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Effect of Intravenous Magnesium Sulfate on Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization: a Randomized Placebo-Controlled Trial

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OBJECTIVE: Magnesium sulfate has been shown to have a bronchodilating effect in asthma, but this effect has not been clearly established in the context of chronic obstructive pulmonary disease (COPD). For this reason we investigated the possible bronchodilating effect of magnesium sulfate in COPD exacerbations.

PATIENTS AND METHODS: We studied 24 patients with exacerbated COPD who required admission to our hospital's pneumology department. All patients underwent baseline spirometry and were subsequently randomized to groups in a double-blind crossover design. Patients received 1.5 g of magnesium sulfate or placebo in an intravenous solution for 20 minutes. Those who received magnesium sulfate the first day were given placebo the second day, and vice versa. Spirometry was performed 15, 30, and 45 minutes after administration of magnesium sulfate or placebo. Finally, 400 µg of salbutamol were administered using a spacer and a final spirometry was performed 15 minutes later. All patients also received treatment with corticosteroids, intravenous antibiotics, oxygen, and regularly-scheduled bronchodilator therapy (salbutamol and ipratropium bromide every 6 hours).

RESULTS: When we compared absolute increase in liters and percentage increase in forced expiratory volume in 1 second (FEV_1) obtained with magnesium sulfate application to the increases obtained with placebo after 15, 30, and 45 minutes, no significant differences were found. When we compared absolute and percentage increases in FEV_1 after administering salbutamol, we found significantly greater increases after magnesium sulfate administration. The mean (SD) absolute increase in FEV_1 was 0.185 (0.42) L after magnesium sulfate administration and 0.081 (0.01) L after placebo (P=.004). The percentage increase in FEV_1 was 17.11% (3.7%) after magnesium sulfate and 7.06% (1.8%) after placebo (P=.008).

CONCLUSIONS: Intravenous administration of magnesium sulfate has no bronchodilating effect in patients with COPD exacerbations. It does, however, enhance the bronchodilating effect of inhaled ß$_2$-agonists.

Key words: *Chronic obstructive pulmonary disease, COPD. Magnesium sulfate. Bronchodilator agents.*

Efecto del sulfato de magnesio intravenoso en la exacerbación de la EPOC que precisa hospitalización

OBJETIVO: El sulfato de magnesio (SM) ha demostrado tener en el asma bronquial un efecto broncodilatador, que resulta dudoso en el caso de la enfermedad pulmonar obstructiva crónica (EPOC). Por ello hemos llevado a cabo un estudio con el objetivo de investigar el posible efecto broncodilatador del SM intravenoso en la EPOC agudizada.

PACIENTES Y MÉTODOS: Se estudió a 24 pacientes diagnosticados de EPOC agudizada que requirieron ingreso en la Unidad de Hospitalización de Neumología. A cada uno se le realizó una espirometría basal. Posteriormente, se efectuó una aleatorización a doble ciego y cruzada de los pacientes para recibir 1,5 g de SM o placebo en solución intravenosa (20 min). A quienes el primer día recibieron SM se les administró placebo el segundo día, y al revés. Se realizaron espirometrías a los 15, 30 y 45 min de la administración de SM o placebo. Por último, se administraron 400 µg de salbutamol inhalados mediante cámara espaciadora y a los 15 min se realizó una última espirometría. Todos los enfermos recibieron además tratamiento con esteroides, antibióticos intravenosos, oxígeno y broncodilatadores pautados (salbutamol y bromuro de ipratropio cada 6 h).

RESULTADOS: Cuando se compararon los incrementos absolutos (en ml) y porcentuales del volumen espiratorio forzado en el primer segundo (FEV_1) obtenidos con SM y placebo a los 15, 30 y 45 min, no se encontraron diferencias significativas. Al comparar los incrementos absolutos y porcentuales del FEV_1 tras la administración de salbutamol se observaron incrementos significativos con el SM (incrementos absolutos FEV_1 SM/placebo: 0,185 ± 0,42 frente a 0,081 ± 0,01 l; p = 0,004. Incrementos porcentuales FEV_1 SM/placebo: 17,11 ± 3,7% frente al 7,06 ± 1,8%; p = 0,008).

