Bronchodilating Effect of Inhaled and Intravenous Magnesium Sulfate (Compared with Aeresol Terbutaline)

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Zusammenfassung

Die Autoren haben die durch intravenöse Infusion von Magnesiumsulfat ($MgSO_4$) — induzierte Bronchodilatation bei 25 Asthmatikern mit geringer bis mäßiger Reaktionsfähigkeit der Bronchien untersucht. In dreitägigen Abständen erhielten die Patienten in zufallsbedingter Reihenfolge je eine Inhalation von Salzlösung (NaCl) und $MgSO_4$. An jedem Prüftag wurde vor und 5 Minuten nach der Inhalation eine Untersuchung mit dem Spirometer durchgeführt. NaCl und $MgSO_4$ hatten keine statistisch signifikante Wirkung auf die Ergebnisse dieser Untersuchung. Drei Tage später wurden die Patienten mit einer intravenösen Infusion von Placebo (Salzlösung) oder 2 g $MgSO_4$ behandelt. Durch die $MgSO_4$-Infusion wurde die Bronchokonstriktion schnell beseitigt, und die funktionellen Lungenparameter signifikant gebessert.

Summary

The bronchodilating effect of intravenous magnesium sulfate ($MgSO_4$) was studied in 25 asthmatic patients with mild to moderate bronchial reactivity. Subjects received, in random order, on separate days, 3 days apart, saline (NaCl) and $MgSO_4$ inhalation. Spirometry was recorded on each test day before and 5 minutes after NaCl and $MgSO_4$ inhalation. Neither NaCl nor $MgSO_4$ were found to have a significant effect on spirometric measurements. Three days later the patients were administered with an intravenous infusion of saline placebo and 2 g of $MgSO_4$. Magnesium sulfate infusion rapidly relieved bronchoconstriction and produced significant improvement in lung function measurements.
The results thus obtained were found to be similar to the effect of additional terbutaline inhalation and no significant difference between magnesium and terbutaline was found for any of the parameters.

Résumé

Les auteurs ont étudié la bronchodilatation induite par le sulfate de magnésium ($MgSO_4$) intraveineux chez 25 asthmatiques présentant une réactivité bronchique légère à modérée. A trois jours d'intervalle, les patients ont reçu, selon un ordre aléatoire, une inhalation de solution saline (NaCl) et de $MgSO_4$. Lors de chaque jour d'épreuve, un examen spirométrique a été effectué avant, puis 5 minutes après l'inhalation. Le NaCl et le $MgSO_4$ n'ont eu aucun effet significatif sur les résultats des examens spirométriques. Trois jours plus tard, les patients ont été traités par une perfusion intraveineuse de placebo (solution saline) ou de 2 g de $MgSO_4$. La perfusion de sulfate de magnésium a rapidement levé la bronchoconstriction et a significativement amélioré les paramètres fonctionnels pulmonaires.

Introduction

Calcium ion acts as the intracellular messenger for stimulus response coupling in many different cell types, most notably in reference to asthma, in smooth muscle cells of the bronchial tree, mediator releasing cells, mucus producing cells and parasympathetic nerve endings. The availability of calcium to the contractile or secretory apparatus of the cytosol represents the final common pathway for all influences upon the cells involved in the asthmatic diathesis. An increase in Ca^{+2} influx through bronchial smooth muscle cells may be the fundamental abnormality in asthma and might be an explanation for bronchial hyperreactivity [1, 2].

Calcium antagonist drugs have been shown to inhibit in vitro the synthesis of a variety of chemical mediators and to exert a significant protection against exercise, histamine and metacholine induced bronchoconstriction in asthmatics [2, 3]. Magnesium is a weak antagonist of calcium entry into smooth muscle cells and it influences the intracellular content and disposition of calcium [4, 5].

Besides its calcium antagonist effect on smooth muscle contraction the magnesium ion has also been reported to have an inhibitory action on histamine release from cholinergic nerve terminals and to have a sedative action. As far as we know, only two or three controlled studies on the bronchodilating effects of intravenous magnesium sulfate in mild to moderate asthmatics have been published [6, 7, 8]. Currently there are no studies about the bronchodilating effects of inhaled and intravenous magnesium sulfate in asthmatics who are not in remission. The present study was designed to evaluate the bronchodilating effects of inhaled and intravenous magnesium sulfate. Another aim of our study is to investigate the possible usefulness of magnesium sulfate as a bronchodialator in routine asthma treatment and to compare the bronchodilating effects of magnesium with terbutaline inhalation.

Methods

We studied 25 nonsmoking patients (15 males and 10 females), 20–36 years of age (mean 28.4 ± 6.2), ten with atopic and twenty with intrinsic bron-

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chial asthma. All of them were outpatients making routine visits to the Pulmonary Diseases Department of Medical Faculty of Istanbul University. They were diagnosed according to the American Thoracic Society's definitions of asthma [9]. All patients gave voluntary informed consent. They had mild to moderate bronchial reactivity. They exhibited neither cardiac nor renal dysfunciton.

