CLINICAL INVESTIGATION

Comparison of Two High-Dose Magnesium Infusion Regimens in the Treatment of Status Asthmaticus

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OBJECTIVES: To determine the feasibility and safety of a simplified high-dose magnesium sulfate infusion (sHDMI) for the treatment of status asthmaticus.

METHODS: We retrospectively compared 2 different high-dose magnesium sulfate infusion regimens, as adjunctive treatment in status asthmatics, using data that were previously collected. The initial high-dose, prolonged magnesium infusion (HDMI) regimen consisted of a loading dose of 75 mg/kg (weight $\leq$ 30 kg) or 50 mg/kg (weight $>$ 30 kg) over a period of 30 to 45 minutes followed by a continuous infusion of 40 mg/kg/hr for an additional 4 hours. This was compared to the sHDMI regimen that consisted of 50 mg/kg/hr for 5 hours. No loading dose was given to the patients in the sHDMI arm. Obese patients were dosed by using ideal body weight. Physiologic parameters (i.e., heart rate, blood pressure, respiratory rate, oxygen saturation) and serum magnesium (SrMg) concentrations were monitored during administration of magnesium sulfate.

RESULTS: Nineteen patients receiving the initial HDMI regimen were compared with 10 patients who received the sHDMI regimen. There was no significant difference in SrMg concentrations or physiologic parameters between the 2 dose regimens.

CONCLUSIONS: The HDMI and sHDMI regimens both produced SrMg concentrations that are associated with bronchodilation. The safety profile was also similar for the 2 regimens. The unambiguity of sHDMI has the potential to reduce medication errors that are associated with calculation of the loading dose, product preparation, and ultimate administration.

INDEX TERMS: asthma, infusion, magnesium sulfate, pediatric, status asthmaticus

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INTRODUCTION

Asthma is a disease of hyperresponsiveness of the lower airways that causes 3 processes: bronchospasm of the smooth muscle lining the respiratory tract, increased mucous production, and airway inflammation/edema.¹ It has a prevalence of about 54 per 1000 children and is a leading cause of both lost school days and hospitalizations.²

Although the first-line treatment for status asthmaticus remains inhaled β -agonists in conjunction with muscarinic antagonists and corticosteroids, more recent research has focused on the adjunctive use of magnesium sulfate. Supraphysiologic unbound serum magnesium (SrMg), directly related to ionized magnesium (IoMg), produces a proportional but only transient block of the N-methyl-D-aspartate receptor-gated calcium channels with subsequent muscle relax-

ation.³ In the kidney, renal tubular reabsorption of SrMg is at maximal capacity with normal SrMg concentrations with a rapid renal clearance that rises linearly with higher SrMg concentrations. Consequently, prolonged high-dose infusions are needed to achieve sustained spasmolytic effects. High-dose magnesium infusions (HDMIs) ensure that SrMg concentrations remain therapeutic to sustain their bronchodilating effects.⁴ We compared 2 HDMI regimens both on their ability to maintain a target SrMg concentration and on their effects on physiologic parameters such as heart rate, blood pressure, and respiratory rate. The first regimen was designed by calculating the volume of distribution and maintenance of steady state.⁵ However, dose differences for the bolus and infusion had the potential to generate dose and dispensing errors. A second, simplified regimen or sHDMI (simplified high-dose

Table. Results of Model Showing No Difference Among the 2 Infusions

Model	Regimen	LS-Means	Standard Error	p Value
SBP	HDMI	108.3	2.036	0.77
	sHDMI	107.3	2.880	
Log DBP	HDMI	3.786	0.0377	0.57
	sHDMI	3.748	0.0533	
Log HR	HDMI	4.947	0.0272	0.37
	sHDMI	4.904	0.0385	
Sqrt SrMg	HDMI	1.884	0.0331	0.5
	sHDMI	1.923	0.0465	
SpO ₂	HDMI	96.73	0.4236	0.65
	sHDMI	96.39	0.5979	
RR	HDMI	30.52	1.473	0.43
	sHDMI	28.70	1.995	

DBP, diastolic blood pressure; HDMI, high-dose magnesium infusion; HR, heart rate; LS-Means, least squares means; RR, respiratory rate; SBP, systolic blood pressure; sHDMI, simplified high-dose magnesium infusion; SpO₂, saturation of peripheral oxygen; Sqrt, square root; SrMg, serum magnesium

magnesium sulfate infusion) was developed by taking a more pragmatic approach.

