Pharmacokinetics and Pharmacodynamics of Intravenous Magnesium Sulfate in Pediatric Acute Asthma Exacerbations

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Abstract

Pediatric asthma exacerbations represent a significant cause of emergency department use and hospitalizations. Despite available treatment options, many children's exacerbations are refractory to standard therapies and require adjunct treatments. The Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department study investigated the pharmacology of intravenous magnesium sulfate (IVMg) in treating pediatric asthma exacerbations. Specifically, the objectives of the study included (1) externally validating a previously published population pharmacokinetic model and (2) linking serum magnesium concentrations with outcomes including asthma severity score (efficacy) and hypotension (safety). Data were obtained from 49 children prospectively treated with IVMg (placebo, 50 or 75 mg/kg) after presenting to the pediatric emergency department with an acute asthma exacerbation. Reductions in Pediatric Respiratory Assessment Measure scores were associated with both total and ionized serum magnesium area under the concentration–time curve ($AUC_{0–2\ h}$). Despite frequent study-specific blood pressure monitoring, hypotension was uncommon in IVMg-treated participants (n = 2/31), and no concentration dependence was observed. The findings signal that IVMg may be an efficacious and safe option for treating moderate–severe pediatric acute asthma exacerbations in the ED. Importantly, this study is the first to suggest a serum exposure target (total serum magnesium $AUC_{0\text{-}2\ h}$ >63.1 mg h/L) reflective of effective IVMg dosing in pediatric acute asthma. While further study in a larger clinical trial is needed to refine and validate this exposure target, these findings support the continued study of IVMg therapy as an adjunct therapeutic option in the setting of pediatric asthma exacerbations.

Keywords

blood pressure, magnesium sulfate, pediatric asthma, Pediatric Respiratory Assessment Measure, pharmacodynamics, pharmacokinetics

Introduction

Asthma exacerbations are a primary cause of pediatric emergency care, resulting in 1,258,046 Emergency Department (ED) visits and 110,983 hospitalizations for children 1-17 years old in the United States in 2021.[1] While many treatment options exist for the emergency care of asthma (such as albuterol, ipratropium bromide, and/or corticosteroids), some exacerbations are refractory to these treatments. However, evidence supporting the appropriate use of adjunct therapeutic options is limited. One such adjunct therapeutic option is intravenous magnesium sulfate (IVMg), which causes bronchodilation via several mechanisms including inhibition of calcium influx into smooth muscle cells in the bronchioles leading to their

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relaxation, inhibition of acetylcholine release in the neuromuscular junction, anti-inflammatory effects by inhibition of histamine release from mast cells, and by helping in mucus clearance from the airways.[2–7] IVMg is suggested to reduce asthma-related hospitalizations, but lacks sufficient evidence to support its efficacy or the appropriate dose for this indication.[8] Thus, there is a critical need for studies to define the utility of IVMg and guide its use within the pediatric ED.

To date, nine clinical trials have evaluated IVMg, but only five have investigated IVMg efficacy in the context of a placebo-controlled trial.[9–19] Importantly, dosing protocols in these studies have varied widely, from 25 to 100 mg/kg, with some imposing an arbitrary maximum dose limit of 2 g. As a result of this limited evidence, the clinical use of IVMg varies by site, with one study indicating that one pediatric ED uses IVMg in as few as 15.9% of cases, while another opts to use IVMg in 50.6% of the cases.[20,21] When surveyed, physicians relate the rationale for using IVMg to largely be a desire to prevent intensive care unit (ICU) admission, rather than using IVMg early enough to prevent hospitalization.[22,23]

The Intravenous Magnesium: Prompt use for Asthma in Children Treated in the Emergency Department (IMPACT-ED) study was a pilot trial targeting an understanding of the role of IVMg in pediatric acute asthma exacerbations.[24] As part of this study, pharmacologic measures including total and ionized serum magnesium concentrations following various IVMg doses, asthma severity score, and blood pressure were collected to guide IVMg dosing in a future, appropriately powered clinical trial. Using these data collected from IMPACT-ED, the objectives of the current study were: (1) to externally validate our previously published population pharmacokinetic (PK) models of both total and ionized serum magnesium;[6,25] and (2) to define concentration–effect relationships for both efficacy and safety measures following IVMg administration.

Methods

Study Design

Full study design and protocol details for the IMPACT-ED trial were previously published.[24] Briefly, IMPACT-ED was a prospective, double-blind, placebo-controlled trial of IV $MgSO_4$ in children with a severe acute asthma exacerbation. Study procedures were approved by the University of Utah under a single Institutional Review Board (sIRB) protocol (#00104082) and a United States Federal Drug Administration Investigational New Drug protocol (#133781). The trial was monitored by an independent data safety and monitoring board and is registered with ClinicalTrials.gov (NCT05166811).

