

Higher-Dose Intravenous Magnesium Therapy for Children With Moderate to Severe Acute Asthma

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Objective: To evaluate the efficacy of a 40-mg/kg dose of intravenous magnesium sulfate for moderate to severe asthma exacerbations in pediatric patients.

Study design: Double-blind placebo-controlled trial.

Setting: Two urban tertiary care pediatric emergency departments.

Subjects: Thirty patients, aged 6 to 17.9 years, being treated for an acute asthma exacerbation.

Intervention: Eligible patients received either a magnesium sulfate infusion of 40 mg/kg or saline solution.

Results: At 20 minutes, the time at which the infusion was completed, the magnesium group had a significantly greater percentage of absolute improvement from

baseline in each of the following: predicted peak expiratory flow rate (8.6% vs 0.3%, $P < .001$), forced expiratory volume in 1 second (7.0% vs 0.2%, $P < .001$), and forced vital capacity (7.3% vs -0.7%, $P < .001$). The improvement was greater at 110 minutes: peak expiratory flow rate (25.8% vs 1.9%, $P < .001$), forced expiratory volume in 1 second (24.1% vs 2.3%; $P < .001$), and forced vital capacity (27.3% vs 2.6%, $P < .001$). Patients who received intravenous magnesium were more likely to be discharged to their homes than those who received the placebo (8/16 vs 0/14; $P = .002$).

Conclusion: Children treated with 40 mg/kg of intravenous magnesium sulfate for moderate to severe asthma showed remarkable improvement in short-term pulmonary function.

Arch Pediatr Adolesc Med. 2000;154:979-983

FROM 1984 to 1994 the national hospitalization rate for asthmatic children increased by 17%. The national death rate for asthma in children and adults more than doubled from 1975 to 1995.¹ Despite refinements in the therapeutic strategies for acute asthma, emergency department visits and hospitalizations continue to account for the predominant proportion of health care costs for asthma.² These facts stress the need for innovative emergency department-based interventions. The administration of β -agonist nebulizations in conjunction with corticosteroids is an effective treatment strategy, but corticosteroids require several hours before their effects are appreciated.³⁻⁶ An efficient asthma adjunct is needed to help bridge the time to onset of corticosteroid therapy effects in the subpopulation of patients with asthma who are resistant to standard bronchodilating treatments. This ideal agent should be fast-acting, safe, and effective. It has been proposed that intravenous magnesium sulfate (IVMg) has all of these properties.

The first investigations to study the role of magnesium in asthma date back to 1938. Haury⁷ demonstrated that magnesium relaxes smooth muscle and reduces histamine-induced bronchoconstriction in guinea pigs. More than 50 years later, Spivey et al⁸ described a dose-related effect of magnesium on bronchial smooth muscle. The effects of magnesium may be

See also pages 977 and 984

mediated through its action as a calcium antagonist or through its function as a cofactor in enzyme systems involving sodium and potassium flux across cell membranes.^{9,10} These effects result in the relaxation of smooth muscle, the inhibition of cholinergic neuromuscular transmission, and the stabilization of mast cells.^{11,12}

The results of clinical studies using magnesium in adult asthmatic patients have been conflicting¹³⁻²¹ and few studies have been completed in children.^{22,23} We conducted the first controlled investigation of IVMg in childhood asthma, which

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PATIENTS, MATERIALS, AND METHODS

