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Bronchodilating Effect of Intravenous Magnesium Sulfate in Acute Severe Bronchial Asthma*

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We investigated the bronchodilating effect of intravenous $MgSO_4$ in acute severe bronchial asthma. Infusion of $MgSO_4$ caused a significant improvement in FEV_1 (0.94 ± 0.39L to 1.3 ± 0.44 L) and an improvement in clinical signs and symptoms in ten out of 12 administrations. The bronchodilating effect of $MgSO_4$, however, was significantly less than that of subsequent albuterol inhalation (FEV_1 improvement from 1.13 ± 0.41 L to 1.72 ± 0.49 L). These findings confirm that intravenous $MgSO_4$ may be used as an adjunct to classic $beta_2$-agonist therapy in cases of severe acute asthma; its exact place in the treatment of asthma remains to be determined in large-scale studies.

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Apart from anecdotal report of symptomatic relief after infusion of $MgSO_4$ in bronchial asthma half a century ago,[1,2] only two controlled studies on the bronchodilating effects of intravenous $MgSO_4$ in mild to moderately severe asthma[3] and in moderate to severe asthma[4] have been published. In the first study, infusion of $MgSO_4$ caused a rapid but temporary bronchodilation which did not significantly differ from the subsequent bronchodilation induced by beta-agonist therapy;[3] the second study indicated that $MgSO_4$ infusion was capable of inducing bronchodilation in severely asthmatic patients who were unresponsive to maximal beta-agonist therapy.[4]

In the present study, we examined the bronchodilating effects of intravenous $MgSO_4$ in severe acute asthma and compared this effect with the bronchodilating capacity of subsequent inhaled albuterol.

Methods

All patients presenting to the emergency department of our hospital with acute severe asthma received standard treatment: 2.5 mg (=0.5 ml) albuterol in 4.5 ml saline solution delivered by a powered nebulizer every 4 h; methylprednisolone, 40 mg given intravenously every 12 h; ampicillin, 4 g daily intravenously, or doxycycline, 200 mg orally if signs of infection were present; intravenous aminophylline, 720 to 960 mg daily, adjusted in order to achieve serum theophylline levels between 10 and 20 μg/ml; supplemental oxygen, when necessary, delivered by nasal prongs.

Patients were then admitted to the study protocol after informed consent was received and when meeting the following criteria: a previous diagnosis of bronchial asthma (atopic or nonatopic), with spirometry confirming reversible bronchoconstriction (FEV_1 below 75 percent predicted, FEV_1/FVC less than 60 percent, and an FEV_1 increase of 15 percent or more after $beta_2$-agonist administration) and the present diagnosis of acute, severe asthma, defined by clinical examination and by a FEV_1 of less than 40 percent predicted.[5]

Exclusion criteria were: heart failure, pneumonia, life-threatening conditions or neoplastic disorders, acidemia or hypercapnia, and patients who required mechanical ventilation.

Six patients entered the study (aged 45 to 60 years); 12 studies were performed as follows: the first morning after admission, early albuterol administration was suspended under close medical supervision. All other medications were given as before. At 8 AM, the best result of three successive blows into a Vitalograph spirometer (Vitalograph Ltd., Buckingham, England) was used to measure baseline FEV_1. Infusion of $MgSO_4$ was then started for 20 min at 0.615 mmol/min. Spirometry was repeated at the end of the $MgSO_4$ infusion and again 30 min later. The latter FEV_1 values were considered as baseline data for the evaluation of the effect of albuterol inhalation (2.5 mg in 4.5 ml saline by a powered nebulizer in 20 min), which was started immediately after the third session of blows. Finally, spirometry was again performed at the end of the albuterol inhalation.

Throughout the $MgSO_4$ infusion and the albuterol inhalation period, blood pressure, heart rate, auscultatory phenomena, subjective findings and adverse effects were closely monitored. Venous blood was sampled just before and at the end of the $MgSO_4$ infusion, to measure serum Mg concentration (dry chemistry method, Kodak Ektachem) and red blood cell Mg content (FAAS method). The same procedure was repeated the next day.

Statistical analysis was performed with an IBM PC XT computer running a SPSS/PC + statistics program (SPSS Inc, Chicago).

The Wilcoxon paired test at a significance level of $p<0.05$ was used when appropriate.

Results

Patient characteristics are listed in Table 1. The changes in FEV_1 during $MgSO_4$ infusion and during albuterol inhalation on two consecutive days are shown in Figure 1.

On day 1 as well as on day 2, there was a significant ($p<0.05$) improvement in FEV_1 after $MgSO_4$ infusion, as well as a subjective improvement of dyspnea (five out of six patients) and of wheezes (five out of six patients) (Table 2).

