Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial

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Summary

Background Intravenous magnesium can cause bronchodilation in treatment of severe asthma, however its effect by the nebulised route is uncertain. We aimed to assess the effectiveness of isotonic magnesium sulphate as an adjuvant to nebulised salbutamol in severe attacks of asthma.

Methods We enrolled 52 patients with severe exacerbations of asthma presenting to the emergency departments at two hospitals in New Zealand. A severe exacerbation was defined as a forced expiratory volume at 1 s (FEV₁) of less than 50% predicted 30 min after initial administration of 2·5 mg salbutamol via nebulisation. In this randomised double-blind placebo-controlled trial patients received 2·5 mg nebulised salbutamol mixed with either 2·5 mL isotonic magnesium sulphate or isotonic saline on three occasions at 30 min intervals. The primary outcome measure was FEV₁ at 90 min. Analysis was per protocol.

Findings At 90 min the mean FEV₁ in the magnesium group was 1·96 L (95% CI 1·68–2·24) and in the saline group 1·55 L (1·24–1·87). The difference in the mean FEV₁ was 0·37 L (0·13–0·61, p=0·003).

Interpretation Use of isotonic magnesium as an adjuvant to nebulised salbutamol results in an enhanced bronchodilator response in treatment of severe asthma.

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Introduction

Magnesium is an inorganic cation that is a cofactor in many intracellular phosphorylation processes. Hypomagnesaemia has been implicated in chronic asthma through mechanisms involving modulation of inflammatory processes. Magnesium is also a powerful relaxant of smooth muscle in the airway, and this is the mechanism through which intravenous magnesium is proposed to have a substantial bronchodilator effect in treatment of severe exacerbations of asthma in children and adults. However, this mode of administration requires careful monitoring, since peripheral vasodilation and systolic hypotension can occur and patients sometimes have unpleasant flushing, nausea, and venous phlebitis from the infusion.

Previous attempts to administer magnesium by nebulisation have shown mixed results. Results of some studies have shown that magnesium nebulised as an adjuvant to nebulised salbutamol in treatment of acute asthma, however not all studies have shown similar results. In a dose-response study indicated that inhaled magnesium does not act as a bronchodilator. In acute exacerbations of asthma in adults, Magnat and colleagues have shown that nebulised magnesium results in a bronchodilator response similar in magnitude to salbutamol. A similar study in children reported that whereas inhalation of magnesium has a bronchodilator effect in acute asthma, the magnitude and duration of the effect was less than that due to salbutamol.

The effect of magnesium administered as an adjunct to nebulised salbutamol has been investigated in two studies. Nannini and colleagues reported that administration of a single 2·5 mg dose of salbutamol with adjuvant magnesium sulphate caused a significantly greater improvement in peak expiratory flow than salbutamol administered in isotonic saline in patients with asthma and severe airflow obstruction. By contrast, Bessmertny and colleagues reported that use of adjunct magnesium provides no benefit to that of nebulised salbutamol in adult patients in moderately severe exacerbations of asthma.

We have therefore undertaken a randomised placebo-controlled trial to investigate the effectiveness of nebulised isotonic magnesium sulphate as an adjuvant to salbutamol administered by nebuliser according to a standard emergency department protocol for treatment of severe asthma.

Methods

Participants We invited all patients aged between 16 and 65 years who presented between July, 2000, and June, 2001, with severe attacks of asthma to the emergency departments of two university hospitals in New Zealand to participate in the study. Inclusion in the study required a known history...
of asthma, and presentation with a severe exacerbation with a recorded forced expiratory volume in 1 s (FEV₁) of less than 50% predicted normal values. We excluded patients if they needed immediate intubation or had evidence of pneumonia, hypotension (systolic blood pressure <100 mm Hg), previously documented chronic airflow limitation with fixed airways obstruction, cardiac or renal disease, or were pregnant.

**Study protocol**

On presentation to the emergency department with asthma, we clinically assessed all potential patients, measured their FEV₁, then gave them 2·5 mg salbutamol by jet nebulisation and 100 mg hydrocortisone intravenously. A brief questionnaire was administered, informing about duration and severity of symptoms, drug use, and smoking status. The FEV₁ measurement was repeated at least 30 min after salbutamol nebulisation was started, and only those patients with an FEV₁ less than 50% predicted at this stage were randomised for inclusion in the study. We obtained written informed consent and randomly allocated patients to receive one of two treatment regimens. Patients received by jet nebulisation (Aeroneb Face Mask Nebuliser, Allied Medical Limited, Auckland, New Zealand) 2·5 mg of salbutamol (GlaxoSmithKline, London, UK) mixed with either 2·5 mL isotonic magnesium sulphate (250 mmol/L, toxicity 289 mosmol; 151 mg per dose) or 2·5 mL isotonic saline (placebo) on three occasions at 30 min intervals. Patients and investigators were unaware of treatment allocation through provision by the hospital pharmacy of preprepared identical unmarked syringes containing the study drug. The study investigators enrolled the patients, who were randomly assigned to their treatment groups in accordance with the allocation sequence determined by the hospital pharmacy.