From February 1996 through June 1996, patients were recruited from the emergency department at Children's Memorial Hospital, Chicago, Ill, and from September 1996 through August 1997, patients were recruited from the Hasbro Children's Hospital Emergency Department in Providence, RI. Both are urban tertiary care children's hospitals. The study was approved by the institutional review boards at each of these centers. Patients aged 6 to 17.9 years, coming to the emergency department with an acute asthma exacerbation, were evaluated for the study. The peak expiratory flow rate (PEFR) was measured in patients who required 3 nebulized bronchodilating treatments (albuterol or ipratropium bromide or a combination of the 2) while in the emergency department. The best value of the 3 attempts, using a Wright Peak Flow Meter (Ferraris Medical Inc, Holland, NY), was recorded. The patient's age, sex, and height were used to determine the predicted values. Study personnel (L.C. and D.B.) assisted patients in all PFTs. If PEFR was less than 70% of the predicted value, the patient was presumed to be resistant to nebulization therapy. A PEFR less than 70% of the predicted value has been previously accepted as defining a moderate to severe exacerbation.²⁵ Informed consent was obtained and the patient was enrolled in the study. Exclusion criteria consisted of a body temperature greater than 38.5°C, the use of theophylline within the previous week, and a history of cardiac, renal, or pulmonary disease other than asthma.

After enrollment, intravenous access was established and a baseline serum sample was obtained for magnesium concentration. Intravenous methylprednisolone (2 mg/kg [maximum, 100 mg]) was administered to patients who had not yet received corticosteroids. Each patient was randomly assigned by the investigational drug pharmacist to receive either magnesium sulfate (40 mg/kg [maximum 2 g] in 100 mL of normal saline solution) or an equivalent volume of normal saline solution (placebo) in a double-blind fashion. The magnesium and placebo solutions were prepared by the hospital pharmacy and randomization was blocked in groups of 10.

Serial clinical asthma scores, blood pressure measurements, deep tendon reflexes, and the results of PFTs were recorded at the start of the infusion, halfway through the

infusion (at 10 minutes), and at the conclusion of the 20-minute infusion. The same measurements were then recorded every 15 minutes for an additional 90 minutes. The modified Wood-Downes clinical asthma score was used, which incorporates oxygen saturation by pulse oximetry, color, quality of breath sounds, retractions, wheezing, and mental status.²⁶ The entrance PEFR value was measured with a Wright Peak Flow Meter and verified at the start of the study protocol with a computerized handheld spirometer. All of the PFTs (PEFR, forced expiratory volume in one second [FEV₁] and forced vital capacity [FVC]) just prior to and during the study infusion were calculated using a computerized handheld spirometer (Jones Medical Instrument Co, Oak Brook, Ill), which incorporated age, sex, race, height, and weight. The spirometer validated each recording using the American Thoracic Society criteria for acceptable spirometric curves.²⁷ Nebulized bronchodilators (albuterol and ipratropium) continued to be administered at the discretion of the medical team. The physicians on the medical team acted independently from the study physicians and were blinded to the patient's magnesium treatment status. A second serum sample was analyzed for magnesium concentration 30 minutes after the completion of the infusion. The results of the serum magnesium concentration determinations were not made known to the investigators or to the medical team caring for the patient, except for values lower than 0.4 mmol/L or greater than 3.3 mmol/L.

Follow-up of patients discharged from the emergency department consisted of a telephone call 48 to 72 hours after discharge. Questions were asked to determine whether the patient's status had worsened, whether a second emergency assessment by a physician was required, and whether admission to a hospital had become necessary.

The primary outcome of this study was a change in PEFR. Secondary outcome measures were changes in FEV₁ and FVC and emergency department disposition. Data were analyzed with the χ^2 statistic for categorical variables, a repeated-measures analysis of variance, and the 2-tailed paired *t* test with a Bonferroni adjustment for continuous variables. An a priori power analysis indicated that 40 patients (20 in each group) would be necessary to detect a 25% difference in PEFR (with α equal to .20, and β equal to .05). At interim analysis, 30 patients were enrolled in the study. Clinically important differences were noted between the 2 groups at that time and study enrollment was closed.

demonstrated the considerable potential of IVMg treatment in the acute care setting.²³ In that randomized double-blind placebo-controlled trial, patients treated with 25 mg/kg of magnesium sulfate showed significant improvements compared with controls in short-term pulmonary function tests (PFTs), beginning 30 minutes after the infusion was completed. The study also suggested that 1 of every 4 patients treated with IVMg could potentially avoid hospitalization.

