloaded From: http://journal.publications.chestnet.org/pdfeaccess.ashx?url=/data/journals/chest/20382/ on 06/26/2017
Table 1—Study Group Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Bolus</th>
<th>Infusion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>36.2</td>
<td>42.9</td>
<td>41.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>52.3%</td>
<td>53.3%</td>
<td>16.7%</td>
<td>0.17</td>
</tr>
<tr>
<td>Initial magnesium, mg/dl</td>
<td>2.01</td>
<td>2.06</td>
<td>2.04</td>
<td>0.73</td>
</tr>
<tr>
<td>Initial theophylline, mg/dl</td>
<td>6.42</td>
<td>6.66</td>
<td>9.46</td>
<td>0.53</td>
</tr>
<tr>
<td>Initial FEV₁, L</td>
<td>.96</td>
<td>.93</td>
<td>.91</td>
<td>0.95</td>
</tr>
<tr>
<td>Initial PEFR, L/min</td>
<td>131</td>
<td>117</td>
<td>123</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*PEFR = peak expiratory flow rate.

260 min. The best of three efforts for PEFR and FEV₁ were recorded at each time point. Clinical decision making was left to attending physicians. This study was approved by the Wayne State University Human Investigation Committee.

Data Analysis

Groups were analyzed for differences with respect to age, initial magnesium and theophylline levels, and initial PEFR and FEV₁ determinations using analysis of variance (ANOVA). Differences in the sex composition of the groups were analyzed with a contingency table. Spirometric measurements were analyzed for differences both in absolute values and change from baseline using ANOVA for repeated measures. Additionally, the bolus and infusion groups had received identical treatment over the first 20 min and were combined for analysis at these time points in order to study the immediate effect of a magnesium bolus. The PEFR and FEV₁ in this analysis were compared using an unpaired Student's t test. Significance was taken as p<0.05.

Ad hoc power analysis was performed using β = 0.20, α = 0.05, and a two-tailed ANOVA. Desired improvement was a ΔPEFR of 30 L/min, chosen based on one half the effect observed in a previous study. We considered this a reasonable minimal therapeutic effect for "clinical significance." To fulfill these criteria, 42 patients were required.

RESULTS

Forty-eight patients were enrolled in the study. No significant differences were found between the groups at study entry (see Table 1). Serum magnesium levels at the conclusion of the study were 1.99 ± 0.27 mg/dl in the placebo group, 2.26 ± 0.26 mg/dl in the bolus group, and 4.60 ± 0.64 mg/dl in the bolus group.

No significant differences were observed over time in either PEFR (F = 0.188, p = 0.83) (Fig 1) or FEV₁ (F = 0.57, p = 0.94) (Fig 2). Results were similar when ΔPEFR and ΔFEV₁ were used rather than absolute PEFR and FEV₁ (ΔPEFR, F = 0.51, p = 0.61; ΔFEV₁, F = 0.36, p = 0.96, data not shown).

In order to study the immediate effect of a magnesium bolus, the bolus and infusion groups were combined at 0 and 20 min. Over this time, PEFR improved by 12.4 ± 5.3 L/min in the combined magnesium groups compared with a worsening of 1.6 ± 6.6 L/min in the control group (p = 0.10). Post hoc power analysis shows a power of 0.90 for finding a difference of 30 L/min between the means, and a power of 0.80 for a difference of 26 L/min. The FEV₁ improved by 0.013 ± 0.015 L/min in the placebo group and 0.024 ± 0.039 L/min in the magnesium group (p = 0.86). Post hoc power analysis revealed a power of 0.80 for a difference of 0.19 L between the means.

DISCUSSION

In 1938, Haury demonstrated that magnesium blocks the bronchoconstrictor action of histamine and pilocarpine in human subjects. Recent in vitro work has confirmed the efficacy of magnesium as a bronchial smooth-muscle relaxant. Magnesium competes with calcium for entry into smooth muscle cells, inhibits release of calcium from the sarcoplasmic reticulum, inhibits histamine release from mast cells, and inhibits acetylcholine release from nerve terminals, all of which contribute to the clinical effect of magnesium in asthma.
which have the effect of relaxing smooth muscle. Human studies have confirmed that IV magnesium attenuates the bronchoconstrictor response to histamine and methacholine\(^\text{10,30}\) and can produce improvement of results of pulmonary function tests in stable asthmatics withdrawn from treatment with medications prior to testing\(^\text{4,5}\) in a dose-dependent fashion.\(^4\)