CONCLUSIONES: La administración de SM intravenoso carece de efecto broncodilatador en pacientes con EPOC agudizada; sin embargo, sí potencia dicho efecto de los betamiméticos inhalados.

Palabras clave: *Enfermedad pulmonar obstructiva crónica (EPOC). Sulfato de magnesio. Broncodilatadores.*

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Manuscript received May 3, 2005. Accepted for publication January 3, 2006.

Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical condition characterized by usually irreversible bronchial obstruction secondary to an underlying inflammatory process, the anomalous contraction of bronchial smooth muscle fibers, and the presence of excessive mucus that is usually viscous and difficult to clear through coughing or ciliary movement in the bronchial epithelium.[1] During COPD exacerbations there is a worsening of bronchial obstruction, leading to alterations in the process of oxygenation in the alveoli and possibly to respiratory failure.

Traditional therapy for COPD exacerbations has included the use of bronchodilators, systemic corticosteroids, oxygen and, in cases of severe respiratory acidosis, assisted ventilation (either classic mechanical ventilation, with orotracheal intubation, or newer forms of noninvasive ventilation).[2] One of the cornerstones of therapy for COPD exacerbations is the use of bronchodilators, especially high dose inhaled bronchodilators. The most common of these are β_2-agonists (salbutamol and terbutaline) and anticholinergics (ipratropium bromide). Although the effect of these bronchodilators is considerably more limited in COPD than in asthma, with smaller increases in FEV_1, their use is accompanied by an improvement in both the dyspnea and blood gas alterations that patients with COPD present, especially during exacerbations.[3,4] This improvement is due not only to the direct effect of the relaxation of smooth muscle fibers, but also to the ability of these drugs to reduce hyperinflation by reducing functional residual capacity and, therefore, dynamic airway compression.[5,6]

Magnesium sulfate, especially when administered intravenously, has been shown to have a slight bronchodilating effect, especially in exacerbations of bronchial asthma.[7] Furthermore, patients receiving early intravenous magnesium sulfate in an emergency department have required fewer hospital admissions than those receiving conventional therapy.[8] It has also been observed that this bronchodilating effect occurs particularly in patients with exacerbations of bronchial asthma that are refractory to conventional treatment with β_2-agonists.[9-11] Studies on the parenteral use of magnesium sulfate in COPD exacerbations have been few and inconclusive.[12]

The objectives of the present study were as follows: *a)* to determine whether intravenous magnesium sulfate has a bronchodilating effect in COPD exacerbations and *b)* to observe whether the administration of magnesium sulfate enhances the bronchodilating effect of β_2-agonists.

Patients and Methods

We carried out a randomized placebo-controlled double-blind crossover trial enrolling 24 men admitted to the pneumology department of the Hospital Universitario de Canarias between October 2003 and September 2004 who had been diagnosed with an exacerbation of COPD and who showed a high level of cooperation. Informed consent was obtained in all cases and the study was approved by the local hospital ethics committee. The average time between admission and the initiation of the study was 24 hours. Each patient received a standard treatment consisting of intravenous methylprednisolone, parenteral fluid therapy, antibiotics (amoxicillin-clavulanic acid or, in cases of allergy to β-lactam antibiotics, a quinolone antibiotic), inhaled bronchodilators (salbutamol and ipratropium bromide) using a spacer, and oxygen (in order to obtain a transcutaneous oxygen saturation reading greater than 90%). Patients diagnosed with pneumonia, heart failure, arrhythmias, or kidney failure and those who did not show a sufficient level of cooperation were excluded. All patients underwent simple baseline spirometry with a Datospir pneumotachograph (Sibelmed, Barcelona, Spain) that was calibrated daily with a 3-L syringe. Spirometry was performed according to the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR),[13] with patients in a sitting position. On the first day of the study, patients were randomized to groups in a crossover design (Figure 1). Twelve patients received a 20-minute intravenous infusion of 1.5 g of magnesium sulfate dissolved in 100 mL of 0.9% saline solution and the other 12 patients 100 mL of 0.9% saline solution (placebo). The 2 solutions were in identical containers. On the second day, the patients who had received placebo were given magnesium sulfate and those who had received magnesium sulfate were given placebo. Magnesium sulfate and placebo were administered 6 hours after the last dose of inhaled bronchodilators. After the infusion of each of the solutions, serial spirometry was performed at 15, 30, and 45 minutes. Finally, we administered 400 µg of salbutamol inhaled through a Volumatic (Glaxo Wellcome, Evreux, France) spacer and performed a final spirometry 15 minutes later. Throughout the experiment, we checked blood pressure, pulse, and breathing rate in order to detect any side effects.