Other clinical situations, such as preeclampsia, warrant the use of higher doses of magnesium sulfate to obtain optimal effects without sacrificing safety.²⁴ A small case series of pediatric patients reported the beneficial effects of repeated 40- to 50-mg/kg doses of IVMg for patients with severe asthma.²² No controlled studies to date have investigated this dose range in children. The objec-

tive of this study was to determine the efficacy of higher-dose IVMg therapy for moderate to severe asthma exacerbations in pediatric patients.

RESULTS

PATIENT CHARACTERISTICS

Thirty-eight patients were enrolled in the study, 8 of whom were excluded because of unacceptable spirometry efforts (as determined by the computerized spirometer). Of the 30 remaining patients, 16 were randomly assigned to the IVMg group and 14 to the placebo group. These subjects had a suboptimal response to β -agonist therapy in the emergency department. The mean age of the patients in the IVMg group was 10.9 \pm 0.9 years, and 68% were

Table 1. Patient Baseline Characteristics*

| Characteristic | Intravenous Magnesium Sulfate Group (n = 16) | Placebo Group (n = 14) | P |
|----------------------------------|--|------------------------|-----|
| Age, y | 10.9 ± 0.9 | 12.0 ± 1.0 | .39 |
| Male, No. | 11 | 7 | .30 |
| SaO ₂ , mean, % | 92.0 ± 0.7 | 91.6 ± 0.6 | .64 |
| CAS | 4.2 ± 0.4 | 3.4 ± 0.3 | .12 |
| PEFR, % predicted | 29.9 ± 1.7 | 33.1 ± 1.2 | .14 |
| FEV ₁ , % predicted | 28.9 ± 1.9 | 31.3 ± 1.3 | .31 |
| FVC, % predicted | 30.7 ± 2.2 | 33.3 ± 1.8 | .38 |
| Systolic BP, mm Hg | 120 ± 2 | 114 ± 3 | .05 |
| Baseline magnesium level, mmol/L | 0.63 ± 0.01 | 0.63 ± 0.02 | .85 |

*Data are given as mean ± SD unless otherwise indicated. SaO₂ indicates oxygen saturation; CAS, clinical asthma score; PEFR, peak expiratory flow rate; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; and BP, blood pressure.

Table 2. Patient Characteristics During the Study Period*

| Characteristic | Intravenous Magnesium Sulfate Group (n = 16) | Placebo Group (n = 14) | P |
|---|--|------------------------|-------|
| No. of nebulizations | 1.6 ± 0.3 | 1.2 ± 0.4 | .41 |
| No. of ipratropium bromide nebulizations | 1.2 ± 0.2 | 1.1 ± 0.3 | .48 |
| Serum magnesium level at 30 min after the start of the infusion, mmol/L | 1.47 ± 0.02 | 0.62 ± 0.02 | <.001 |

*Data are given as mean ± SD unless otherwise indicated.

male. **Table 1** demonstrates that baseline demographic and clinical variables were evenly distributed between the 2 groups except for systolic blood pressure, which was slightly, but significantly, higher in the IVMg group.

There were no differences between the 2 groups in the number of emergency department visits, or hospital ward or intensive care unit admissions in the 12 months prior to enrollment in the study. The most common trigger for asthma exacerbation varied equally between the 2 groups and included upper respiratory tract infections, allergens, and changes in the weather.

The types of home therapies used were consistent between the 2 groups, including β-agonists (oral, inhaler, nebulization), cromolyn sodium, and/or corticosteroids. Of note, 2 patients in the placebo group and 1 patient in the IVMg group were given 1 mg/kg of oral prednisolone within the 24 hours prior to the start of the study infusion. Each of these 3 patients received only 1 dose of oral corticosteroids prior to coming to the emergency department.

The mean time between receiving corticosteroids (orally or intravenously) in the emergency department and the start of infusion was 33.6 ± 28.2 minutes for the IVMg group and 27.4 ± 19.8 minutes for the placebo group. There were also no significant differences between the 2 groups in the amount or timing of nebulizations given in the emergency department before or during infusion (**Table 2**).