Study participants were enrolled at three sites within Pediatric Emergency Care Applied Research Network (PECARN): Primary Children's Hospital (PCH) in Salt Lake City, UT; Nationwide Children's Hospital (NWCH) in Columbus, OH; and Children's Hospital of Philadelphia (CHOP) in Philadelphia, PA. Parental permission was obtained for all subjects, and children >7 years of age provided assent to participate in the study. Key eligibility criteria were children between 2 and 17 years of age with an existing asthma diagnosis and who presented to the emergency department (ED) with an acute asthma exacerbation, defined as a Pediatric Respiratory Assessment Measure (PRAM) score 7 or greater. Full inclusion/exclusion criteria and the PRAM scoring criteria are published and included in Tables S1 and S2, respectively. Eligible participants providing consent were randomized to a treatment arm using a sequential randomization scheme with random-sized blocks stratified by site, which was prepared in advance by the study statistician.

Participants were treated with a 20 min infusion of either placebo (0.9% NaCl solution ["normal saline"], 50 mg/kg IV $MgSO_4$ (2000 mg maximum), or 75 mg/kg IV $MgSO_4$ (3000 mg maximum). These doses were selected based on our prior modeling efforts, current clinical practice, international guidelines, and prior clinical trial data.[6,19,26,27] Blood samples were collected prior to drug administration, as well as 20-40 and 90-150 min after the start of drug infusion. Blood samples were processed to isolate serum, which was stored at −80°C until shipment to and analysis of total and ionized magnesium using validated assays on a Nova Biomedical Critical Care Express Blood Analyzer within the study laboratory at the University of California, Davis. PRAM scores were determined by the treating physician immediately before drug infusion and 20-40 and 120 min after the start of drug infusion. Blood pressure was measured within 10 min before the start of study infusion, every 10 (±4) min thereafter until 90 min after the start of infusion, and again at 120 (±10) min after the start of drug infusion. All study data were stored in a centralized data repository curated by study statisticians at the University of Utah. Major deviations from the above-described protocol were documented and stored with study data.

Pharmacokinetic Modeling

PK modeling used NONMEM v7.4.3 (ICON Development Software, Ellicott City, MD) interfaced with Pirana v 2.9.9 (Certara, Sheffield, UK). As in our prior publications,[6,25] magnesium concentrations (total and ionized are separately modeled) were modeled using a one compartment model (ADVAN1) parameterized on

clearance and volume (TRANS 2), with weight as a covariate on both clearance and volume. Minimization used first order conditional estimation with interaction (FOCE-I). Parameter estimates from this prior work are included within Table S3 for both total and ionized magnesium.[25] As magnesium is present endogenously, a parameter describing baseline magnesium concentration is estimated and incorporated into the model using Equation (1). In this equation, $C_{endogenous}$ represents the endogenous magnesium concentration for either the individual (ind) or population (pop), $C_{exogenous}$ represents the exogenous (dosed) magnesium, ETA(j) represents the individual's deviation from the population mean value (in this case, for $C_{endogenous}$), and ERR(i) represents the residual error for the individual.

$$C_{endogenous,ind} = C_{endogenous,pop} * EXP(ETA(j))$$
$$C_{total} = C_{exogenous} + C_{endogenous,ind}$$
$$C_{observed} = C_{total} + ERR(i) \quad (1)$$

External validation of the total and ionized magnesium model was accomplished by comparing the concentration data observed in the study to model-simulated data. Prediction error (PE, a measure of bias) and absolute prediction error (APE, a measure of accuracy) were determined using Equations (2) and (3), respectively, where C_{pred} represents the individual predicted concentration (commonly known as IPRED) at the same time point as the study observed concentration (C_{obs}).

$$PE = \frac{C_{pred} - C_{obs}}{C_{obs}} \quad (2)$$

$$APE = \frac{|C_{pred} - C_{obs}|}{C_{obs}} \quad (3)$$

The median PE (MPE) and APE (MAPE) were then determined and compared to acceptance criteria of $<\pm 15\%$ for MPE and $<30\%$ for MAPE. These acceptance criteria have been used in our prior publications,[25,28,29] and are based on the typical accuracy/precision of the assays used to measure drug concentrations.