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Table 1—*Patient Characteristics and Evolution of FEV_1 after $MgSO_4$ Infusion and after Beta-agonist Inhalation on Two Consecutive Days*

Subject, Sex, Age (yr)	Day of Study	FEV_1 in Liters (and in % Predicted) before Mg	FEV_1 in Liters after Mg	FEV_1 Improvement in % after Mg	FEV_1 in Liters (and in % Predicted) before $Beta_2$-agonist	FEV_1 in Liters after $Beta_2$-agonist	FEV_1 Improvement in % after $Beta_2$-agonist
1,F,49	1	1.12 (40)	1.25	12	1.16 (41)	1.94	67
	2	1.16 (42)	1.73	49	1.34 (48)	2.36	76
2,M,60	1	0.56 (17)	0.71	27	0.70 (21)	1.12	60
	2	0.64 (19)	0.78	22	0.66 (20)	1.35	104
3,M,45	1	1.13 (29)	1.28	13	1.23 (31)	1.54	25
	2	1.92 (49)	2.30	20	2.19 (56)	2.49	14
4,F,55	1	0.82 (32)	1.01	23	0.97 (38)	1.28	32
	2	0.56 (22)	1.01	80	0.79 (31)	1.31	66
5,F,46	1	0.47 (16)	1.09	132	0.8 (27)	1.44	80
	2	1.07 (36)	1.40	31	1.05 (35)	1.33	27
6,F,24	1	0.88 (25)	1.50	70	1.32 (38)	2.21	67
	2	1.13 (36)	1.65	46	1.37 (42)	2.30	68

Thirty minutes after the end of the $MgSO_4$ infusion, there was a drop in FEV_1 in all patients, but FEV_1 did not reach the baseline values before $MgSO_4$ administration ($p<0.05$). Inhalation of albuterol, 30 minutes after ending the $MgSO_4$ infusion, resulted again in a significant ($p<0.05$) improvement of FEV_1 in all patients, with subjective and auscultatory improvement in all six patients, on both days. This improvement in FEV_1 was significantly more pronounced than the FEV_1 improvement after $MgSO_4$ infusion ($p<0.02$). Although some patients (*eg*, patients 1 and 4) showed variable responses of FEV_1 improvement on two consecutive days after $MgSO_4$ infusion, as a group there was no significant difference in FEV_1 improvement on day 1 compared with day 2.

Serum Mg concentrations significantly increased from 0.87 ± 0.04 mmol/L before to 1.95 ± 0.2 mmol/L after the $MgSO_4$ infusion, and had returned to baseline values 24 h later.

The Mg concentrations in red blood cells did not significantly differ after the $MgSO_4$ infusion. There were no differences in heart rate or blood pressure during $MgSO_4$ infusion or during albuterol inhalation. Side effects which occurred during $MgSO_4$ infusion are listed in Table 2; local burn at the perfusion site was noted by three patients and hot flushes in two. Both side effects were well tolerated and were limited to the infusion period.

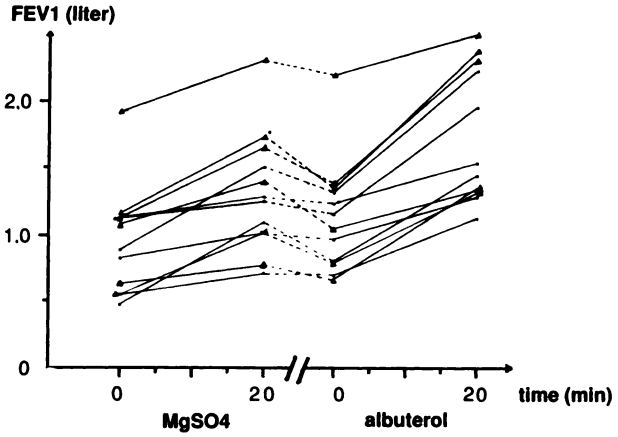

FIGURE 1. Evolution of FEV_1 after $MgSO_4$ infusion and after $beta_2$-agonist inhalation on two consecutive days (day 1, *squares*; day 2, *triangles*).

DISCUSSION

Few contolled data are available on the bronchodilating effect of intravenous $MgSO_4$ in bronchial asthma. In 1987, Okayama et al[3] showed that $MgSO_4$ relieved bronchoconstriction in mild asthma in a dose-dependant manner. Maximal responses were similar to the effects of additional albuterol inhalation. Bronchodilation occurred soon after the beginning of $MgSO_4$ infusion and reached its maximum at the end of the 20 min of infusion. Ten minutes after ending the infusion, respiratory parameters had returned to pre-

Table 2—*Evolution of Clinical Signs and Symptoms and Occurrence of Adverse Effects During $MgSO_4$ Infusion**

Subjects, Sex, Age (yr)	Day of Study	Wheezing	Subjective Improvement of Dyspnea	Adverse Effects
1,F,49	1	↙	. . .†	Local burn
	2	↙↙↙ to 0	. . .‡	...‖
2,M,60	1	↙↙	. . .‡	Flush
	2	↙	. . .‡	Flush, local burn
3,M,45	1	↙↙	. . .†	. . .‖
	2	↙↙	. . .†	. . .‖
4,F,55	1	↙	. . .†	Local burn
	2	↙↙↙ to 0	. . .§	Local burn
5,F,46	1	. . .‖	. . .‖	. . .‖
	2	. . .‖	. . .‖	. . .‖
6,F,24	1	↙↙	. . .‡	Flush
	2	↙↙	. . .‡	Flush