We recorded FEV₁ (2120 Recording spirometer, Vitalograph, Buckingham, UK), blood pressure, pulse and respiratory rate before and 30 min after each nebulisation. Although arterial pulse oximetry and blood gas assessment were done in some patients when needed, we did not do serial recording in all individuals since administration of supplemental oxygen varied during the study. After the final recordings, the decision to admit the patient was made at the discretion of the investigator, with a recommendation that patients be admitted if the FEV₁ remained less than 30% of that predicted.

**Statistical analysis**

The primary outcome measure was FEV₁ at 90 min. To take account of the repeated measures on individual patients, we used a general linear mixed model to model the response to treatment over time and to take into account the correlation between consecutive measurements on individual patients. The baseline level of the outcome variable was used as a covariate to compare the treatment groups.

On the basis of an SD of 0·4 L for FEV₁, we needed 29 patients in each group to detect an effect size of 0·3 L, with 80% power at a two-sided α of 0·05. The risk of admission was the secondary outcome measure, and was compared by a χ² test. We did a posthoc subanalysis in patients whose FEV₁ was less than 30% predicted at randomisation, which indicated a life-threatening attack of asthma. SAS version 8 was used. The data were double-entered by two investigators.

**Role of the funding source**

The study sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Results**

We initially enrolled 58 patients, six of whom were subsequently excluded after a review of their hospital notes revealed a history of chronic obstructive pulmonary disease (n=4) or there was radiographic evidence of pneumonia (n=2; figure 1). Of the 52 patients remaining, we randomly allocated 28 to the magnesium adjuvant group. Table 1 shows patients’ baseline characteristics. Of note, prehospital use of inhaled β agonist was high in both groups.

At 90 min (30 min after the third administration of the study drug) the mean FEV₁ in the magnesium group was

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**Table 1: Patients’ characteristics**

| Age (years) | 27 (7-4) | 31·2 (11-4) |
| Female sex | 14 | 13 |
| Admissions in past 12 months | 0-5 (0-4) | 0 (0-4) |
| Prednisone courses in past 12 months | 2 (0-11) | 2 (0-11) |
| Regular nocturnal wakening* | 10 | 6 |
| History of previous intubation | 3 | 2 |
| History of admission to intensive care unit | 11 | 5 |
| Current smokers | 12 | 12 |
| Daily inhaled steroid dose (µg per day)‡ | 1258 (937) | 1680 (907) |
| β-agonist doses in past 24 h | 20-1 (16-9) | 29-8 (39) |
| Presentation FEV₁, (L) | 1·13 (0-42) | 1·09 (0-43) |
| % predicted presentation FEV₁ | 28·6% (9·4) | 28·7% (9·0) |
| Baseline FEV₁, (L) | 1·24 (0-44) | 1·20 (0-45) |
| % predicted baseline FEV₁ | 31·9% (9·6%) | 32·2% (10·0%) |

Values are mean (SD), median (range), or number of patients. *At least 2 nights a week. †Beclamethasone dipropionate dose or equivalent. ‡At time of presentation to the emergency department. ¶At time of randomisation.

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**Figure 1: Trial profile**

COPD=chronic obstructive pulmonary disease.

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**Table 1: Patients’ characteristics**
1.96 L (95% CI 1.68–2.24) and in the saline group was 1·55 L (1·24–1·87) (figure 2). The FEV₁ at 90 min was significantly greater (difference 0.64 L [95% CI 0.34–0.93], p<0.0001) than the same dose of salbutamol administered with an isotonic saline nebuliser solution.

We considered several methodological issues in the design of the study that are relevant to its interpretation. The first was the decision to assess patients with severe exacerbations of asthma, based on previous studies that investigated the effectiveness of intravenous magnesium. In these studies the greatest bronchodilator response was in patients with life-threatening attacks defined as an FEV₁ of less than 25% to 30% of that predicted, an initial peak expiratory flow (PEF) of less than 200 L/min, or failure to respond to initial nebulised β-agonist therapy, or both.1-12 Thus, we based the study in the emergency department, and excluded patients who had an FEV₁ that was greater than 50% of that predicted after initial salbutamol treatment.

Another issue was the safety requirement that all potential patients received 2·5 mg nebulised salbutamol and 100 mg intravenous hydrocortisone at presentation, before informed consent was obtained, with randomisation and administration of the first dose of nebulised salbutamol in the trial 30 min later. This protocol worked well with no patients needing to withdraw during this initial period, despite severe airflow obstruction being present, with a mean baseline FEV₁ of about 32% predicted in both groups. This protocol also ensured standardisation of β-agonist treatment in the 30 min before randomisation.

