Br J Clin Pharmacol 1996; **42**: 629–631

Effect of intravenous magnesium sulphate on airway calibre and airway reactivity to histamine in asthmatic subjects

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In a randomized, double-blind, placebo controlled cross-over study we have investigated the effect of intravenous magnesium on airway calibre and airway reactivity to histamine in 20 subjects with mild to moderate asthma. After baseline measurements of forced expiratory volume in one second (FEV_1), subjects received 100 ml normal saline with or without 2 g of magnesium sulphate by infusion over 20 min. Measurements of FEV_1 were repeated at 5 min intervals throughout the infusion, and the provocative dose of histamine required to drop the FEV_1 by 20% from baseline ($PD_{20}FEV_1$) was determined at 20 min. The area under the curve (AUC) in litre minutes for change from baseline in FEV_1 between 0 and 20 min was significantly higher on the magnesium study day (mean difference in AUC (95% CI) 1.71 (0.02–3.4), $P=0.049$). The increase in FEV_1 from baseline with magnesium relative to saline was maximal at 20 min (mean difference (95% CI) 0.13 (0.02–0.23) l, $P=0.01$). Log $PD_{20}FEV_1$ to histamine was not significantly different after magnesium and saline (mean difference in log $PD_{20}FEV_1$ (95% CI) 0.04 (−0.19 to 0.27), $P=0.7$). We conclude that intravenous magnesium is a weak bronchodilator but does not alter airway reactivity at this dose in stable asthmatic subjects.

Keywords magnesium histamine bronchial reactivity asthma

Introduction

Magnesium is a cation with several actions of potential relevance to the asthmatic airway, and we have recently reported that a lower dietary magnesium intake in the general population is associated with impaired lung function and bronchial hyperreactivity [1]. The aim of this study was to investigate the effect of intravenous magnesium sulphate on lung function and airway reactivity to histamine in stable asthmatic subjects.

Methods

We studied 20 (16 male) non-smoking asthmatic subjects aged 25–55 years. All had been shown to increase their forced expiratory volume in one second (FEV_1) by at least 15% after 200 μg inhaled salbutamol, to have a provocative dose of histamine causing a 20% drop in FEV_1 ($PD_{20}FEV_1$) of less than 4 μmol, and were using inhaled β-adrenoceptor agonist therapy at least once per 24 h. Eighteen were taking regular inhaled corticosteroids and one an oral methylxanthine. All gave written informed consent to the study which was approved by the City Hospital Ethics Committee.

The study involved a randomized, double-blind, placebo controlled cross-over design with two visits at the same time of day at least 1 week apart. Subjects withheld caffeine-containing beverages and β-adrenoceptor agonists for 6 h, and oral methylxanthines for 12 h before each visit. After 15 min rest, baseline measurements of FEV_1, blood pressure, and heart rate were made and an electrocardiogram (ECG) recorded. FEV_1 was measured using a dry bellows spirometer as the higher of two successive readings within 100 ml. A butterfly cannula was inserted into a forearm vein in each arm, one to administer the infusion of magnesium or saline, and the other to sample venous blood for magnesium estimation by colorimetric assay. On the active treatment day subjects received 2 g magnesium sulphate in 100 ml normal saline and on the placebo day 100 ml normal saline infused over 20 min. The infusions were administered double-blind. FEV_1, heart rate and blood pressure were measured at 5 min intervals during and at 15 and 30 min after the infusion. Blood pressure, heart rate and ECG measures were recorded again at 70 min. Immediately on completion

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of the infusion, $PD_{20}FEV_1$ was measured using histamine aerosols delivered from a breath-actuated dosimeter (MEFAR, Brescia, Italy), set to nebulise for 1 s with a pause time of 6 s, at a pressure of 22 lb/inch^2 (152 kPa), and to deliver 10–11 μl/breath. Subjects inhaled doubling doses of histamine (from 0.021–42 μl) during rapid inspiration from functional residual capacity to total lung capacity. FEV_1 was measured 1 min after each inhalation. The challenge was discontinued when the FEV_1 had fallen by more than 20% from the baseline value. $PD_{20}FEV_1$ was estimated by linear extrapolation on a log dose-response plot.

