Feasibility of Short-Term Infusion of Magnesium Sulfate in Pediatric Patients With Status Asthmaticus

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OBJECTIVE This report describes the feasibility of high-dose magnesium sulfate infusion in pediatric patients with status asthmaticus.

METHODS Retrospective chart review over a 3-year period of all patients younger than 18 years of age with status asthmaticus who underwent a high-dose magnesium sulfate infusion for 4 hours. All patients were breathing spontaneously but were refractory to conventional therapy. The magnesium sulfate infusion regimen was 50 mg/kg (for patients weighing >30 kg) or 75 mg/kg (for those weighing ≤30 kg) over a period of 30 to 45 minutes, followed by a continuous infusion of 40 mg/kg/hr for 4 hours. Information regarding vital and clinical respiratory signs, serum magnesium (SrMg), ionized magnesium (iMg), electrocardiograms, and cardiac troponin levels were retrieved. We analyzed the relationship between SrMg and iMg by using linear regression analysis.

RESULTS Nineteen patients were included. At the end of the infusion, SrMg levels were 4.4 ± 0.8 mg/dL, and iMg levels were 0.95 ± 0.2 mmol/L. SrMg levels only moderately predicted iMg ($r^2 = 0.541$). There were no reports of hypotension, respiratory failure, neurological problems, or nausea. Discomfort at the site of infusion was reported in three cases. Troponin levels ($n = 12$) and electrocardiograms ($n = 12$), when available, were noted at the end of the infusion and were normal in all patients $p=0.01$.

CONCLUSIONS In this case series, short-term high-dose administration of magnesium sulfate in the context of status asthmaticus was feasible, and we did not observe clinical complications with its use. Total SrMg was inadequate to reflect the active form of magnesium, iMg. The dose used achieved theoretical therapeutic levels of iMg.

INDEX TERMS asthma, feasibility, infusion, magnesium sulfate, status asthmaticus

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INTRODUCTION

High levels of magnesium in serum (SrMg) act as a muscle relaxant. Magnesium sulfate, as an adjunctive therapy in the treatment of asthma, has been used with inconsistent results.^{1,2} A short-term infusion of magnesium sulfate is the typical regimen. This approach may be inconsistent with the pharmacokinetics of magnesium sulfate and desired pharmacodynamics. The rapid elimination of magnesium by the kidney as clearance rises linearly with increasing serum concentrations poses a significant therapeutic challenge. Tubular reabsorption of magnesium is at maximal capacity with normal serum levels. During magnesium sulfate

therapy, renal clearance is the major determinant of SrMg levels, as nearly all magnesium above normal serum levels is excreted in the urine.³ Therefore, the maximum serum level during therapy depends on the rate of infusion and not on the total dose or duration of the infusion. Magnesium sulfate's spasmolytic effect, when administered as a continuous infusion, has been used in patients with preeclampsia, pulmonary hypertension, brain injury, and subarachnoid hemorrhage.^{4–7} In these settings, the strategy of continuous infusion produces a sustained effect by exceeding the rate of magnesium elimination by the kidney. A sustained effect may be the one desirable effect for asthma. In addition, ionized magnesium (iMg), the biologically

active component capable of penetrating the cell, is a portion of total SrMg and is rarely targeted or reported in the literature. The relationship between total SrMg and iMg is complex, altered in asthma and also affected by changes in serum pH.^{3,8,9}

Concerns about potential side effects of high-dose magnesium sulfate have limited the use of this therapy outside the pharmacokinetic rationale. For example, many studies limited the maximal dose to 2000 mg, regardless of patient size.¹⁰ Muscle weakness with the consequent risk of respiratory failure, vasodilation with subsequent hypotension, and nausea and vomiting are the major concerns when magnesium is used in the context of asthma. We hypothesized that a prolonged infusion of magnesium sulfate is feasible in the context of pediatric status asthmaticus and that SrMg does not reflect iMg.

The primary objective was to describe the feasibility of 4 hours of magnesium sulfate infusion in pediatric patients with status asthmaticus. Secondary objectives were to assess treatment side effects and the relationship between SrMg and iMg during magnesium sulfate treatment.

