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Dose-response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects

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1 Magnesium is a dietary cation with a wide range of actions of potential relevance to asthma.

2 To determine the dose-response relationship and time-course of the effect of inhaled magnesium sulphate on the airway, we have studied the effect of 0, 90, 135, 180 and 360 mg of magnesium sulphate given by nebulizer on specific airways conductance (sGaw) in 20 normal subjects, and forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), flow at 25% forced vital capacity (Vmax25) and peak expiratory flow (PEF) in 19 asthmatic subjects.

3 On five occasions after baseline measurements of airway calibre, one of the five doses of magnesium sulphate in 3 ml normal saline was administered by nebulizer in a randomized, double-blind design. Measurements of sGaw or FEV_1, FVC, Vmax25 and PEF were made at 5 and 10 min after nebulization and at 10 min intervals thereafter up to 90 min.

4 There was no significant difference in the mean area under the curve (AUC) for change from baseline in sGaw or maximum increase from baseline between doses in normal subjects.

5 In asthmatic subjects there was no significant difference in the mean AUC for change from baseline in FEV_1, FVC or Vmax25 when compared between doses by analysis of variance. There was a difference in the mean AUC for change from baseline in PEF between doses (ANOVA P for all groups 0.052) but this can be explained by a detrimental effect of the maximum dose of magnesium sulphate.

6 It would appear that inhaled magnesium does not act as a bronchodilator in normal or asthmatic subjects.

Keywords magnesium asthma bronchodilator airway resistance

Introduction

Magnesium is the second commonest intracellular cation in human tissue and is an essential component of the diet. It has a wide range of actions of potential relevance to the airway including the inhibition of vascular [1] and bronchial [2, 3] smooth muscle contraction, the inhibition of acetylcholine release from cholinergic nerve terminals [4] and histamine release from mast cells [5], and the stimulation of nitric oxide generation [6, 7] and prostacyclin synthesis [8, 9]. We have previously shown that a lower dietary intake of magnesium in the general population is associated with impairment of FEV_1 and a higher risk of wheezing and of airway hyperreactivity [10].

Benefit from intravenous magnesium in acute and stable asthma has been reported in several uncontrolled [11–14] and controlled [15–17] studies, although not all studies have confirmed this [18, 19]. There is much less information available on the effects of inhaled magnesium on the airway, but two studies of single doses of nebulized magnesium have demonstrated protection against bronchoconstriction induced by methacholine and histamine, by the order of a two fold

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increase in the PD_{20} for these agents [20, 21]. One double-blind study in 84 asthmatic subjects assessed the benefit of nebulized magnesium sulphate (1.5 g) as an adjunct to β-adrenoceptor agonist therapy in the treatment of acute asthma [22], and concluded that this therapy reduced hospital admissions in mild acute asthma and pulsus paradoxus in severe acute asthma. Thus there is evidence that magnesium may be a bronchodilator, but to date the time-course and dose-response relationship of the effect of inhaled magnesium on the airways has not been characterized in placebo-controlled studies. The present study was conducted to explore these effects in normal and asthmatic airways.

Methods

Subjects

We studied 20 normal non-smoking subjects and initially 20 subjects with stable asthma aged 25–55 years. The asthmatic subjects were documented as showing an increase in FEV_1 of at least 15% after 200 μg inhaled salbutamol. All were receiving therapy with inhaled β-adrenoceptor agonists and inhaled corticosteroids. Subjects were included if taking oral theophylline so long as their dose was kept constant throughout the study. All subjects were asked to withhold β-adrenoceptor drugs for 6 h prior to each study visit and were asked to keep their intake of caffeine-containing beverages constant on each of the study days. Subjects gave written consent and the study was approved by the City Hospital Ethics Committee.