MATERIALS AND METHODS

This study was approved by the institutional review committee, as well as both studies compared here. Two prospective studies that examined the characteristics of different high-dose magnesium sulfate infusion regimens were compared head-to-head. They were conducted in a 20-bed pediatric intensive care unit in an academic affiliated children's hospital with on-site support/supervision from pediatric pharmacists. Magnesium sulfate infusions at a concentration of 150 mg/mL given via a peripheral intravenous line were used. The studies had similar inclusion and exclusion criteria.

Patients with status asthmaticus were included in the study. Patients who failed to improve in 1 hour of conventional therapy (Asthma Score < 8) were defined as having status asthmaticus.⁶ Conventional therapy encompassed continuous albuterol nebulization (20 mg/hr), 2 doses of nebulized ipratropium, and intravenous corticosteroids. Exclusion criteria included renal or chronic respiratory compromise, instrumented airway, age below 1 year or above 18 years, and protocol deviations.

In the HDMI arm, 19 patients were given a loading dose of 75 mg/kg (≤30 kg) or 50 mg/kg

(weight > 30 kg) over a period of 30 to 45 minutes followed by a continuous infusion of 40 mg/kg/hr for an additional 4 hours. Patients with body mass index (BMI) above 30 kg/m² were dosed on the basis of ideal body weight instead of actual body weight. Serum magnesium concentrations were measured before receiving a loading dose, 15 minutes after receiving a loading dose, in the middle of continuous infusion (3 hours into regimen), and at the end of the 5-hour regimen. Physiologic parameters such as heart rate, blood pressure, respiratory rate, and oxygen saturation were also gathered at these time points.

The sHDMI regimen omitted the loading dose and patients were started on a continuous magnesium sulfate infusion of 50 mg/kg/hr for 5 hours. Ten patients were enrolled in this study in which similar adjustment for BMI above 30 kg/m² was performed. The SrMg concentrations were also measured for this study but obtained before the infusion, 1 hour into the infusion, 3 hours into the infusion, and at the end of the 5-hour infusion. Physiologic data were collected at these time points as well.

Mixed-model, repeated-measures analysis of covariance models were fit to systolic blood pressure (SBP), log diastolic blood pressure (DBP), respiratory rate, log heart rate, saturation of peripheral oxygen (SpO₂), and square root of magnesium concentration individually. Diastolic blood pressure, heart rate, and SrMg were all

Figure 1. Comparison of resultant serum magnesium concentration in the HDMI and sHDMI regimens during 4 hours of administration.

HDMI, high-dose magnesium infusion (includes loading dose); sHDMI, simplified high-dose magnesium infusion (without a loading dose); SrMg, serum magnesium

The bottom line of the box-and-whisker plot represents the 25th percentile and the upper line of the box is the 75th percentile. The line in the middle of the box represents the median and the diamond depicts the mean.

transformed to meet normality assumptions. Factors in these models were treatment group and time (baseline, 1 hour, 3 hour, post treatment). All analyses were done in SAS version 9.3 for Windows (SAS Inc, Cary, NC).

RESULTS

There was no significant difference in the pharmacokinetics of SrMg concentrations between groups (Table). Figure 1, the plot for SrMg, clearly shows the increasing trend over time for both groups reaching concentrations associated with bronchodilation. Figures 2 and 3 show the lack of difference between the 2 dose methods in regard to cardiorespiratory parameters. There was no discontinuation of therapy owing to clinical side effects, and no patients had any side effects.

DISCUSSION

Our study demonstrates that sHDMI is comparable to the original HDMI regimen in producing similar concentrations of SrMg and is devoid of unwanted adverse effects. The literature has been inconsistent with regard to the efficacy of magnesium sulfate therapy in the treatment of status asthmaticus. Prospective, randomized controlled studies of magnesium sulfate in the

pediatric population have had mixed results,⁷⁻¹³ while studies in the adult population failed to show benefit.¹⁴ However, in these studies magnesium sulfate was administered for short periods of time, and it is not clear whether concentrations of SrMg were close to the ones associated with smooth muscle relaxation³ (IoMg near or above 1 mmol/L). The inconsistency of these results may be ascribed to an inability to achieve sustained therapeutic SrMg concentrations and/or spasmolytic effects for primary therapies (inhaled β -agonists) to reach the site of action. Magnesium sulfate is still conceptualized as an adjunctive therapy for asthma.