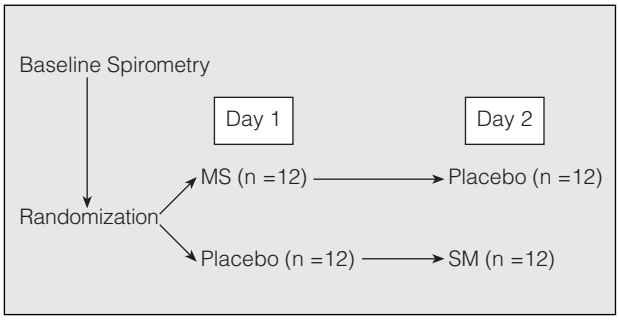

Figure 1. Study Protocol. MS indicates intravenous magnesium sulfate

Statistical Analysis

Results are expressed as means (SD) for quantitative variables. Variations in FEV_1 are given both as absolute values in milliliters and as percentages. These percentages defined variability (final FEV_1 – baseline FEV_1/baseline $FEV_1 \times 100$). The nonparametric Wilcoxon signed rank test was used to compare means. Statistical significance was established at $P<.05$. Statistical analysis was performed using the statistical package SPSS version 12.0 for Windows (Chicago, Illinois, USA).

Results

Twenty-four male patients were included in the study. The mean age was 64 years (range, 57-78 years),

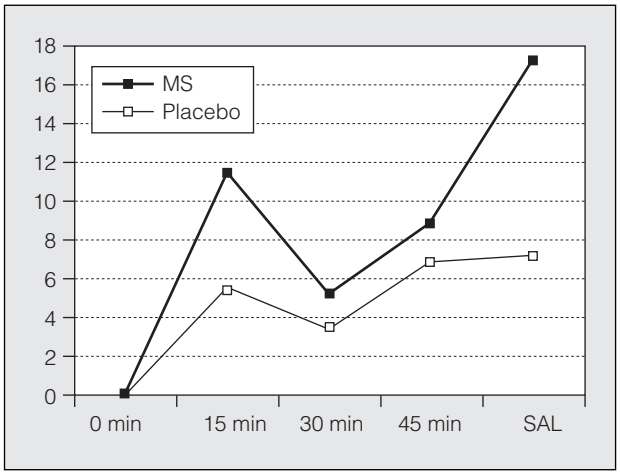

Figure 2. Percentage increases in forced expirotory volume in 1 second in patients who received magnesium sulfate and placebo. SAL indicates after salbutamol.

mean weight was 76 (7) kg (range, 67-98 kg), and mean height was 162 (13) cm (range, 157-176 cm). Mean baseline FEV_1 values on the first and second days were similar for those patients who received magnesium sulfate and those who received placebo (Table 1). Table 2 shows absolute and percentage increases in FEV_1, at 15, 30, and 45 minutes, and after the administration of salbutamol for both groups.

When we compared percentage increases in FEV_1 obtained with magnesium sulfate with those obtained with placebo after 15, 30, and 45 minutes, the values obtained with intravenous magnesium sulfate were higher, although the difference was not statistically significant. However, in the comparison between percentage increases in FEV_1 after 45 minutes and after administration of salbutamol, the group that had received intravenous magnesium sulfate showed a significant increase in FEV_1 (absolute increases in FEV_1 magnesium sulfate/placebo 0.185 [0.42 L compared to 0.81 [0.17] L; $P<.004$. Percentage increases in FEV_1 magnesium sulfate/placebo: 17.11% [3.74%] compared to 7.06% [1.85%]; $P<.008$) (Figure 2). No significant differences were observed in heart rate or in blood pressure between the 2 groups.