*Legend: ↙ = slight decrease; ↙↙ = marked decrease; ↙↙↙ to 0 = disappearance of wheezes.
†Less than usual after $beta_2$-agonist inhalation.
‡Equal to usual $beta_2$-agonist inhalation.
§More than usual after $beta_2$-agonist inhalation.

treatment values. Spivey et al[4] compared intravenous $MgSO_4$ with saline placebo for the treatment of moderate to severe asthmatic subjects who failed to respond to conventional beta-agonists (two metaproterenol or albuterol nebulized treatments 45 min apart, and solumedrol). If PEFR 15 min after the second nebulized treatment had not doubled from the initial values, either saline solution or $MgSO_4$ (1.2 g over 20 min equiv 0.246 mmol/min) was injected. Infusion of $MgSO_4$ resulted in significantly better bronchodilation than did saline infusion, indicating that $MgSO_4$ may be a useful adjunct to conventional beta-agonist therapy in the emergency treatment of moderate to severe bronchospasm.

In our study we evaluated the bronchodilating effect of intravenous $MgSO_4$ in patients with severe acute asthma. Infusion of $MgSO_4$ caused a significant improvement in FEV_1 (0.94 ± 0.39 L to 1.3 ± 0.44 L), and an improvement in clinical signs and symptoms in ten out of 12 administrations.

Thirty minutes after the infusion period, FEV_1 had not returned to the preinfusion values in our patients, in contrast with the findings of Okayama et al,[3] suggesting some persistence of the bronchodilating effect. This is in accordance with data of Spivey et al[4] which also show that the $MgSO_4$ -induced bronchodilation persists for more than 20 min.

Again in contrast with the findings of Okayama et al,[3] the bronchodilating effect of $MgSO_4$ was significantly less than that of subsequent albuterol inhalation (FEV_1 improvement from 1.13 ± 0.41 L to 1.72 ± 0.49 L); however, the fact that FEV_1 had not returned to preinfusion values 30 min after stopping the $MgSO_4$ infusion could account for the greater improvement of FEV_1 after albuterol inhalation, since $MgSO_4$ and $beta_2$-agonists may have additive bronchodilating effects.[4]

Another reason for the lesser potency of $MgSO_4$ in our study could reside in the difference between the populations studied: "our" patients had significantly more severe asthma when entering the study (mean 30.25 percent predicted FEV_1 *vs* mean 61.8 percent predicted FEV_1 in the Japanese study). Although patients of Spivey et al[4] (who also had "severe asthma") showed a marked bronchodilation after $MgSO_4$ infusion, the data presented do not allow comparison of PEFR changes in their patients between $beta_2$-agonist therapy and $MgSO_4$ infusion.

The mechanism of the observed Mg-induced bronchodilation is not clear. Hypomagnesemia has been reported in patients with asthma;[2] we do not think, however, that repletion of Mg deficiency can be considered in our patients since pretreatment serum and intracellular Mg concentrations were within normal limits, and since no patient was at risk for hypomagnesemia.[6] Intravenous $beta_2$-agonists (*ie*, albuterol), in a therapeutic dose, can cause a significant fall in serum magnesium concentrations,[7] probably due to a beta-adrenergic-induced intracellular shift of Mg. Although all our patients regularly used $beta_2$-agonists, no albuterol or other $beta_2$-agonist were given at least 4 h before the Mg infusion.

Calcium channel blockers have been shown to blunt or abolish the bronchoconstrictor response to exercise,[8] histamine[9] and metacholine;[10] the effect of Mg is similar to that observed with calcium-channel blockers.[11,12] This, and experimental data,[13,14] suggest that Mg may exert its effect on the final common path of bronchoconstriction by interfering with calcium handling of the bronchial smooth muscle cells.

Magnesium sulfate also is used in the treatment of seizures associated with acute nephritis and with eclampsia of pregnancy: typically, 4 g of $MgSO_4$ is injected over 5 min, followed by 10 to 20 g in drip infusion at the rate of approximately 1 g of $MgSO_4$ per hour. Magnesium concentrations of 6 to 8 mEq/L (equiv 3 to 4 mmol/L) are within the therapeutic range. Respiratory failure can occur at concentrations of approximately 12 to 15 mEq/L (6 to 7.5 mmol/L).[15,16]

We decided to inject 3 g of $MgSO_4$ (in Belgium, $MgSO_4$ is available in ampules of 3 g $MgSO_4$ in a 30 percent solution) over a 20-min period, in analogy to Okayama et al,[3] resulting in an infusion rate of 0.615 mmol/min. Maximal Mg concentrations observed were far within safety limits.

We conclude that intravenous $MgSO_4$ infusion causes significant bronchodilation and subjective improvement in patients with severe bronchial asthma; we therefore consider it a safe and efficient adjunct to classic $beta_2$-agonist therapy in cases of severe acute asthma.

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