In terms of the dose regimen used, nebulisation of three 2·5 mg doses of salbutamol at 30 min intervals is within the therapeutic range recommended for treatment of severe asthma in the emergency department.2,22 Although some regimens have used greater doses of salbutamol, or more frequent administration, they are unlikely to lead to a greater degree of bronchodilation than that used in this study.23 Perhaps the most crucial issue in terms of the use of magnesium as an adjuvant was its formulation as an isotonic solution. Both hypotonic and hypertonic nebuliser solutions cause bronchoconstriction in patients with asthma and indeed are two methods whereby bronchoconstriction is induced in assessment of non-specific bronchial hyper-responsiveness.24,25 For this reason, the magnesium sulphate solution we used was formulated to 250 mmol/L, resulting in a tonicity of 289 mosmol.

Administration of the nebulised salbutamol solution with magnesium adjuvant resulted in a significantly greater improvement in FEV₁, compared with salbutamol with the isotonic saline (placebo) adjuvant solution. The difference was clinically significant with almost double the increase in FEV₁, with the magnesium adjuvant solution—an additional 365 mL improvement in FEV₁. The requirement for admission, the decision for which was made by an investigator who remained unaware of the treatment that the patients had received, was also significantly reduced.

### Table 2: Change in FEV₁ in subgroups defined by baseline FEV₁, measurements*

<table>
<thead>
<tr>
<th>FEV₁, at baseline (L)</th>
<th>Magnesium (n=12)</th>
<th>Baseline FEV₁ &lt;30% predicted</th>
<th>Saline (n=12)</th>
<th>Baseline FEV₁ &gt;30% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·90 (0·35)</td>
<td>0·82 (0·17)</td>
<td>1·50 (0·30)</td>
<td>1·58 (0·30)</td>
<td></td>
</tr>
<tr>
<td>1·73 (0·70)</td>
<td>1·01 (0·22)</td>
<td>2·14 (0·71)</td>
<td>2·09 (0·68)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD). *Baseline FEV₁ at time of randomisation.

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Figure 2: FEV₁, after administration of 2·5 mg nebulised salbutamol with either magnesium sulphate or saline adjuvant

Arrows indicate the start of study drug administration. Data are mean and 95% CI (bars).

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In our post-hoc subanalysis, the enhanced bronchodilator response with magnesium was greater in those with life-threatening asthma, as defined by a baseline FEV₁ of less than 30%, than in those with less severe asthma. Although this finding could be a result of regression to the mean rather than a true difference, it is consistent with studies that showed that administration of intravenous magnesium resulted in significant bronchodilation in patients with life-threatening, but not less severe, attacks of asthma.1–5 As quantified in the meta-analysis from the Cochrane Airways Group, administration of intravenous magnesium in life-threatening asthma is associated with a ten-fold reduction in the requirement for admission.

Our findings are also consistent with previous studies, in which administration of magnesium by nebulisation was assessed in exacerbations of asthma. The bronchodilator effectiveness of nebulised magnesium in severe exacerbations of asthma has been shown in adults17 and children.18 When used as a adjuvant to β-agonist therapy, it results in additional bronchodilation in severe exacerbations (initial PEF 38% predicted),19 but not in less severe exacerbations (initial FEV₁ 60% predicted).20 Thus, our findings that the bronchodilator effectiveness of intravenous magnesium is seen in life-threatening, rather than less severe exacerbations of asthma, is generally consistent with these previous studies.

As with these reports, our study did not assess the potential mechanisms whereby magnesium enhanced the bronchodilator response to salbutamol. Possible mechanisms include direct relaxation of bronchial smooth muscle17, inhibition of smooth muscle contraction mediated by calcium,14 increased β-receptor affinity,15 inhibition of cholinergic neuromuscular transmission,16 and prostacyclin generation.18 The relative importance of these, and other mechanisms awaits further investigation.

Thus, use of isotonic magnesium sulphate as an adjuvant to nebulised salbutamol results in clinically significant enhancement of bronchodilation in the treatment of severe asthma. Further research is now needed to determine whether salbutamol nebuliser solution with intravenous magnesium sulphate should become the preferred agent for treatment of severe asthma, and whether it has a role in treatment of severe exacerbations of chronic obstructive pulmonary disease.

Contributors
The study was designed by R Hughes, R Beasley, and C Burgess. R Hughes coordinated the study, gathered the data with A Goldkorn and M Masoli, and assisted M Weatherall with the analyses. R Hughes and R Beasley wrote the report with help from the other authors.

Conflict of interest statement
R Beasley M Masoli, and M Weatherall are also participating in two other clinical trials. The first trial compares the efficacy of magnesium as an adjuvant to salbutamol nebuliser solution with intravenous magnesium in acute severe asthma. The second trial investigates the efficacy of magnesium as an adjuvant in salbutamol/pratropium bromide nebuliser solution in exacerbations of chronic obstructive pulmonary disease.

Acknowledgments
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References