Methods

Specific airways conductance (sGaw) was measured in normal subjects using a body plethysmograph (Gould 2800 Autobox) on line to a microprocessor, and calculated from the mean of three consecutive measurements, each of which analysed three panting breaths. In the asthmatic subjects 1 s forced expiratory volume (FEV_1) was measured from a flow-volume manoeuvre using the Alpha spirometer (Vitalograph Ltd, Buckingham, UK) so that forced vital capacity (FVC), maximum flow at 25% forced vital capacity (Vmax25) and peak expiratory flow (PEF) could also be derived, and the best of three attempts was accepted. Twenty sets of 0, 90, 135, 180 and 360 mg dried magnesium sulphate BP (Thornton and Ross, Huddersfield, UK) were weighed and stored in the Pharmacy department in airtight containers. These doses were selected on the basis that previous workers have reported a reduction in bronchial reactivity to histamine and methacholine after doses of 198 and 97 mg respectively [20, 21]. We also included a higher dose to investigate the dose-response curve of inhaled magnesium.

Procedure

Subjects were studied at the same time of day on 5 different days. Baseline sGaw or FEV_1 was measured, and the study continued providing that the baseline sGaw on each study day was within 15% of that on day 1. One of the four doses of magnesium sulphate or placebo was then dissolved in 3 ml normal saline by an independent technician and administered according to a randomized, double-blind protocol. The 3 ml solution was nebulized to dryness in an Inspiron nebuliser (Rusch, High Wycombe, UK) driven by air at 8 l min^{-1}, and sGaw or FEV_1, FVC, Vmax25 and PEF measured at 5 and 10 min after nebulisation in normal and asthmatic subjects respectively, and at 10 min intervals thereafter for a total of 90 min.

Analysis

Change in sGaw and change from baseline in FEV_1, FVC, Vmax25 and PEF were plotted against time and the area under the curve (AUC) calculated by trapezoid integration for each magnesium sulphate dose in each subject. AUC was compared between doses by analysis of variance within subjects using SPSS.PC Version 4.1. The maximum increase in sGaw or FEV_1, FVC, Vmax25 and PEF was compared between doses for all subjects.

Power

The study was of a conventional randomized, double-blind, crossover design and therefore involved within subject comparisons of the endpoints. Taking the coefficient of variation of sGaw measurements to be 15% [23] we calculated using standard formulae [24] that 20 normal subjects would provide more than 95% power to detect a 20% or greater increase in sGaw after any single magnesium dose. Defining a 150 ml change in FEV_1 as the minimum change we wished to detect and taking published evidence that the within-subject standard deviation for repeated measures of FEV_1 is less than 100 ml [25, 26] we calculated that 20 subjects would provide more than 90% power to detect these effects at the 5% significance level.

Results

Normal subjects

There were 11 male and 9 female normal subjects with a mean age of 32.8 years (range 26–45 years). The mean baseline (s.e. mean) sGaw for all 20 subjects was 0.22 (0.019) $s^{-1}\,kPa^{-1}$. Figure 1 shows the change in mean sGaw from baseline over time for each of the five doses of magnesium sulphate. There was an increase in the mean sGaw over time with all five doses of magnesium sulphate, the peak response occurring at around 70 min. However there was no obvious difference