PRAM Measurements and Statistics

The PRAM scoring tool used in this study was previously published[30,31] and is included as Table S2. Reduction in PRAM score from the measurement prior to drug infusion represents improvement in asthma severity and was calculated for both the measurement at 20-40 and 120 min after the start of infusion, such that a greater reduction in PRAM is signified by a larger negative number. For example, an individual with a baseline PRAM of 12 and a 120 min PRAM score of 0 would be determined to have a change in PRAM score of -12, which is the greatest possible reduction in PRAM score. We initially attempted to link this PD with our PK model to create a PK–PD model, however, parameter estimation failed to provide reliable results. We therefore compared reductions in PRAM score to the measured maximum serum concentration (C_{max}) of magnesium (the observed value obtained from the immediate post-infusion sample), the IPRED at the time which the PRAM was obtained (typically a concentration $\sim$2 h after infusion initiation, $C_{120\,min}$), or the area under the concentration–time curve ($AUC_{0\text{-}2\,h}$, calculated via integration within the NONMEM code) using Pearson rho correlations. Pearson rho correlations, and subsequent receiver operating characteristic (ROC) curve analyses, were performed in GraphPad Prism v10.1.1 (La Jolla, CA). Reported *P*-values test the hypothesis that the slope of the correlation is non-zero; thus, a *P*-value ($P < .05$) indicates a significant non-zero slope.

Blood Pressure Measurements and Statistics

Blood pressures were monitored frequently following drug infusion, addressing prior reports of blood pressure reductions following IV $MgSO_4$ infusion. To evaluate the potential for an exposure-dependent reduction in blood pressure, maximum reductions in both systolic and diastolic blood pressures were correlated, as well as mean arterial pressure[32] (MAP = [SYS + 2 × DIA]/3) with total or ionized magnesium C_{max}. Maximum reductions in blood pressure were determined by subtracting the pre-infusion blood pressure from the minimum of the 10 observed blood pressures during or after drug infusion. For example, a patient with a pre-infusion systolic pressure of 127 and a minimum systolic pressure of 101 at 1.5 h after the infusion start would have a maximum change of -26. Hypotension was defined in the study protocol as a systolic blood pressure (mmHg) of less than $70 + 2 \times$ Age (children 1-10 years of age) or less than 90 (children >10 years of age).[33] Correlation analysis utilized Pearson rho analyses in GraphPad Prism, as described for PRAM score correlations.

Results

Study Demographics

Participants were screened between September 2022 and May 2023. During that time, 347 participants were screened, 119 met eligibility criteria, 93 were approached for enrollment, and 52 were consented and enrolled. All 52 enrolled participants were randomized, however, one withdrew prior to receiving study drug and two were found to be ineligible after randomization (one for an enrollment assessment $\geq$60 min after the start of treatment in the ED, the other for a PRAM

Table 1. Study Population Demographics by Study Medication Receipt

	Placebo (N = 18)	IVMg 50 mg/kg (max 2 gm) (N = 16)	IVMg 75 mg/kg (max 3 gm) (N = 15)	Overall (N = 49)
Site				
A	6 (33.3%)	4 (25.0%)	5 (33.3%)	15 (30.6%)
B	5 (27.8%)	5 (31.3%)	5 (33.3%)	15 (30.6%)
C	7 (38.9%)	7 (43.8%)	5 (33.3%)	19 (38.8%)
Age at Randomization (years): Mean [SD]	7.3 [3.7]	7.4 [2.7]	6.9 [4.4]	7.2 [3.6]
Age Group				
2-4 years	7	4	6	17
5-17 years	11	12	9	32
Weight (kg): Mean [SD]	29.4 [16.8]	32.7 [21.3]	26.1 [19.3]	29.4 (18.9)
Sex				
Male	13 (72.2%)	11 (64.7%)	10 (66.7%)	34 (69.4%)
Female	5 (27.8%)	5 (29.4%)	5 (33.3%)	15 (30.6%)
Race				
American Indian or Alaskan Native	1 (5.6%)	0 (0.0%)	2 (13.3%)	3 (6.1%)
Asian	1 (5.6%)	0 (0.0%)	1 (6.7%)	2 (4.1%)
Black or African American	6 (33.3%)	8 (50.0%)	4 (26.7%)	18 (36.7%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (2.0%)
White	10 (55.6%)	6 (37.5%)	4 (26.7%)	20 (40.8%)
Multiple	0 (0.0%)	1 (6.3%)	1 (6.7%)	2 (4.1%)
None of the above	0 (0.0%)	1 (6.3%)	1 (6.7%)	2 (4.1%)
Unknown or not reported	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (2.0%)
Ethnicity				
Hispanic or Latino	3 (16.7%)	5 (31.3%)	0 (0.0%)	8 (16.3%)
Not Hispanic or Latino	14 (77.8%)	11 (68.8%)	14 (93.3%)	39 (79.6%)
Unknown or not reported	1 (5.6%)	0 (0.0%)	1 (6.7%)	2 (4.1%)
PRAM Reduction at 120 min: Mean [SD]	−1.69 [2.82]	−2.63 [1.63]	−2.07 [2.59]	−2.13 [2.37]
Maximum Mean Arterial Pressure Reduction (mmHg): Mean [SD]	−17.4 [10.4]	−22.2 [14.9]	−16.8 [11.6]	−18.8 [12.4]

score below inclusion criteria). As a result, a total of 49 participants received study drug and are the focus of this manuscript. Of these 49 participants, one had blinded study drug administered for a different treatment arm than the one to which the participant was randomized; we made the post hoc modification for this manuscript to analyze this participant according to the as-administered treatment arm rather than the randomized arm, as this was deemed more relevant for PK/PD analyses.