Area under the curve (AUC) in litre minutes for change in FEV_1 from baseline to 20 min was calculated for each subject by trapezoid integration. $PD_{20}FEV_1$ values were logarithmically transformed. Period and carry over effects were calculated as described by Hills & Armitage [2], and comparisons made by Students' paired *t*-test. The study was designed to provide 90% power to detect a 150 ml change in FEV_1 and a doubling dose difference in $PD_{20}FEV_1$ at the 5% level of significance.

Results

Baseline mean (s.e. mean) FEV_1 on saline and magnesium study days was 2.81 (0.18) and 2.69 (0.16) l respectively, and was significantly lower on the magnesium study day (mean difference (95% CI) 0.12 (0.01–0.23), $P=0.028$). Change in FEV_1 over time for magnesium and saline study days is shown in Figure 1. The AUC for change from 0 to 20 min was significantly higher after magnesium than after saline (mean difference in AUC (95% CI) 1.71 (0.02 to 3.4) l min, $P=0.049$). There was no difference in mean (s.d.) log $PD_{20}FEV_1$ for histamine after saline (−0.41 (0.68)) and magnesium (−0.46 (0.57), mean difference (95% CI) 0.04 (−0.19 to 0.27), $P=0.70$, Figure 2). Baseline mean serum magnesium was similar but increased to 1.3 mmol l^{-1} at 20 min and fell again to 1.15 mmol l^{-1} at 50 min after magnesium infusion (Figure 1). There were no significant differences in systolic or diastolic blood pressure between study days. Heart rate was significantly lower immediately after magnesium (mean difference in change in heart rate at 20 min (95% CI) 3.55 (0 to 7.1) beats min^{-1}, $P=0.051$), and at 35 min (mean difference in change in heart rate (95% CI) 6.1 (1.63 to 11.14) beats min^{-1}, $P=0.014$), but not at 50 or at 120 min. There was no significant difference between magnesium and placebo for total AUC for heart rate over 120 min.

Discussion

This study was designed to determine whether systemic administration of magnesium improved airway calibre or airway reactivity to histamine in asthmatic subjects. We chose a dose of 2 g intravenous magnesium sulphate on the basis of previous studies in patients with acute

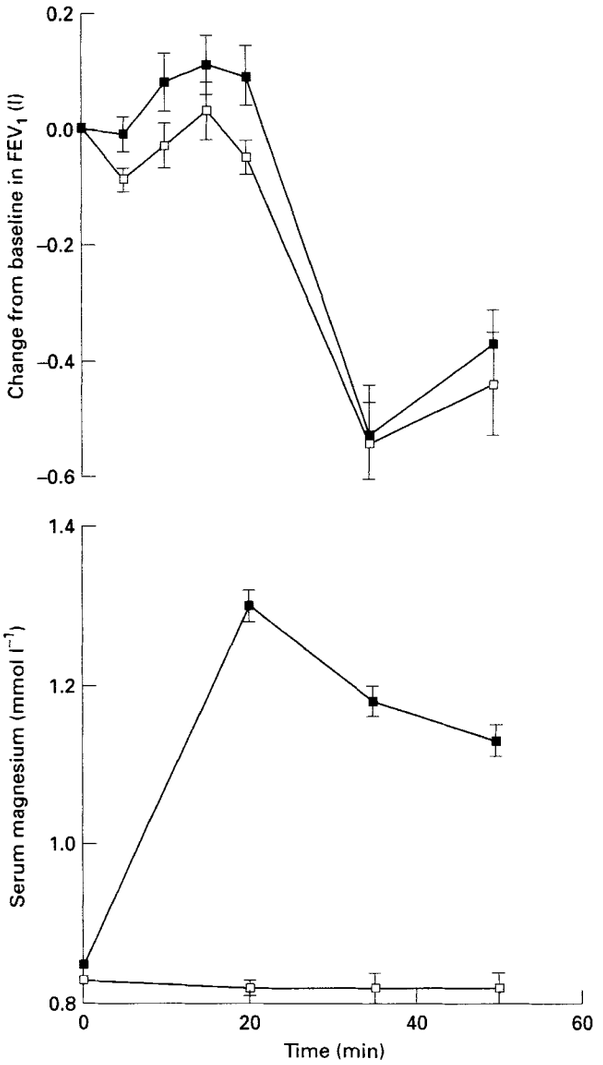

Figure 1 Mean change from baseline in FEV_1 and serum magnesium over time during and after intravenous saline (□) and magnesium (■).