METHODS

For this retrospective review series, we evaluated the medical records of all patients younger than 18 years of age admitted from the emergency room to the pediatric intensive care unit (PICU) at Wolfson Children's Hospital between January 2006 and December 2008, with status asthmaticus, who received magnesium sulfate infusion in accordance with PICU guidelines. Unit guidelines consisted of a rapid infusion of 50 mg/kg for patients weighing more than 30 kg and 75 mg/kg for those equal to or less than 30 kg over a period of 30 to 45 minutes. This bolus was given in addition to the one that patients previously received in the emergency department (see below). The bolus was followed by a continuous infusion of 40 mg/kg/hr for 4 hours. Patients who were intubated or received noninvasive mechanical ventilation prior to magnesium sulfate were excluded. Status asthmaticus was defined in patients who failed to improve despite conventional therapy, assessed by an Asthma Score of less than 8.¹¹ Conventional therapy was defined as albuterol administered as three consecutive nebulized treatments in less than 30 minutes or continuous albuterol nebulization (20 or 40 mg/hr) for greater than 1 hour, in addition to intravenous corticosteroids, two doses of ipratropium, and one dose of magnesium sulfate, 50 mg/kg, intravenously, in the emergency room.

A pediatric emergency room physician and pediatric intensivist performed a clinical evaluation, which, along with asthma score, documented the fact that the patient had not improved and hence had failed conventional therapy. Feasibility was defined in patients in whom magnesium sulfate infusion therapy was begun and was not subsequently discontinued due to complications. Data including age, weight, hourly heart rate and blood pressure, neurological assessment, magnesium sulfate dosing, and levels of SrMg and iMg were collected. Troponin and electrocardiogram (ECG) findings were retrieved if available. The presence of clinical hypotension, administration of fluid bolus, initiation of mechanical ventilator support or vasoactive medication, and other side effects were extracted from the medical records. Neurological assessments that included cognitive status, appropriate movement of extremities, pupillary size and light reflex, and a Glasgow coma score were performed every 2 hours.

The study was approved by the Institutional Review Board committee, which waived the need for informed consent. Descriptive statistics were calculated using means and standard deviations; the relationship between SrMg and iMg was compared via least squares linear regression.

RESULTS

During the study period, 325 patients were admitted for asthma from the emergency room without mechanical ventilator support. Nineteen patients matched our study criteria for receiving the dosing scheme as outlined in our PICU guidelines. Patients' ages ranged from 22 months to 16 years old (mean, 9.3 ± 4.6 years old) (Table). None of the patients required discontinuation of the infusion. Following magnesium sulfate infusion, none of the patients deteriorated from a cardiorespiratory point of view, and no patient required invasive or noninvasive mechanical ventilator support. There were no symptoms of hypotension, flushing, nausea, or vomiting; neither fluid bolus nor vasoactive medications were added during the magnesium sulfate infusion. Neurologic assessments were reported as normal. Three patients complained of discomfort at the site of infusion. Normal cardiac troponin levels (mean, 0.02 ± 0.01 ng/mL) were recorded in 12 patients at the end of the 4-hour infusion; 12 patients had ECGs performed, and all of those results were normal.

SrMg levels at the end of the infusion were 4.4 ± 0.8 mg/dL (1.8 ± 0.33 mmol/L) and iMg levels were 0.95 ± 0.2 mmol/L. SrMg levels exhibited only moderate predictive value of iMg ($r^2 = 0.541$). To

Table. Demographics

Age (yr)	Sex	Race	Weight (kg)	Magnesium Bolus (mg/kg)	Magnesium Infusion (mg/kg/hr)	Troponin (ng/mL)	EKG
1	M	AA	9	75	40	NA	NL
2	M	W	12	50	40	NA	NL
7	F	W	30	75	40	NA	NL
7	M	AA	28	75	40	0.01	NL
8	F	AA	30	50	40	0.03	NL
9	M	AA	41	75	40	0.09	NL
13	F	W	62	50	40	0.02	NL
15	F	AA	53	50	40	0.1	NL
15	M	AA	83	75	40	NA	NL
16	F	W	62	50	40	0.01	NL
8	M	AA	30	75	40	0.02	NA
2	F	AA	11	75	40	0.01	NL
11	M	W	32	50	40	0.02	NL
15	M	AA	58	50	40	0.03	NA
11	M	AA	41	75	40	0.04	NA
13	M	AA	44	50	40	0.02	NA
6	M	W	21	50	40	NA	NA
9	M	AA	40	50	40	NA	NA
10	M	W	45	50	40	NA	NA

AA, African American; W, Caucasian; NA, not available; NL, normal

illustrate, two close measurements of SrMg, 4.4 and 4.8 mg/dL, differed vastly in their proportions of iMg, that is, 63% and 35%, respectively (Figure). As a point of comparison, normal SrMg levels in our laboratory range from 1.6 to 2.5 mg/dL and iMg from 0.53 to 0.67 mmol/L.