Demographic data for these 49 participants are described in Table 1. Briefly, 34/49 participants were male, 20/49 were white, 18/49 were black/African American, and enrollment was similar at each site (ranging from 15/49 to 19/49). Mean (standard deviation, SD) age of all participants was 7.2 (3.6) years, while the mean (SD) weight was 29.4 (18.9) kg. Notably, 8/49 participants had a weight >40 kg, resulting in these participants receiving a dose of less than 50 mg/kg (2000 mg maximum dose in this cohort) or 75 mg/kg (3000 mg maximum dose in this cohort). Of these eight, four were in the placebo arm, two were in the 50 mg/kg arm (21 and 29 mg/kg, as treated), and two were in the 75 mg/kg arm (40 and 45 mg/kg, as treated).

External Model Validation

We previously described a population PK for both total and ionized magnesium following administration of 50 mg/kg IV $MgSO_4$ in participants from a single institution (PCH).[25] Data in the current study were collected from three institutions (PCH, NWCH, and CHOP) and used to externally validate the previously described population PK models. The MPE and MAPE (interquartile range) for total magnesium were 1.2% (−7.9%, 9.3%) and 8.7% (4.0%, 15.1%), respectively, well within acceptance criteria. The same values for ionized magnesium were −0.3% (−3.7%, 4.0%) and 3.8% (2.0%, 8.0%). Combined, these values demonstrate the external validity of our previously published total and ionized magnesium models

Table 2. Median Prediction Error (MPE) and Median Absolute Prediction Error (MAPE) and the Associated Interquartile Ranges for Both Total and Ionized Magnesium

	Total	Ionized
MPE (IQR)	1.2% (−7.9%, 9.3%)	−0.3% (−3.7%, 4.0%)
MAPE (IQR)	8.7% (4.0%, 15.1%)	3.8% (2.0%, 8.0%)

to describe IV $MgSO_4$ PK in children with minimal bias and high accuracy (Table 2). Interestingly, dose-normalized $AUC_{0\text{-}2\,h}$ at the 75 mg/kg dose was 79% (total) and 86% (ionized) that of the 50 mg/kg dose and C_{max} values were similar between the two dosing groups, indicating that magnesium PK may not be dose linear.

Association Between PRAM and Serum Magnesium Exposures

We next evaluated the effects of IV $MgSO_4$ on acute asthma exacerbations by correlating total and ionized magnesium exposures with changes in PRAM scores. For all participants (placebo and treated), the median (interquartile range) change in PRAM scores were −1 (0.25, −2.25) and −2 (0, −4) at the post-infusion and 120 min time point, respectively. The PRAM reductions at the post-infusion ($P = .89$) and 120 min time point ($P = .54$) did not differ by dose when tested using one-way ANOVA. In comparing the PRAM reductions observed immediately post-infusion versus the 120 min time point by paired *t*-test, only the 50 mg/kg dosing arm demonstrated a significantly greater reduction in PRAM score ($P = .03$).

No correlation between magnesium exposures and PRAM reduction immediately post-infusion were evident. Neither maximum total (Pearson $\rho = -0.06$; $P = .74$) nor ionized (Pearson $\rho = -0.12$; $P = .52$) magnesium concentrations in treated participants were associated with PRAM reduction at the 120 min time point. A stronger, but still non-significant, correlation was observed between the PRAM reduction at the 120 min time point and the concentration observed at that same time point for both total (Pearson $\rho = -0.12$; $P = .52$) and ionized (Pearson $\rho = -0.28$; $P = .13$) magnesium. While a single time-point concentration was not significantly associated with the PRAM reduction at 120 min, both total (Pearson $\rho = -0.44$; $P = .018$) and ionized (Pearson $\rho = -0.45$; $P = .014$) magnesium $AUC_{0\text{-}2\,h}$ were significantly associated with the observed PRAM reduction (Figure 1).

Due to the strength of this relationship, we subsequently analyzed ROC curves to determine if a threshold $AUC_{0\text{-}2\,h}$ indicative of a PRAM reduction of −3 points could be determined. The ROC curve identified total and ionized $AUC_{0\text{-}2\,h}$ of 63.1 and 24.1 mg h/L, respectively, to provide >80% sensitivity for a PRAM reduction of −3. At this threshold, the specificity was ~40% and the AUC of the ROC curve was ~0.60 for both total and ionized magnesium. The total serum magnesium threshold was attained by 50% (n = 7/14) of participants receiving 75 mg/kg and 40% (n = 6/15) of participants receiving 50 mg/kg IVMg. Of these, 62% (n = 8/13) had a PRAM reduction ≥−3, and 31% (n = 4/13) had a PRAM reduction of −2.