Although recent case reports have suggested a beneficial effect of magnesium on patients with acute exacerbations of asthma,\(^\text{6,7}\) few studies have tested magnesium therapy prospectively. In 1989, Skobeloff et al\(^\text{8}\) reported on 38 asthmatics who were given a single dose of IV magnesium. A statistically significant increase in PEFR of 72 L/min was observed in treated patients compared with 8 L/min in control subjects.\(^8\) Noppen et al\(^\text{9}\) reported an unblinded crossover study in which six hospitalized asthmatics were given IV magnesium, followed 30 minutes later by albuterol inhalation.\(^9\) A statistically significant improvement in FEV\(_1\) occurred following the magnesium bolus; however, the subsequent albuterol treatment resulted in even greater improvement. Additionally, these data showed a rapid worsening of FEV\(_1\) after the completion of the bolus, consistent with previous work showing a short duration of action for IV magnesium.\(^10\) This may reflect the fact that hypermagnesemia causes only a transient depression of intracellular calcium levels.\(^21\)

Since these studies withheld \(\beta\)-agonist therapy during the study period, they failed to address the clinically important question of magnesium's efficacy in addition to standard bronchodilator therapy. The single previous study that used magnesium in addition to a standard treatment regimen found no benefit on PEFR, hospital admission rates, or time spent in the emergency department.\(^22\) However, this study was not blinded and enrolled all asthmatic patients presenting to the emergency department, including some who responded rapidly and completely to \(\beta\)-agonists. This may have obscured a beneficial effect on patients unresponsive to standard therapy.

In the present study, we evaluated the efficacy of IV magnesium in addition to standard bronchodilator therapy with \(\beta\)-agonists, methylprednisolone and amionophylline over 4 h and 20 minutes. Our study was prospective, randomized, and double blind. Magnesium given as either a 2-g bolus or a 2-g bolus followed by continuous infusion of 2 g/h did not significantly improve PEFR or FEV\(_1\) at any time point. Power analysis indicates that under the conditions of our study, the mean benefit on PEFR from a magnesium bolus is unlikely to be greater than 26 L/min. A therapeutic effect of this magnitude is not sufficient to merit routine use of magnesium as a component of standard therapy for moderate to severe asthmatic exacerbations.

Several considerations limit the generalizability of our results. First, our patients were having moderate to severe asthma exacerbations and were responding poorly to initial therapy. Therefore, our conclusions may not apply to less severely ill patients, many of whom are treated with inhaled \(\beta\)-agonists, improve rapidly, and are discharged from the hospital. On the other hand, patients who respond to standard therapy are unlikely to require treatment with additional therapeutic agents. We cannot exclude the possibility that some subsets of patients may respond well to magnesium therapy. For example, intubated patients were excluded from this study, which may underrepresent patients with life-threatening bronchospasm. Gender may also play a role, since there are well-documented hormonal influences on airway reactivity. Pregnant asthmatic patients appear to have less severe disease and are more responsive to bronchodilator therapy,\(^23\) and estrogen has been observed to augment the bronchodilator effect of magnesium.\(^24\) The study by Skobeloff et al\(^8\) had a preponderance of women (25 of 34), while our study population had a smaller
proportion of women (29 of 48), a difference that may partially explain the disparity in our conclusions. We did observe a trend in our data toward female responsiveness to magnesium infusion, although this trend did not achieve statistical significance. Since this study was not designed to measure the effect of magnesium on such subpopulations, it does not have a sufficient number of subjects to perform meaningful subgroup analyses. However, the response of such subgroups may prove to be clinically important and should be addressed with controlled clinical trials.

CONCLUSION

We conclude that IV administered magnesium sulfate does not provide clinically meaningful improvement in pulmonary function test results when used in addition to standard bronchodilator therapy in patients with moderate to severe asthmatic exacerbations.

ACKNOWLEDGMENTS: We would like to express our appreciation to Raywin Huang, Ph.D., for his assistance with the statistical analysis of our data. We also appreciate the generosity of the Wayne State University Department of Family Practice for graciously loaning us the spirometer used in this study.

REFERENCES

12. Haury VG. The broncho-dilator action of magnesium and its antagonistic action (dilator action) against pilocarpine, histamine, and barium chloride. J Pharmacol Exp Ther 1938; 64:58-64