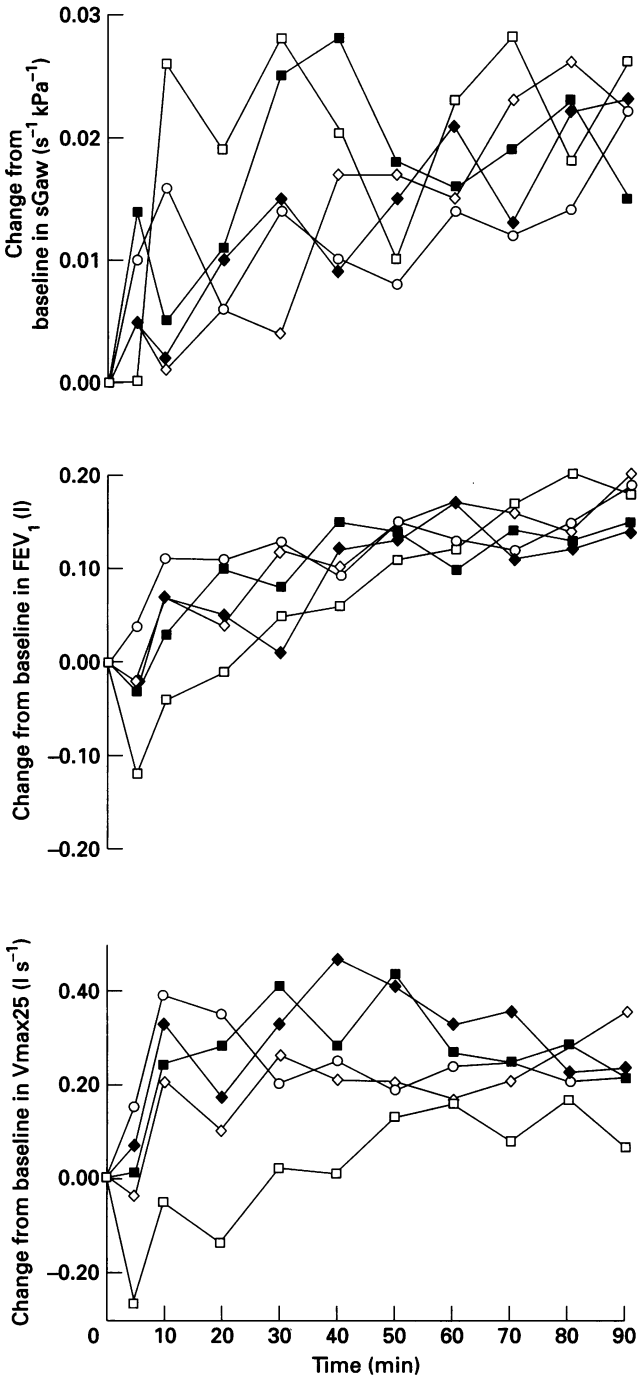

Figure 1 Mean change in sGaw from baseline in 20 normal subjects, and mean change in FEV_1 and Vmax25 from baseline in 19 asthmatic subjects over time for five doses of magnesium sulphate. (○ 0 mg; ■ 90 mg; ◇ 135 mg; ◆ 180 mg; □ 360 mg.)

in the change in sGaw from baseline between any of the five doses. The mean AUC (in $s^{-1}\,kPa^{-1}\,min$) for absolute change from baseline in sGaw for each of the five doses of magnesium sulphate is shown in Table 1. There was no significant difference in the mean AUC for change from baseline in sGaw in normal subjects between doses (ANOVA for all groups $P=0.712$). The mean difference in AUC between dose 5 (360 mg) and dose 1 (placebo) was 0.81 (95% confidence interval (CI) −0.89 to 2.51).

The mean maximum increase in sGaw from baseline with each dose of magnesium sulphate is also shown in Table 1. There was no difference in the mean maximum increase in sGaw from baseline between doses (ANOVA for all groups $P=0.598$). The mean difference in maximum increase between dose 5 and dose 1 was 23.8 (CI −9.77 to 57.37).

Table 1 Mean AUC for change from baseline in sGaw over time and mean maximum increase (MI) in sGaw from baseline in 20 normal subjects

	Dose (mg)				
	0	*90*	*135*	*180*	*360*
Mean AUC	1.05	1.57	1.23	1.20	1.86
S.e. mean	0.43	0.69	0.57	0.59	0.91
Mean MI	0.040	0.051	0.048	0.043	0.063
S.e. mean	0.006	0.011	0.011	0.010	0.014