The other exclusion criteria for the study included a FEV_1/FVC ratio less than 50 % fever, purulent sputum, infection, pregnancy and infiltrate on a chest roentgenogram. None of the subjects had respiratory tract infection for 6 weeks prior to the study. None was receiving cromolyn sodium, ketotifen or corticosteroids. All patients had received maintenance therapy consisting of $ß_2$-stimulants and theophylline derivatives. During the study subjects received only inhaled $ß_2$-agonists and none of them were given any medication, including inhaled $ß_2$-agonists, 12 hours before each test.

Subjects received, on separate days, 3 days apart 5 ml of either normal saline or $MgSO_4$ (1.50 g/10 ml) from a deVilbiss 35B nebulizer in a double blind cross-over design. Lung function tests were recorded on each test day in basal conditions and 5 minutes after saline and $MgSO_4$ inhalation by use of a water-seal spirometer (Godart Expirograph). Measurements were repeated until three lung function tests varying no more than 5 % were obtained in each subject. From these results the best forced vital capacity (FVC) and forced expiratory volume at one second (FEV_1) were selected.

Three days after $MgSO_4$ inhalation each patient received an infusion of 50 ml saline as placebo or 2 g $MgSO_4$ in 50 ml saline in random order, in a double blind cross-over design. The infusion was administered over 20 minutes. In each patient blood pressure, heart rate, respiratory rate and electrocardiograms were monitored through-out the study. Lung function tests were recorded in basal conditions, just after saline and $MgSO_4$ infusion and 45 minutes after $MgSO_4$ infusion. Forty-five minutes after $MgSO_4$ infusion terbutaline was administered from a metered dose aeresol inhaler (MDI) with a volumatic spacer twice, 2 minutes apart. Pulmonary functions were measured 5 minutes after terbutaline inhalation. All measurements were repeated until three results varying no more than 5 % were obtained in each patient. From these results the best FVC and FEV_1 were selected.

The difference between baseline spirometric values of each test day had to be within 10 %. Venous blood was obtained before, just after, 45 minutes and 24 hours after $MgSO_4$ infusion to measure serum magnesium concentration.

Data were expressed as mean ± SE. Comparisons among respiratory function test values of the two test days, before and after NaCl and $MgSO_4$ inhalation, were performed by analysis of variance. For comparison among respiratory function test values before and after NaCl and $MgSO_4$ infusions, analysis of variance was performed. To analyze the difference between two groups, the paired t test was used. Statistical significance was taken to be at $p < 0.05$.

Tab. 1: %FVC and %FEV_1 values before and 5 minutes after NaCl and $MgSO_4$ inhalation.

	Baseline	NaCl	Baseline	$MgSO_4$
%FVC	72.8 ± 8.4	74.2 ± 7.8	71.6 ± 6.4	73.8 ± 5.4
%FEV_1	58.6 ± 6.3	61.2 ± 4.8	60.2 ± 5.7	62.8 ± 3.6

No significant difference by analysis of variance

Results

Subjects did not experience any significant side effects after inhaling $MgSO_4$. Only two patients had dry cough which terminated spontaneously in approximately 5 minutes. We did not observe any difference between lung function on the NaCl or $MgSO_4$ day. Neither NaCl nor $MgSO_4$ produced any significant bronchodilation. No significant difference was obtained, by analysis of variance, between the baseline values and the NaCl or $MgSO_4$ inhalation values of pulmonary function (tab. 1).

In the third stage of the study the patients received NaCl and $MgSO_4$ intravenously. Mean pulmonary function values in basal conditions, just after NaCl and $MgSO_4$ infusion and 45 minutes after $MgSO_4$ infusion are shown in tab. 2. The values were not changed by saline infusion. With $MgSO_4$ infusion, the bronchodilator effect appeared rapidly and returned almost to basal values within 45 minutes after the infusion.

Four patients felt a hotness in the face during the infusion. Two patients experienced a fall of 10 mm Hg in systolic blood pressure and they developed sinus tachycardia of 110 and 114/minute which lasted 10 minutes. None of the side effects required teatment and all terminated spontaneously.

Mean pulmonary function test values obtained in basal conditions, just after NaCl and 45 minutes after $MgSO_4$ infusion are shown in tab. 2. FVC

Tab. 2: %FVC and %FEV_1 values before, just after, 45 minutes after $MgSO_4$ infusion with just before and after NaCl infusion.