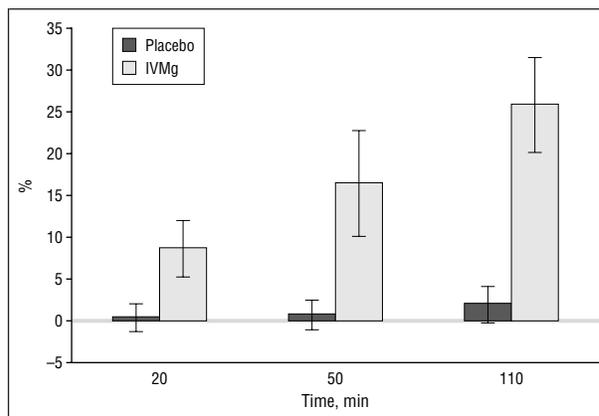


Figure 1. A comparison of the absolute change in percent predicted PEFR (peak expiratory flow rate) values in the intravenous magnesium sulfate (IVMg) and placebo groups. $P < .001$.

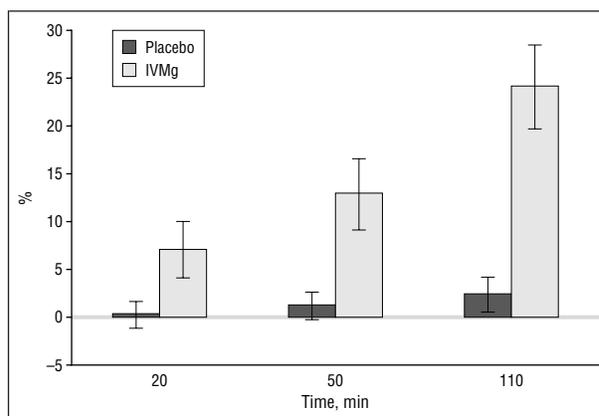


Figure 2. A comparison of the absolute change in percent predicted FEV₁ (forced expiratory volume in 1 second) values in the intravenous magnesium sulfate (IVMg) and placebo groups. $P < .001$.

OUTCOME VARIABLES

The PFTs, represented as percent predicted values, improved significantly for the patients who received IVMg when compared with those who received the placebo infusion (**Figures 1, 2, and 3**). The PEFR improved at all of the analyzed time points (Figure 1): at 20 minutes (completion of infusion) ($P < .001$), 50 minutes ($P < .001$), and 110 minutes ($P < .001$). Comparing the improvement from baseline FEV₁ between the 2 groups yielded a similar pattern (Figure 2). Differences were significant at the end of infusion and 30 minutes after infusion, and most pronounced at the end of the study period ($P < .001$). Forced vital capacity demonstrated similar results (Figure 3) at all 3 time points.

The percentage of improvement from baseline PEFR was compared between the 2 groups. Patients treated with IVMg had a significantly greater change in percentage from entry-level PEFR (**Figure 4**). This effect became significant at 20 minutes ($P < .001$) and continued through to the end of the observation period, displaying an even greater effect at 110 minutes ($P < .001$).

At the end of the assessment period, all 14 of the placebo-treated patients required admission to the hospital, whereas 8 (50%) of 16 patients who received IVMg

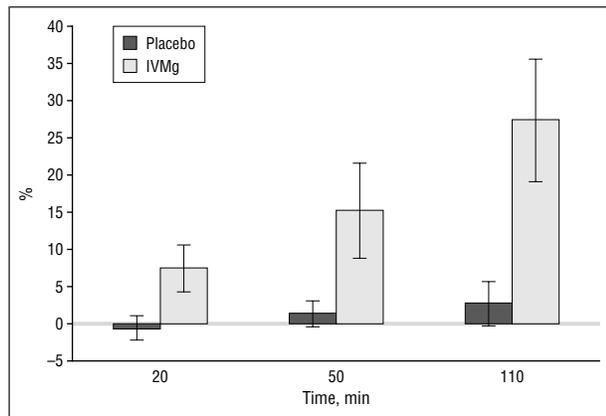


Figure 3. A comparison of the absolute change in percent predicted FVC (forced vital capacity) values in the intravenous magnesium sulfate (IVMg) and placebo groups. $P < .001$.

