

Reduction of histamine-induced bronchoconstriction by magnesium in asthmatic subjects

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The effects of inhaled MgSO_4 on histamine bronchoprovocation test (BPT) were studied in nine asthmatics in clinical remission ($\text{FEV}_1 > 80\%$ of predicted). Patients performed histamine BPT on 2 separate days, one day after saline and the other after MgSO_4 inhalation, in a randomized double-blind design. Spirometry and flow/volume curve were recorded on each test day before and 5 min after NaCl or MgSO_4 . No significant difference was observed in lung function measurements 2 days before and after either NaCl or MgSO_4 . The dose of histamine which produced a 20% decrease in control FEV_1 ($\text{PD}_{20}\text{FEV}_1$) was significantly increased by aerosolized MgSO_4 (from 0.177 ± 0.036 mg after NaCl to 0.350 ± 0.085 after MgSO_4 , $P < 0.05$). After MgSO_4 the dose-steps of histamine concentration increased two-fold in two subjects and one-fold in five.

Key words: asthma; bronchial reactivity; magnesium.

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CLINICAL ASPECTS

Renewed interest has recently been shown in the effect of magnesium in reducing vascular smooth muscle contractility. We wondered whether Mg influences bronchial reactivity as well. We observed a significant decrease of histamine-induced bronchoconstriction after inhalation of MgSO_4 in asthmatics with mild to moderate bronchial hyperreactivity. The decrease in aspecific bronchial reactivity with MgSO_4 suggests that it influences bronchial smooth muscle contractility and may prove to be clinically important in the treatment of asthma.

Intracellular influx of calcium is the final common path of bronchial and vascular smooth muscle contraction. Calcium channel blockers inhibit the contractile mechanism in vascular smooth muscle (5, 6) and have some protective effect on bronchoconstriction induced by several stimuli (7). Magnesium physiologically regulates the flux of Ca^{++} (1) through cell membrane and has been shown to inhibit the vasoconstrictive action of humoral agents in several vascular beds (2).

As calcium antagonists have been shown to have a protective effect against histamine-induced bronchoconstriction in asthmatic subjects (8, 9), we investigated whether magnesium has a similar protective effect.

METHODS

We studied nine non-smoking patients (6 women and 3 men, 20 to 55 years of age (mean 34 ± 4.3 SEM), seven with atopic and two with intrinsic bronchial asthma, in clinical remission, with a forced expiratory volume in 1 s. (FEV_1) over 80% of predicted. No subjects had had respiratory tract infection for 6 weeks prior to the study. None was receiving DSCG or corticosteroids. The only therapy used consisted in inhaled β_2 -agonists, which were withheld for 8 h.

Subjects received, in random order, on 2 separate days 1 week apart, 3 ml of either normal saline or MgSO_4 (0.66 g/10 ml,

258mOsm, pH 6.7) from a deVilbiss 35B nebulizer, in a double-blind cross-over design. Five patients received Mg in the first challenge.

Lung function tests were recorded on each test day in basal conditions and 5 min after saline or MgSO₄ inhalation by use of a computerized dry spirometer (OHIO 840, Airco, Houston, Texas). Measurements were repeated until three graphs varying no more than 5% were obtained in each subject. From these graphs the best forced vital capacity (FVC), FEV₁ and maximal expiratory flow at 50% (MEF₅₀) and 25% (MEF₂₅) of FVC were selected.

Thereafter, each participant underwent histamine challenge performed according to the standard method (3). Histamine was delivered to the lung through a de Vilbiss No. 42 nebulizer, powered by compressed air at 20 psi, attached to a breath-activated dosimeter with 0.6 s timed delivery of aerosol during each inspiration from functional residual capacity. The nebulizer output was 0.021 ml/breath. Phosphate buffered saline was inhaled first, followed by doubling concentrations of buffered histamine diphosphate from 0.25 to 16 mg/ml, five breaths at each concentration. FEV₁ was measured 3 min after each solution until it was decreased by at least 20% from its control value.