Association of Blood Pressure and Magnesium Exposures

Finally, we investigated the association between total and ionized magnesium exposures with changes in blood pressure, to assess the risk of hypotension following IV $MgSO_4$ treatment in this population. No measure of blood pressure (systolic, diastolic, or mean arterial pressure) was associated with either total or ionized magnesium exposures. Figure 2 shows the lack of correlation between mean arterial pressure and total or ionized Cmax or $AUC_{0\text{-}2\,h}$. Importantly, though blood pressure measurements were frequently obtained as per protocol, only 4 of the 49 study subjects had measured hypotension during this period of intensive

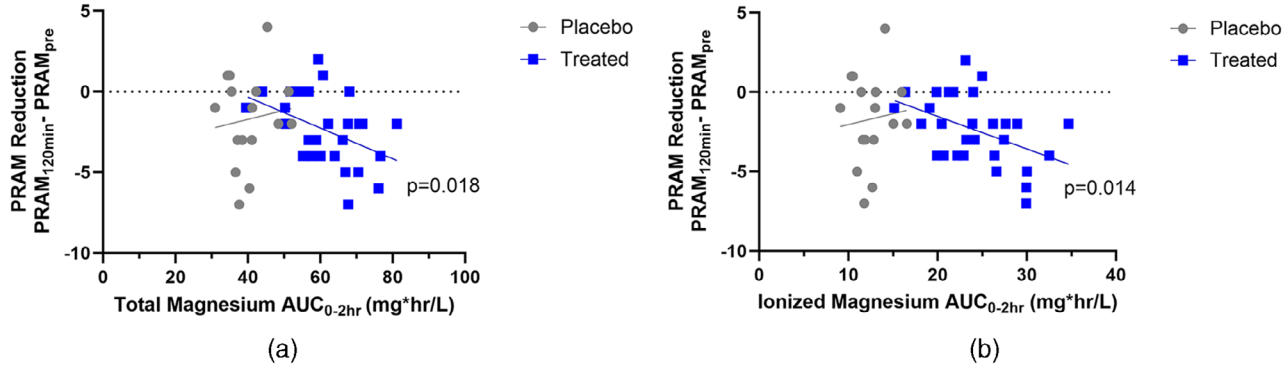

Figure 1. PRAM score reductions at 120 min after initiation of drug infusion correlated to (a) total and (b) ionized magnesium $AUC_{0\text{-}2\,h}$. Regressions are separated by placebo or treated study participants, and the *P*-value reflects the significance of the regression slope (i.e., is the slope non-zero) for the treated participants.