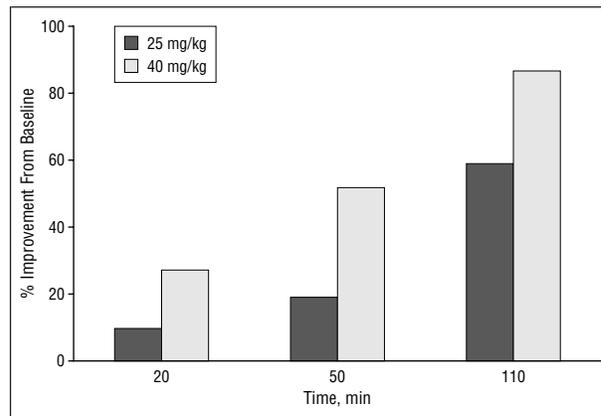


Figure 5. A comparison of percentage of improvement from baseline percent predicted PEFR (peak expiratory flow rate) in our lower- and higher-dose trials. $P < .001$.

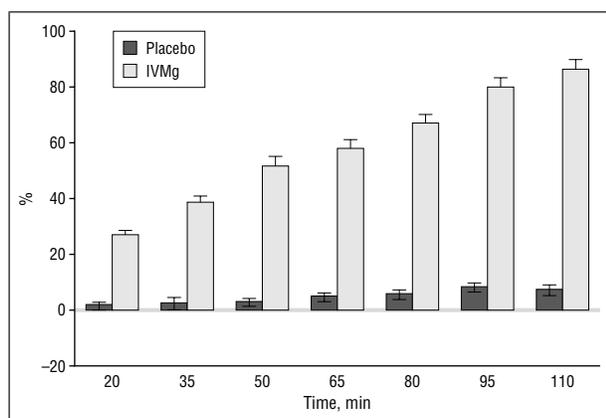


Figure 4. A comparison of the percent change from baseline percent predicted PEFR (peak expiratory flow rate) values in the intravenous magnesium sulfate (IVMg) and placebo groups. $P < .001$.

were discharged to their homes ($P = .002$). Of the 8 discharged patients, 100% completed a follow-up telephone call. All of the discharged patients remained improved and none of these patients required another emergency care visit or hospital admission.

Serum magnesium concentrations obtained 30 minutes after the infusion was completed (Table 2) revealed an increase from 0.63 ± 0.01 mmol/L prior to the infusion to 1.46 ± 0.02 mmol/L in the IVMg group. There was no change in those patients who received placebo (0.63 ± 0.02 mmol/L to 0.62 ± 0.02 mmol/L) 30 minutes after the infusion. Deep tendon reflexes were monitored during each measuring interval during the study period. All patients had normal, 2/4, brachial and patellar reflexes at the start of and throughout the study period.

There were significant differences noted in the clinical asthma scores between the 2 groups, but these differences occurred later in the observation period—at 95 minutes (1.4 for the IVMg group vs 2.5 for the placebo group, $P < .001$) and 110 minutes (1.1 for the IVMg group vs 2.4 for the placebo group, $P < .001$). There were no intergroup differences noted for systolic blood pressure at any point during the infusion or measurement periods.