Asthmatic subjects

One of the initial 20 asthmatic subjects who took part developed symptomatic bronchoconstriction within 10 min of the administration of the third dose of magnesium sulphate studied, which proved to be the maximum dose, and required a nebulizer of β-adrenoceptor agonist. The subject did not therefore contribute any results for further analysis. The remaining 19 subjects, 11 male, had a mean (s.e. mean) baseline FEV_1 of 2.3 litres (0.16), mean % predicted 66.7%, and had a mean age of 42.3 years (range 25–55). All patients were receiving regular inhaled steroids and as required β-adrenoceptor agonist therapy. Three subjects were receiving regular oral methylxanthines. Graphs for the mean change in FEV_1, and Vmax25 from baseline for the remaining 19 subjects for each of the five doses of magnesium sulphate over time are shown in Figure 1. The maximum dose of magnesium sulphate caused a drop in FEV_1, FVC, Vmax25 and PEF at 5 min which increased over time. After this initial drop with the maximum dose of magnesium sulphate there was an increase over time in all of these lung function measures with the peak effect seen between 50 and 60 min. However there was no obvious difference between the five doses in the magnitude of this increase, apart from a suggestion that the 180 mg dose of magnesium might have caused a greater increase in PEF than the other doses. The AUC for absolute mean change from baseline in FEV_1, FVC, Vmax25 and PEF are shown in Table 2 and were compared between doses by analysis of variance within subjects. There was no significant difference in the mean AUC for change from baseline in FEV_1 ($P=0.33$), FVC ($P=0.97$) or PEF ($P=0.058$) between doses for the 19 subjects. There was a borderline significant difference in the mean AUC for change from baseline in Vmax25 (ANOVA for all groups $P=0.052$) but this can be explained by the detrimental effect of the maximum magnesium sulphate dose (dose 1 *vs* dose 4 ANOVA $P=0.12$; dose 1 *vs* dose 5 ANOVA $P=0.034$). The ANOVA was repeated to compare the AUC for change in FEV_1, FVC, Vmax25 and PEF for the

Table 2 AUC for absolute mean change (s.e. mean) from baseline in FEV_1, FVC, Vmax25 and PEF asthmatic subjects

Dose (mg)	*FEV_1*	*FVC*	*Vmax25*	*PEF*
0	7.35	10.82	21.83	1058.68
	(3.1)	(3.7)	(10.1)	(626.8)
90	8.14	9.2	25.12	817.89
	(3.7)	(3.5)	(11.6)	(627.9)
135	8.38	10.17	17.55	930.79
	(4.6)	(6.3)	(11.9)	(653.0)
180	8.88	8.59	26.91	1867.89
	(3.8)	(5.1)	(8.9)	(641.9)
360	1.7	7.02	2.92	−65.26
	(4.5)	(5.9)	(8.0)	(725.5)

ANOVA for all groups *P* value 0.33 0.97 0.052 0.058

four lower doses of magnesium sulphate, excluding the maximum dose because of its bronchoconstrictor effects, and there was no significant difference in the AUC for mean change from baseline in any of the variables with the four lower doses of magnesium. The mean difference in AUC between dose 4 and dose 1 for FEV_1 was 1.53 (CI −5.42 to 8.48), for FVC was −2.23 (CI −11.65 to 7.2), for Vmax25 was 5.1 (CI −15.9 to 26.1) and for PEF was 809 (−556.1 to 2174.8).

There was no difference in the maximum increase from baseline in FEV_1, FVC, Vmax25 or PEF between doses for the 19 subjects (Table 3). The mean difference for maximum increase from baseline between dose 4 and dose 1 for FEV_1 was 0.05 (CI −9.53 to 9.63), for FVC was −8.26 (CI −19.3 to 2.73), for Vmax25 was 0 (CI −0.25 to 0.25) and for PEF was 3.5 (CI −15.9 to 22.9).

Discussion

This study examined the time-course and dose-response relationship of the effect of inhaled magnesium on the airway for the first time in a placebo-controlled trial in normal and asthmatic subjects. In this double-blind, randomized study inhaled magnesium did not alter airway calibre in normal or asthmatic subjects. Our study was designed to detect a change of at least 20% in sGaw and a change of 150 ml in FEV_1 and it therefore seems reasonable to conclude that inhaled magnesium sulphate has no marked effect on airway calibre in normal or asthmatic subjects.