	Baseline	NaCl infusion	$MgSO_4$ infusion	45 minutes after $MgSO_4$ infusion
%FVC	74.2 ± 4.8	76.3 ± 5.4	88.2 ± 3.6	76.3 ± 4.7
%FEV_1	56.4 ± 4.8	58.7 ± 3.2	75.8 ± 4.3	57.6 ± 3.7

significant difference by analysis of variance ($p < 0.01$)

Tab. 3: Mean serum magnesium concentration.

Basal serum Mg (mg/dl)	Mg concentration after $MgSO_4$ infusion	Mg concentration 45 minutes after $MgSO_4$ infusion	Mg concentration 24 hours after $MgSO_4$ infusion
2.08 ± 0.40	4.16 ± 0.54	2.76 ± 0.46	2.18 ± 0.34

and FEV_1 values were improved to 117.6 % ± 4.8 % and 119.4 % ± 5.4 % of their initial values. Within 45 minutes these values returned to 103.6 % ± 3.2 % and to 104.8 % ± 2.4 % of the baseline values. After terbutaline inhalation these values improved to 118.4 % ± 4.6 % and 124.8 % ± 5.2 %, respectively. The pulmonary function test results obtained after $MgSO_4$ infusion were found to be statistically significant ($p < 0.01$). The difference between $MgSO_4$ and terbutaline was not significant for any of the parameters. The mean serum magnesium concentrations obtained before, just after, 45 minutes and 24 hours after $MgSO_4$ infusion are shown in tab. 3 ($p < 0.01$).

Discussion

In this study we wanted to evaluate the effects of magnesium in bronchial asthma. We demonstrated that $MgSO_4$ administered by aeresol did not have any beneficial effect in asthmatics with mild to moderate bronchial reactivity. Our results do not support the findings of *Rolla* et al. *Rolla* concluded that $MgSO_4$ administered by aeresol, effectively inhibited histamine and metacholine induced bronchoconstriction in asthmatics, with mild to moderate bronchial reactivity, who were in clinical remission [10,11]. Our patients were not in remission and had mild or moderate bronchial reactivity at the time of the study. The observations in this study suggest that inhaled $MgSO_4$ does not have any significant bronchodilator effect.

When administered intravenously, there was a distinct effect of magnesium on pulmonary function in mild to moderate asthmatics. The bronchodilation appeared rapidly but the improvement in pulmonary function was temporary and almost terminated in 45 minutes after the infusion was completed. The fact that sulfate ion has a minimal effect on cell function suggests that the bronchodilator effect of intravenous $MgSO_4$ comes from the magnesium ion [12].

The mechanism of action of magnesium in asthma is currently unknown. Magnesium is one of the most abundant ions in the body regulating a large number of enzyme activities, such as those of adenosinetriphosphatases and physiologic processes in various cell types. It has been postulated that it relaxes bronchial smooth muscle and produces dilation of the airways. One explanation for this may be its role in the modulation of calcium ion movement [6]. Not only does magnesium facilitate uptake of calcium into the sarcoplasmic reticulum but it also inhibits slow inward Ca^{+2} induced Ca^{+2} release. With respect to the effects on asthmatic patients, mechanisms such as the inhibitory action on smooth muscle contraction, histamine release from mast cells and acetylcholine release from nerve terminals might be considered [7, 13, 14].

In addition to the effects on bronchial smooth muscle, magnesium influences the function of respiratory muscles. Diminished respiratory muscle power has been reported in alcoholics and patients with chronic obstructive pulmonary disease who have abnormally low serum magnesium levels [15]. Only 5 patients in our study had low serum magnesium levels while the others had serum magnesium concentration at the lower limits of normal. Increase in serum magnesium concentration may have improved muscle power to produce bronchodilation but we did not measure respiratory muscle power and intracellular magnesium concentration in our study.

The sedative effect of magnesium may have produced clinical improvement but we did not observe even a mild sedative effect in our patients during $MgSO_4$ infusion. Even if the sedative action had occured this would not account for such a great bronchodilation obtained in our study.

We have also measured the serum magnesium levels. The serum magnesium concentration increased from 2.08 ± 0.40 mg/dl to 4.16 ± 0.54 mg/dl during $MgSO_4$ infusion. The magnesium level fell to 2.76 ± 0.46 mg/dl and to 2.18 ± 0.34 mg/dl 45 minutes and 24 hours after the infusion respectively. We can conclude that higher serum magnesium levels may alter calcium movement into cells and improve the pulmonary function or produce less bronchoconstriction if magnesium is administered daily. Our study had some limitations. One is the small sample size. To increase the power of statistical analysis, studies with larger populations would be needed. The other limitation is the homogeneity of the patient population. Whether magnesium is clinically useful, safe and effective for more widespread use or whether magnesium could overt the need for steroids or aminophylline cannot be ans-wered precisely. In spite of these limitations, our observations suggest that magnesium may play a role in asthma and intravenous $MgSO_4$ therapy may be useful.

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