COMMENT

With an increase in the dose of IVMg to 40 mg/kg, significant improvements in spirometry were noted earlier and the clinical effects were even greater than previously reported. Our original study using 25-mg/kg IVMg doses showed significant effects in PEFR and FEV₁ 30 minutes after the infusion was completed.²³ The maximum effect was noted at the end of the study period for all 3 measures of pulmonary function. This higher-dose trial demonstrates similar trends but with greater improvements. **Figure 5** compares the percentage of improvement from baseline PEFR in our initial study (25 mg/kg) with the present higher-dose trial at 20 minutes (end of the infusion), 50 minutes (30 minutes after the completion of the infusion), and 110 minutes (the end of the study period). Earlier and more pronounced effects in pulmonary function translated to a lower admission rate for the patients in the 40-mg/kg IVMg group compared with the IVMg group in the lower-dose trial (8/16 [50%] vs 11/16 [69%]). This translates to 1 prevented admission for every 2 pediatric patients with asthma in our study treated with 40-mg/kg IVMg.

The results of our 2 trials using IVMg in children are strikingly different from the results published in the adult literature. The adult studies report inconsistent results: the earlier investigations demonstrated beneficial effects,¹³⁻¹⁹ while the more recent larger trials did not demonstrate significant improvements in pulmonary function.^{20,21} Our results are consistent, displaying similar trends at both of the investigated doses. Also, the improvements in pulmonary function were greater in our pediatric population when compared with the adult data that demonstrated beneficial effects. In the present study we documented a greater than 80% improvement in PEFR in children. In contrast, the greatest effect reported in the adult literature was a 40% improvement in PEFR.¹⁸ These differences may be due to the constructs of the studies themselves or to variability in dosing, though it is conceivable that IVMg is truly more effective in children than in adults. Children do not yet suffer from the detrimental chronic changes of a long-standing pulmonary disease such as asthma. The younger, potentially healthier

respiratory system of a pediatric patient may therefore be more responsive and better able to benefit from IVMg therapy.

This study has pertinent limitations. The data set included patients from 2 different tertiary care pediatric emergency departments. Though the 2 centers approached children with asthma in a similar fashion, they could not be identical. Comparing the 2 centers with regard to baseline characteristics (including demographics, initial vital signs of patients, clinical asthma scores, and PFTs), patient history of asthma exacerbation, and medications given before and during the infusion revealed no statistically significant differences between the 2 patient groups. The PFT outcomes and the number of admitted patients were not significantly different between the 2 centers.

As with all asthma studies, it is difficult to control for the multitude of variables involved. Patients continued to receive other medications at the discretion of the medical team, for the hospital review boards could not approve a predetermined treatment schedule during the study period. The withholding of standard therapies or the addition of possibly unnecessary nebulizations was not considered ethical. This lack of standardization could have posed a significant problem if, for example, delays between bronchodilator treatments disproportionately affected 1 group. Despite this lack of a treatment protocol, there were no significant differences noted in the number or type of nebulizations given, nor in the timing of steroids given prior to the start of the study infusion (Table 2). We chose a randomized double-blinded placebo-controlled study design to minimize these variables.

Another limitation of the study was the 2-g maximum dose. Though this ensured safety, it caused 5 of the 16 patients in the IVMg group to receive less than the 40-mg/kg investigated dose (mean dose, 35 mg/kg). This underdosing of almost one third of the IVMg group may have caused the reported effects to be underestimated. Lastly, patients were excluded if they were unable to perform spirometry. This included children who were younger than 6 years or who were severely distressed. Therefore, our findings cannot be directly applied to younger children or to those in severe respiratory distress.

The salutary effects of IVMg on pulmonary function and on the emergency department discharge rate in this clinical trial recommend further investigation into the role of IVMg in childhood asthma. Future studies may investigate ideal doses of IVMg, possibly higher than 40 mg/kg, to determine the maximum dose necessary to provide safe and optimal effects. Inpatient studies could evaluate the potential of continuous infusion to decrease the length of hospital stay. Additionally, future studies may determine whether IVMg can be used safely and effectively in the intensive care setting or in patients younger than 6 years.

In conclusion, IVMg given as a single 40-mg/kg dose is a safe, fast-acting, and effective adjunct in the treatment of moderate to severe asthma in the pediatric emergency department. It can be considered for patients in status asthmaticus who have not adequately responded to nebulization therapy.