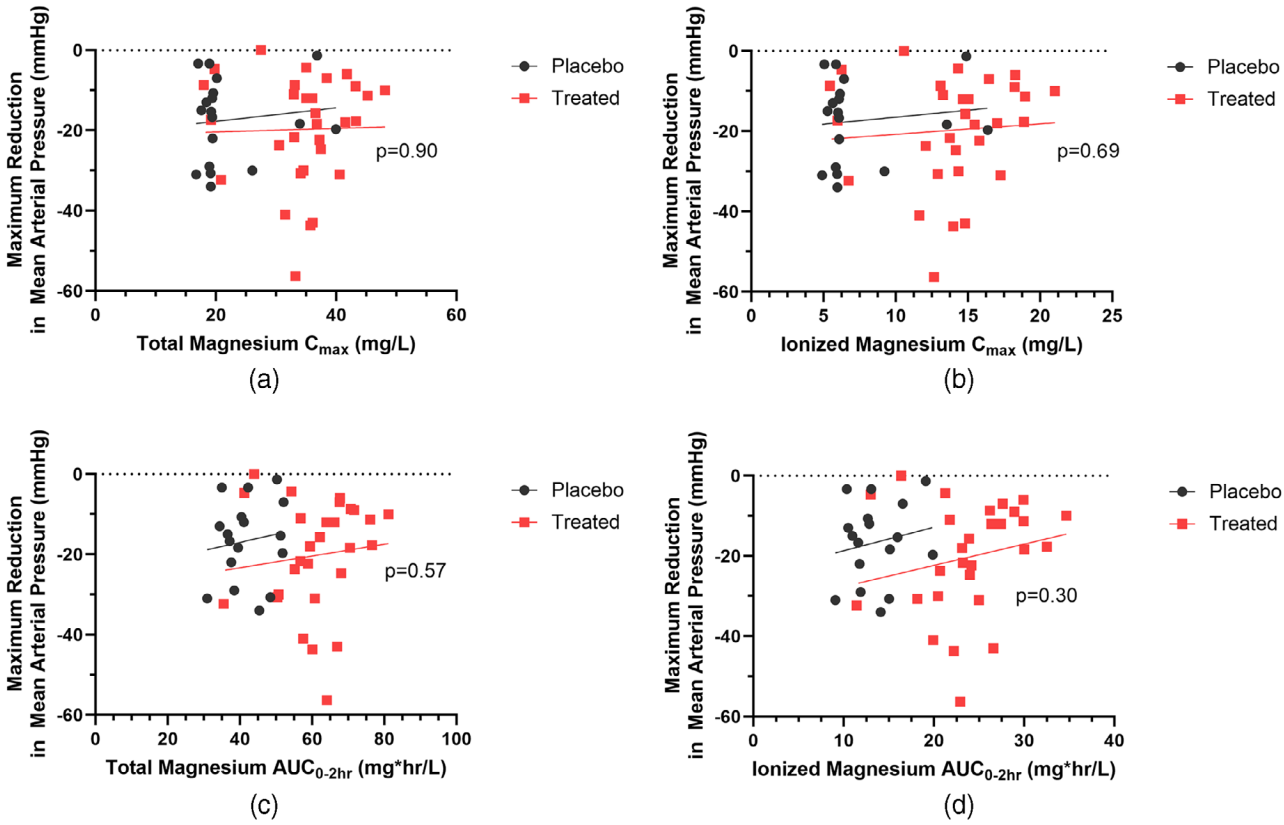

Figure 2. Maximum reduction in mean arterial pressures relative to pre-infusion measures for (a) total and (b) ionized magnesium C_{max} and (c) total and (d) ionized magnesium $AUC_{0\text{-}2\,h}$. Regressions are separated by placebo or treated study participants, and the *P*-value reflects the significance of the regression slope (i.e., is the slope non-zero) for the treated participants.

monitoring, 2 of whom were in the placebo cohort. The two treated participants with measured hypotension were split between the 50 and 75 mg/kg dosing cohorts. Combined, these data support the safety of both 50 and 75 mg/kg IV $MgSO_4$ in children with acute asthma exacerbations.

Discussion

Data from the IMPACT-ED study demonstrated a concentration–effect relationship between PRAM scores of asthma severity and cumulative exposure to IVMg as measured by both total and ionized serum magnesium. The collected concentration data were utilized to successfully validate the external application of our previously published population PK model.[6,25] Despite frequent and rigorous monitoring, few cases of hypotension were observed and no magnesium exposure dependence was identified.

The collected concentration data externally validated our existing, published population PK models of both total and ionized serum magnesium concentrations. This finding supports the broad application of the models to populations more heterogeneous than the ones used to develop our published population PK models. Intriguingly, while the model successfully fit concentrations following both 50 and 75 mg/kg doses, the calculated $AUC_{0\text{-}2\,h}$ for these two doses suggested that IVMg PK may not be dose linear. One likely explanation is the tight control of serum magnesium levels. As less than 1% of total body magnesium is in the blood, fast equilibrium exists with the intracellular compartment to ensure homeostasis is maintained. Another potential explanation is that high doses of IVMg may result in more rapid renal clearance of magnesium during the infusion period, reducing the observed C_{max} and $AUC_{0\text{-}2\,h}$. Indeed, the literature suggests that increased serum magnesium following oral magnesium supplementation results both in more rapid filtration of magnesium by the kidney, as well as a decrease in paracellular reabsorption of magnesium.[34] The combination of increased filtration and decreased reabsorption of magnesium within the kidney can be expected to drive dose nonlinearity of serum magnesium C_{max} (and as a corollary, $AUC_{0\text{-}2\,h}$) observed in our study, likely during the infusion period, while minimally impacting the PK of magnesium once the infusion is stopped. As a result, despite not being parameterized to account for the potential nonlinearity, the model successfully describes the

magnesium PK for both doses evaluated in the current study.

We found that increased cumulative exposure to total and ionized serum magnesium, as measured by $AUC_{0\text{-}2\,h}$, is associated with greater improvement in acute asthma exacerbation severity, as measured by reductions in PRAM scores. Increasing total magnesium $AUC_{0\text{-}2\,h}$ from the mean value in the placebo arm (40.5 mg h/L) to the mean $AUC_{0\text{-}2\,h}$ of treated study participants (61.4 mg h/L) is predicted to change the PRAM score reduction from −0.4 (placebo) to −2.4 (treated). An ROC curve analysis suggested a total magnesium $AUC_{0\text{-}2\,h}$ threshold of 63.1 mg h/L is associated with a PRAM score reduction of at least three points.[30] Although this finding cannot be directly applied to drug monitoring of magnesium during the treatment of asthma due to the impracticality of obtaining multiple blood samples over such a short period of time in every patient, this finding represents an important step forward in the limited data that supports the use of magnesium for this indication.