[3–6] and stable [7, 8] asthma, all of which have involved the administration of between 1.2 and 3 g of magnesium sulphate in an infusion over 20 min and showed improvements in lung function comparible with the increase in FEV_1 of 130 ml seen in our study. Baseline magnesium levels in our subjects of 0.84 mmol l^{-1} were within the normal range of our laboratory of 0.7–0.9 mmol l^{-1}, and increased after magnesium by 0.46 mmol l^{-1}, though the relevance of the plasma level is uncertain since FEV_1 had returned to baseline values while serum levels were still elevated. The lack of any significant effect of intravenous magnesium on blood pressure suggests that the increase in FEV_1 is unlikely to have arisen from baroreflex sympathetic activation. Our findings for histamine reactivity contrast with two previous studies which have reported that inhaled magnesium confers some protection against histamine- and methacholine-induced bronchoconstriction in stable asthmatic subjects [9, 10].

We conclude that intravenous magnesium at this dose induces bronchodilatation, and that although the increase in FEV_1 was small, this could still represent a

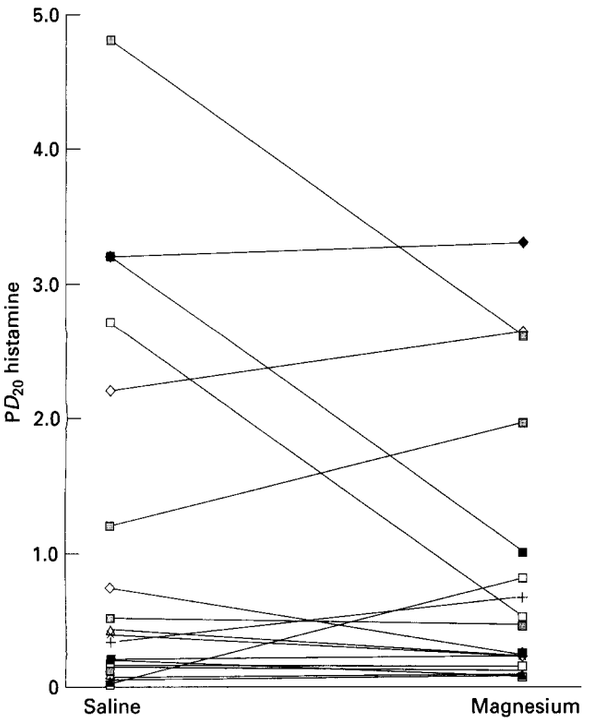

Figure 2 Log_{10} $PD_{20}FEV_1$ histamine (μmol) after saline and magnesium infusions.

clinically important increase in airway calibre in patients with acute severe asthma. Intravenous magnesium at this dose did not protect against histamine-induced bronchoconstriction, suggesting either that systemic magnesium may not possess bronchoprotective properties *in vivo*, or the effect of the acute administration of intravenous magnesium is not sufficiently sustained or does not provide high enough tissue levels of magnesium to confer any bronchoprotection. A further dose-ranging study including higher doses of intravenous magnesium is possibly justified to investigate this further.

Essential statistical advice was provided by Ms S. Lewis, Statistician, in the Division of Respiratory Medicine. Ms K. Richards helped with subject recruitment, and Mrs S. Pacey and Ms H. Tattersall provided randomization codes and drug supplies for the study. This study was supported by a grant from the Medical Research Council, UK.

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(Received 12 April 1996, accepted 26 June 1996)