Accepted for publication May 5, 2000.

Presented at the Presidential Plenary at the American Pediatric Association Meeting, New Orleans, La, May 4, 1998.

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REFERENCES

1. *MMWR Morb Mortal Wkly Rep.* 1998;47:1-28.
2. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med.* 1992;326:862-866.
3. Scarfone RJ, Fuchs S, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics.* 1993;92:513-518.
4. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics.* 1990;86:350-356.
5. Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med.* 1986;314:150-152.
6. Storr J, Barry W, Barrell E, Lenney W, Hatcher G. Effect of a single oral dose of prednisone in acute childhood asthma. *Lancet.* 1987;1:879-882.
7. Haury VG. The bronchodilator action of magnesium and its antagonistic action (dilator action) against pilocarpine, histamine and barium chloride. *J Pharmacol Exp Ther.* 1938;64:58-64.
8. Spivey WH, Skobeloff EM, Levin RM. Effect of magnesium chloride on rabbit bronchial smooth muscle. *Ann Emerg Med.* 1990;19:1107-1112.
9. Gilbert D'Angelo EK, Singer HA, Rembold CM. Magnesium relaxes arterial smooth muscle by decreasing intracellular Ca^{2+} without changing intracellular Mg^{2+} . *J Clin Invest.* 1992;89:1988-1994.
10. McLean RM. Magnesium and its therapeutic uses: a review. *Am J Med.* 1994; 96:63-76.
11. del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. *J Physiol.* 1954;124:370-384.
12. Bois P. Effect of magnesium deficiency on mast cells and urinary histamine in rats. *Br J Exp Pathol.* 1963;44:151-155.
13. Okayama H, Aikawa T, Okayama M, Sasaki H, Mue S, Takishima T. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. *JAMA.* 1987; 257:1076-1078.
14. Rolla G, Bucca C, Bugiani M, et al. Reduction of histamine-induced bronchoconstriction by magnesium in asthmatic subjects. *Allergy.* 1987;42:186-188.
15. Rolla G, Bucca C, Arossa W, et al. Magnesium attenuates methacholine-induced bronchoconstriction in asthmatics. *Magnesium.* 1987;6:201-4.
16. Rolla G, Bucca CX, Caria E, et al. Acute effect of intravenous magnesium sulfate on airway obstruction of asthmatic patients. *Ann Allergy.* 1988;61:388-391.
17. McNamara RM, Spivey WH, Skobeloff EM, Jacobowitz S. Intravenous magnesium sulfate in the management of acute respiratory failure complicating asthma. *Ann Emerg Med.* 1989;18:197-199.
18. Skobeloff EM, Spivey WH, McNamara RM, Greenspon L. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA.* 1989;262:1210-1213.
19. Noppen M, Vanmaele L, Impens N, Schandevyl W. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma. *Chest.* 1990; 97:373-376.
20. Green SM, Rothrock SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med.* 1992;21:260-265.
21. Tiffany BR, Berk WR, Keir I, White SR. Magnesium bolus or infusion fail to improve expiratory flow in acute asthma exacerbations. *Chest.* 1993;104:831-834.
22. Pabon H, Monem GF, Kisoon N. Safety and efficacy of magnesium sulfate infusion in children with status asthmaticus. *Pediatr Emerg Car.* 1994;10:200-203.
23. Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr.* 1996;129:809-814.
24. Williams. *Obstetrics.* 20th ed. Stamford, Conn: Appleton & Lange; 1997:723-724.
25. National Asthma Education Program. *Executive Summary: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: National Institutes of Health; 1991. NIH publication 91-3042A.
26. Wood DN, Downes JJ, Lecks HI. A clinical system for the diagnosis of respiratory failure. *AJDC.* 1972;123:227-228.
27. American Thoracic Society. Standardization of spirometry: 1987 update—statement of the American Thoracic Society. *Am Rev Respir Dis.* 1987;130:1285-1298.