The provocation dose (PD₂₀FEV₁, i.e. the dose of histamine required to produce a 20% decrease in FEV₁) was calculated from the cumulative log dose-response curves by linear interpolation of the last points, expressed in mg (output × concentration) and in log inhalation units (1 IU = one breath of 1 mg/ml histamine solution).

Statistics

Comparisons among respiratory function test values of the 2 test-days, before and after saline or MgSO₄, were performed by the analysis of variance; comparison between PD₂₀FEV₁ after saline and MgSO₄, log-transformed to normalize the distribution as suggested by Cockcroft et al. (4), was performed with Student's t test for paired data.

RESULTS

No subject experienced side effects after inhaling MgSO₄. No significant difference was observed between baseline lung function tests on the NaCl day and the MgSO₄ day. Neither NaCl nor MgSO₄ changed airway caliber (see Table 1).

The histamine threshold was significantly

Table 1

Mean values ± SEM of respiratory function tests before (baseline) and after NaCl and MgSO₄ inhalation

	VC L	FEV ₁ L	FEV ₁ % VC	MEF ₅₀ L/s	MEF ₂₅ L/s
NaCl day					
Baseline	4.21	3.29	77.5	3.45	1.57
SEM	0.31	0.29	2.87	1.34	0.30
NaCl	4.10	3.23	78.4	3.25	1.76
SEM	0.32	0.30	3.70	0.48	0.32
MgSO ₄ day					
Baseline	4.17	3.24	76.7	3.35	1.76
SEM	0.31	0.32	3.74	0.84	0.38
MgSO ₄	4.09	3.13	75.6	3.11	1.61
SEM	0.33	0.32	3.68	0.51	0.37

For abbreviations see text. Multiple comparisons by analysis of variance among respiratory function tests in basal conditions, after NaCl and after MgSO₄ inhalation showed no significant differences.

Table 2

Histamine bronchoprovocation doses (PD₂₀FEV₁) after NaCl and MgSO₄ inhalation

Patient	PD ₂₀ FEV ₁ mg NaCl	PD ₂₀ FEV ₁ mg MgSO ₄	PD ₂₀ FEV ₁ logIU NaCl	PD ₂₀ FEV ₁ logIU MgSO ₄
1	0.164	0.304	1.591	1.857
2	0.168	0.365	1.602	1.939
3	0.235	0.836	1.748	2.298
4	0.227	0.382	1.732	1.959
5	0.005	0.019	0.079	0.672
6	0.357	0.533	1.929	2.103
7	0.109	0.134	1.414	1.505
8	0.067	0.084	1.204	1.301
9	0.265	0.496	1.799	2.070
Mean	0.177	0.350	1.450	1.740
SEM	0.036	0.085	0.180	0.160
Paired t-test		-2.878		-4.849
P <		0.05		0.01

heightened by inhalation of MgSO_4 (see Table 2).

An increase of two and one dose steps of histamine concentration was observed in two and five patients respectively after MgSO_4 .

DISCUSSION

This study demonstrates that MgSO_4 , administered by aerosol, effectively inhibits histamine-induced bronchoconstriction in asthmatics with mild to moderate bronchial reactivity. The inhalation route was chosen to optimize the drug dose so as to enhance any potential effect on airway function, without systemic effects.

The effect displayed by Mg is very similar to that observed with calcium channel blocking drugs (8, 9), so that we may suppose that Mg acts by inhibiting calcium handling of bronchial smooth muscle cells. This hypothesis is supported by experimental evidence on vascular beds (1, 2).

We could not investigate whether Mg has any bronchodilator effect, as our patients had normal baseline airway patency. However, the reduction of bronchial reactivity with MgSO_4 may prove to be a clinically important phenomenon. Further investigation is needed to assess the role of magnesium in the treatment of asthma.

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