The physiology associated with magnesium excretion is challenging and necessitates a high-dose and prolonged magnesium sulfate infusion to reach a sustained supraphysiologic serum concentration. Free magnesium (i.e., not protein bound) is filtered in the glomerulus and reabsorbed in the proximal tubule, loop of Henle, and distal collecting tubule.¹⁵ The remaining magnesium in the filtrate quickly leaves the body via urine. Although many different hormones play a role in magnesium homeostasis,¹⁶ hypermagnesemia is known to be the major regulator of renal magnesium reabsorption.¹⁷ The net effect is that without a continuous infusion of magnesium sulfate, magnesium is rapidly cleared from the body via the kidneys and thus the corresponding spasmolytic effects are lost.

We first attempted to overcome these shortcomings by using a HDMI.^{4,5} However, our first attempt led to the creation of a complex regimen due to the different dosage of the bolus and the continuous infusion. This had the potential of creating errors in the setting of the critical care unit where such errors are especially unacceptable. Although there were no instances of dosage errors in the high-dose study, other studies have shown that simplified medication regimens in the pediatric setting can drastically lead to lower rates of dosage errors. For example, Broselow and Luten developed a simplified method of dosing medications during resuscitation efforts using a color coded tape and a study by Damhoff et al showed that their method completely eliminates clinically significant dosage errors.^{18,19} We expect our sHDMI regimen to have a similar effect.

Although the exact mechanism of magnesium sulfate is unclear, it is thought to act by transient inhibition of voltage-dependent Ca^{2+} channels on

Figure 2. Effects of HDMI and sHDMI regimens during 4 hours of administration on hemodynamic parameters and heart rate.

DBP, diastolic blood pressure; HDMI, high-dose magnesium infusion (includes loading dose); HR, heart rate; SBP, systolic blood pressure; sHDMI, simplified high-dose magnesium infusion (without a loading dose).

The bottom line of the box-and-whisker plot represents the 25th percentile and the upper line of the box is the 75th percentile. The line in the middle of the box represents the median and the diamond depicts the mean.

the surface of the smooth muscle cells, thereby depriving the cell of calcium necessary to produce contraction.²⁰ Magnesium may also produce a mild inhibition of the bronchoconstriction by reducing the release of histamine from mast cells.²¹

Magnesium therapy is not without its risks; side effects of hypermagnesemia range from mild (nausea, cutaneous flushing, emesis) to life-threatening (respiratory depression, hypotension, cardiac arrest).²² However, a literature review did not show any reports of toxicity in a pediatric patient and other researchers have also noted the paucity of reports of magnesium toxicity.²³ Indeed, in our study none of the patients had magnesium toxicity. We have recently concluded a study in which the early utilization of sHDMI for non-infectious-mediated asthma expedites discharges from the emergency department with significant reduction in health care cost.²⁴

CONCLUSIONS

Our study demonstrates that a simplified HDMI has similar pharmacokinetics to the previously described HDMI, with a safety profile similar to that of other asthma medications. Future studies are needed to determine the optimal dose and duration for a simplified high-dose magnesium sulfate infusion. Studies are also needed to determine if this simplified regimen leads to decreased duration of stay in the intensive care unit, decreased duration of hospital stay, and decreased hospital re-admission rates for status asthmaticus.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abbreviations BMI, body mass index; DBP, diastolic blood pressure; HDMI, high-dose magnesium infusion; IoMg, ionized magnesium; sHDMI, simplified high-dose magnesium sulfate infusion; SBP, systolic blood pressure; SpO₂, saturation of peripheral oxygen; SrMg, serum magnesium

Figure 3. Effects of HDMI and sHDMI regimens during 4 hours of administration on oxygen saturation and respiratory rate.

HDMI, high-dose magnesium infusion (includes loading dose); sHDMI, simplified high-dose magnesium infusion (without a loading dose); RR, respiratory rate; SpO₂, oxygen saturation.

The bottom line of the box-and-whisker plot represents the 25th percentile and the upper line of the box is the 75th percentile. The line in the middle of the box represents the median and the diamond depicts the mean.

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