Despite increasing use in children with acute asthma over multiple decades and inclusion as a therapeutic option in multiple national and international consensus management guidelines, IVMg has never been studied in a properly powered clinical trial of children with asthma. These results represent, to our knowledge, the first pharmacometric evidence that IVMg functions to relieve symptoms in pediatric asthma. Our description of an exposure target for IVMg therapy in acute asthma exacerbations suggests that both tested dosages (50 and 75 mg/kg) warrant evaluation and comparison in a future trial. In a larger population of patients, similar sampling could also clarify whether subpopulations of patients respond variably due to variability in their total exposure or other factors. For example, a 50 mg/kg dose is delivered at a 2000 mg maximum, effectively delivering a lower per-kilogram dosage to patients weighing more than 40 kg that may arbitrarily produce less clinical improvement. While there is a clear need for additional work to refine and validate this threshold, the finding that 12 of the 13 participants attaining an $AUC_{0\text{-}2\,h} > 63.1$ mg h/L experienced a reduction in PRAM score of ≥ -2 supports the potential benefit of targeting this threshold in future IVMg studies.

The dose nonlinearity observed in our study data, combined with the similar percentages of study participants in each dose arm achieving the target threshold supports the continued need to determine the optimal IVMg dose necessary to drive a reduction in asthma exacerbation severity. Our prior work in developing the PK model explored the possibility that dosages lower than 50 mg/kg (25 mg/kg) would produce effective serum concentrations.[6] The findings from this simulation study strongly suggested that dosages below 50 mg/kg were extremely unlikely to produce therapeutic serum concentrations. Because participants in the current study did not receive dosages lower than 50 mg/kg, we could not directly assess the possibility that PD effects could be saturated below 50 mg/kg, although our prior PK modeling suggests that this is extremely unlikely.

Importantly, while total exposure to serum Mg was associated with reduced asthma severity, it was not associated with an increased risk for hypotension. Two of the 31 (6.5%) patients treated with magnesium in our cohort experienced hypotension despite frequent monitoring during the study period, similar to the 6.8% in our recent large database study of 6497 children who received IVMg after presenting to the ED with an asthma exacerbation.[20] Hypotension during or immediately after infusion of IVMg is a primary safety concern regarding its use for acute asthma.[8,9,18,19,35] Reduction of blood pressure is a documented effect of IVMg in other conditions, and in some cases is the desired effect, such as reducing hypertension in (pre)-eclampsia[36–38] and inducing hypotension to reduce blood loss during surgery.[39–41] Even oral magnesium can reduce blood pressure in patients with uncontrolled hypertension.[42] Reduction of blood pressure and hypotension are not intended effects of administration of IVMg to children with asthma, but our findings suggest that they are not accompanied by other adverse effects and are not isolated to children who receive IVMg. Continuous inhalation of albuterol, considered standard treatment for severe acute asthma,[43] is associated with diastolic hypotension,[44] possibly explaining the presence of hypotension in some participants. However, this trial did not record the timing of albuterol administration and was too small to analyze associations of hypotension with medication dosing. Future studies should monitor for hypotension following IVMg administration to understand any possible associations with other asthma treatments.

Though our findings provide important evidence for the use of IVMg to treat acute asthma exacerbations in the pediatric ED, there are some limitations. First, the small sample size across three study arms does not allow more definitive inferences regarding efficacy and safety, and a well-powered clinical trial is indicated. Second, the ROC AUC and specificity of the proposed target threshold were low, limiting the prognostic strength of this threshold. This represents the first time a target exposure has been proposed in the setting of acute pediatric asthma exacerbations and provides important information for the clinical use of IVMg in that setting. However, future studies with a greater number of participants will be required to refine and validate the proposed $AUC_{0\text{-}2\,h}$ target. Third, while we were able to show improvement in asthma exacerbation

severity with increased systemic exposure to IVMg, clinicians are not equipped with these data at the bedside in real time and must target effective $AUC_{0\text{-}2\,h}$ exposures through a dosing regimen. However, our study identified nonlinearity between IVMg dose and serum concentration, therefore achieving such $AUC_{0\text{-}2\,h}$ may be challenging. Next, while our data suggested dose nonlinearity, our 2 h sampling window was insufficient to characterize the time at which serum magnesium returned to endogenous baseline concentrations. This prevents us from parameterizing our model to evaluate a β elimination phase. While future studies may consider collecting additional samples at later time points, our finding that $AUC_{0\text{-}2\,h}$ was associated with a reduction in asthma severity scores, indicates that these additional concentration data may not have direct relevance to the clinical use of IVMg for the rapid treatment of acute asthma exacerbations. Last, we used PRAM as a responsive measure of change in asthma symptoms because of its prior validation in our patient population and its ability to be measured in every child. However, other measures may have more discriminatory ability, such as spirometry or forced oscillometry, or be more clinically meaningful, such as a larger change in PRAM, and may be reasonable to explore as outcomes of interest in future investigation.