TABLE 1
FEV_1 Values in Patients Who Received MS and Placebo*

	FEV_1		*P*
	Day 1	Day 2	
MS	0.86 (0.11) L; 32.5% (3.2%)	0.86 (0.86) L; 30% (3.2%)	.9
Placebo	0.85 (0.92) L; 28% (3%)	0.87 (0.11) L; 30.7%(3.3%)	.8
P	.4	.6	

*FEV_1 indicates forced expiratory volume in 1 second; MS, magnesium sulfate.

Discussion

In our study we observed that the administration of 1.5 g of intravenous magnesium sulfate had no bronchodilating effect in patients with exacerbated COPD. These results differ from those obtained by Skorodin et al,[12] who found a bronchodilating effect in patients with acute exacerbations of COPD. This effect was greater than that obtained with inhaled β_2-agonists alone. These authors used only serial peak expiratory flow measurements to evaluate the bronchodilating effect of magnesium sulfate, and not conventional spirometry, as in the present study. The discrepancy between our results and theirs may be due to the technique used to measure the degree of bronchial obstruction (peak expiratory flow compared to conventional spirometry). It is well known that measurement of peak expiratory flow is less sensitive than FEV_1 in quantifying airflow obstruction and that it may underestimate the degree of bronchial obstruction.[14-16]

In our study a significant increase in the bronchodilating effect of salbutamol was observed only when it was administered after infusion of intravenous magnesium sulfate. In other words, magnesium sulfate seems to enhance the bronchodilating effect of inhaled β_2-agonists in patients with exacerbations of COPD. In this respect, our results are consistent with those of Nannini et al,[17] who showed that inhaled isotonic magnesium sulfate (as a nebulizer solution) plus salbutamol had a greater bronchodilating effect than salbutamol plus saline solution in exacerbations of bronchial asthma. Furthermore, Skorodin et al[18] observed that intravenous magnesium sulfate enhanced the metabolic and cardiovascular effects of terbutaline in healthy subjects. It is thought that magnesium may increase the bronchodilating response of β_2-agonists by increasing receptor affinity for the agonist or by facilitating the externalization of the receptor on the surface of the cellular membranes of the target organ.[19] COPD is defined as a disease in which airway

TABLE 2
Percentage and Absolute Increases in FEV_1 in Patients Who Received MS and Placebo*

	Increase in FEV_1							
	15 min	*P*	30 min	*P*	45 min	*P*	After Salbutamol	*P*
MS	11.43% (5.17%); 0.16 (0.1) L		5.25% (1.92%); 0.18 (0.1) L	.06	8.84% (2.7%); 0.19 (0.1) L	.1 .2	17.11% (3.7%); 0.18 (0.4) L	.008 .004
Placebo	3.45% (1.29%); 0.05 (0.01) L		3.34% (1.16%); 0.06 (0.01) L		6.74% (1.9%); 0.07 (0.02) L		7.06% (1.85%); 0.08 (0.01) L	

*FEV_1 indicates forced expiratory volume in 1 second; MS, magnesium sulfate.

obstruction is irreversible and bronchodilator response limited.[20-22] We believe the enhancing effect on salbutamol-induced bronchodilation that we observed with the administration of intravenous magnesium sulfate in patients with exacerbations of COPD to be noteworthy in view of the limited bronchodilating effect of β_2-agonists in COPD and of the fact that there are no other drugs that increase this effect in this disease, as both systemic and inhaled corticosteroids are known to do in bronchial asthma.[23] We believe, therefore, that our findings may constitute a future therapeutic advance. The administration of intravenous magnesium sulfate in patients with exacerbations of COPD may decrease the number of hospital admissions, the length of hospital stays, and perhaps even the need for assisted ventilation.

In conclusion, the administration of intravenous magnesium sulfate in patients with COPD exacerbations has no bronchodilating effect in itself. However, it does enhance the effect of inhaled β_2-agonists.

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