There is considerable, although not consistent evidence [18, 19] of a beneficial effect of intravenous magnesium in acute and stable asthma [11–17] and it is not clear why magnesium sulphate administered by the inhaled route should not have the same effect. Magnesium is a vasodilator and it is possible that the apparent bronchodilator properties of intravenous magnesium are due to baroreflex sympathetic activation because of vasodilatation and resultant hypotension. It is also possible that intravenous magnesium *does* have direct bronchodilator activity, and there is evidence that magnesium causes dilatation of rabbit bronchial smooth muscle *in vitro* [3]. If magnesium has bronchodilator properties why was this effect not seen when it was administered by the inhaled route? There is no published work on the deposition of magnesium in the lungs when administered by the inhaled route, and it is possible that lack of absorption explains our negative results. A randomized, double-blind, placebo controlled study showed significant, albeit small, improvements in peak flow in mild acute asthma and pulsus paradoxus in acute severe asthma after 1.2 g magnesium sulphate nebulized in 5 ml normal saline [22]. However, this group of patients admitted to hospital with acute asthma is not comparable with that in our study who had stable asthma, and the effects on asthma in that study were very small.

Two previous studies have reported a reduction in bronchial reactivity after inhaled magnesium sulphate given at doses comparable with doses 2 and 4 in our study [20, 21]. However, some of the calcium antagonists have weak inhibitory effects on bronchoconstriction induced by spasmogens such as histamine, methacholine, exercise and cold air, without clinical evidence that they are bronchodilators [27, 28]. This has been explained by the suggestion that the release of endogenous spasmogens in airway inflammation is mediated largely via release of calcium from phosphoinositide hydrolysis and from internal stores and less from calcium entry to the cell, which is affected by calcium antagonists. Although the maintenance of tone may depend on some

Table 3 Maximum increase (MI) from baseline (mean (s.e. mean)) in FEV_1, FVC, Vmax25 and PEF for asthmatic subjects

Dose (mg)	*Mean MI FEV_1*	*Mean MI FVC*	*Mean MI Vmax25*	*Mean MI PEF*
0	0.26	0.35	0.73	49.3
	(0.045)	(0.053)	(0.124)	(7.3)
90	0.26	0.37	0.77	37.9
	(0.043)	(0.043)	(0.172)	(6.5)
135	0.22	0.32	0.62	44.53
	(0.055)	(0.067)	(0.158)	(7.9)
180	0.26	0.27	0.73	52.74
	(0.049)	(0.057)	(0.128)	(8.9)
360	0.19	0.33	0.54	33.79
	(0.052)	(0.071)	(0.124)	(9.5)

ANOVA for all groups *P* value 0.51 0.32 0.33 0.3

calcium entry to the cells, this may be via receptor operated channels, not affected by calcium channel blockers which act on voltage-dependent channels [28]. However there is evidence from *in vitro* work that magnesium acts on receptor-operated as well as voltage-dependent channels on the cell membrane [29–32] and intracellularly to prevent calcium release from the sarcoplasmic reticulum [29, 30, 33, 34]. Thus the explanation for our apparent lack of any bronchodilator effects of magnesium sulphate is not clear.

Our asthmatic subjects had evidence of an increase of at least 15% in FEV_1 after 200 μg inhaled salbutamol and therefore clearly had room for improvement in lung function. A pilot study in 10 of the 20 normal subjects showed a mean % increase in sGaw of 43.9 (s.e. mean 8.84) after the same dose of inhaled salbutamol.

The maximum dose of magnesium sulphate had a detrimental effect on lung function in the asthmatic subjects. The osmolarity of this solution was 1428 mosm kg^{-1} and the solution had a pH of 7.9. When administered slowly using an Inspiron nebulizer it has been shown that solutions with osmolarities up to 3005 mosm kg^{-1} do not cause bronchoconstriction at 20 min after inhalation [35]. It therefore seems unlikely that this bronchoconstriction is simply a result of inhaling a more concentrated solution and may be because magnesium sulphate has bronchoconstrictor properties at higher doses.

In the light of these results it would seem reasonable to conclude that inhaled magnesium sulphate does not possess significant bronchodilator properties in normal or asthmatic subjects.

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