DISCUSSION

Our study demonstrates the feasibility of prolonged, high-dose administration of magnesium sulfate infusion in status asthmaticus, producing iMg levels near values associated with muscle relaxation in preeclampsia. Administration in this small sample was not associated with significant safety concerns. We also validated that SrMg levels are not an adequate surrogate for iMg in patients with status asthmaticus, as only 54% of the

variation in iMg could be explained by SrMg values.

Status asthmaticus is a complex disease with components of inflammation, oxygenated stress,

Figure. Ionized Magnesium (iMg) as Percentage (%) of Serum Magnesium.

bronchial constriction, and mucous plugging. Magnesium blocks *N*-methyl-D-aspartate receptor-gated calcium channel in muscles, exhibits spasmolytic effects, and also attenuates the production of reactive oxygen species. Multiple articles have addressed short-term infusion of magnesium sulfate in asthma exacerbations, and different regimens have been used with conflicting results.^{1,2} Previous work in our institution demonstrated that magnesium sulfate has a volume of distribution of 0.3 L/kg and a half-life of 2 hours in children.¹² A dose of 50 to 80 mg/kg is required to achieve a SrMg level above 4 mg/dL. However, an attempt to define goal-directed therapies using target SrMg levels may have been misguided, as iMg is the active form. The relationship between SrMg and iMg is altered under several conditions, including asthma, where SrMg is disproportionately higher than that of iMg.⁹ Although the ability to measure iMg in the clinical setting has become available in the last few years, unfortunately, it costs more. Our review reflects the possibility that iMg and not SrMg should be used as the therapeutic marker.

The rapid elimination of magnesium by the kidney needs to be considered in any therapeutic strategy. A continuous infusion of magnesium sulfate exerting a sustained spasmolytic effect is an effective strategy under several clinical conditions and an attractive adjunctive strategy for patients with status asthmaticus; however, the target serum level has not yet been defined. The obstetrics and gynecology literature suggests reaching putative therapeutic SrMg levels of between 4 and 7 g/dL, without losing patellar reflexes.¹³ While the amount of iMg capable of producing relaxation is not completely understood, recent reports for preeclampsia describe target values of 0.9 to 1.6 mmol/L.^{4,14-16} The asthma literature is hesitant to target dosing that achieves decreases in reflexes for fear of inducing respiratory failure due to decreased respiratory muscle strength.

There are no established dosing regimens or target SrMg concentrations for the optimal treatment of patients with asthma. A wide range of magnesium sulfate bolus doses (25-100 mg/kg) have been used. Early reports suggest targeting a SrMg level of 3 to 5 mg/dL while disregarding iMg and its complex relationship in asthma. We question whether the lack of efficacy in some of the studies is the result of a dose of magnesium sulfate that is insufficient to block voltage-sensitive calcium channels.^{17,18}

Glover et al¹⁹ described the feasibility of administering a loading dose of 35 mg/kg and 25 mg/kg/hr intravenous magnesium for up to 3 days in patients with status asthma. This was a heterogeneous group with a large variation in

dosing regimen and duration, and no patient experienced cardiovascular adverse affects. Similarly, no cardiac conduction irregularities were found in any of our patients. We excluded patients on invasive and noninvasive mechanical support who received magnesium sulfate infusions as we attempted to analyze the impact on respiratory muscles. None of our patients exhibited respiratory deterioration, and we surmise the absence of significant induced respiratory muscle weakness.

This was a retrospective chart review of a small number of patients and cannot fully address safety or efficacy. Some limitations to our study are variability in the dosing regimen and times that concentrations were drawn due to the retrospective nature of the study. We are in the process of initiating a prospective study using the knowledge acquired from our observations.

In summary, a continuous infusion of high-dose magnesium sulfate in patients with status asthmaticus was feasible and well tolerated in our patient population. In order to produce iMg close to 1 mmol/L, patients received a loading dose of 50 to 75 mg/kg, followed by continuous infusion of 40 mg/kg/hr for 4 hours. Further prospective studies with larger patient populations are needed to evaluate safety and efficacy for the consistent use of magnesium sulfate in status asthmaticus.²⁰

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ABBREVIATIONS ECG, electrocardiogram; iMg, ionized magnesium; PICU, pediatric intensive care unit; SrMg, serum magnesium

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