Conclusion

The IMPACT-ED study data externally validated our prior population PK model and enabled the proposal of a target $AUC_{0\text{-}2\,h}$ >63.1 mg h/L for significantly reducing asthma severity as measured by the PRAM scoring system. Furthermore, the rate of hypotension events was consistent with prior research and similar to the rate observed in the placebo group. Changes in blood pressure were not correlated with Mg serum exposure data. Combined, these data support the continued evaluation and use of IVMg to treat acute asthma exacerbations in the pediatric ED.

Acknowledgments

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Author Contributions

Joseph E. Rower constructed the population pharmacokinetic model and wrote the manuscript. Joseph J. Zorc and Michael D. Johnson designed the study, secured funding for the project, and served as PI at their respective institutions. Bashar Shihabuddin served as the PI at Nationwide Children's Hospital. Bradley J. Barney and Mengtao Dai served as study statisticians and maintained the electronic data warehouse for the study data. Yaron Finkelstein assisted with study design. All authors reviewed the manuscript and approved its publication.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Sharing

Data that can be reasonably shared without compromising participants' protected health information can be made available upon request. Upon study completion and close-out, de-identified data will be stored in the PECARN repository. The code for the population pharmacokinetic model can also be shared upon request.

Ethics Statement

Study procedures were approved by the University of Utah under a single Institutional Review Board (sIRB)

protocol (#00104082) and a United States Federal Drug Administration Investigational New Drug protocol (#133781). The trial was monitored by an independent data safety and monitoring board and is registered with ClinicalTrials.gov (NCT05166811; registration date: 12/28/2021). Parental permission to participate in the study was obtained from all subjects, and assent was obtained from all children 7 years and older. All study procedures were conducted in accordance with the Declaration of Helsinki.

References

1. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Accessed August 3, 2024. http://www.hcup-us.ahrq.gov/
2. Bichara MD, Goldman RD. Magnesium for treatment of asthma in children. *Can Fam Physician*. 2009;55(9):887-889.
3. Gontijo-Amaral C, Ribeiro M, Gontijo L, Condino-Neto A, Ribeiro JD. Oral magnesium supplementation in asthmatic children: a double-blind randomized placebo-controlled trial. *Eur J Clin Nutr*. 2007;61(1):54-60.
4. Bois P. Effect of magnesium deficiency on mast cells and urinary histamine in rats. *Br J Exp Pathol*. 1963;44(2):151.
5. Del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. *J Physiol*. 1954;124(2):370.
6. Rower JE, Liu X, Yu T, Mundorff M, Sherwin CM, Johnson MD. Clinical pharmacokinetics of magnesium sulfate in the treatment of children with severe acute asthma. *Eur J Clin Pharmacol*. 2017;73:325-331.
7. Liu X, Yu T, Rower JE, Campbell SC, Sherwin CM, Johnson MD. Optimizing the use of intravenous magnesium sulfate for acute asthma treatment in children. *Pediatr Pulmonol*. 2016;51(12):1414-1421.
8. Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2016;4(4):CD011050.
9. 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(6):809-814.
10. Devi PR, Kumar L, Singhi SC, Prasad R, Singh M. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatr*. 1997;34(5):389-397.
11. Irazuzta JE, Paredes F, Pavlicich V, Domínguez SL. High-dose magnesium sulfate infusion for severe asthma in the emergency department: efficacy study. *Pediatr Crit Care Med*. 2016;17(2):e29-e33.
12. Shan Z, Rong Y, Yang W, et al. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. *Respir Med*. 2013;107(3):321-330.
13. Su Z, Li R, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children: a systematic review and meta-analysis. *Pediatr Emerg Care*. 2018;34(6):390-395.
14. Cheuk D, Chau T, Lee S. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child*. 2005;90(1):74-77.
15. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg Med J*. 2007;24(12):823-830.
16. Ambrożej D, Adamiec A, Forno E, Orzołek I, Feleszko W, Castro-Rodriguez JA. Intravenous magnesium sulfate for asthma exacerbations in children: systematic review with meta-analysis. *Paediatr Respir Rev*. 2024;52:23-30.
17. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo Jr CA. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med*. 2000;36(3):181-190.
18. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med*. 2000;154(10):979-983.
19. Scarfone RJ, Loiselle JM, Joffe MD, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med*. 2000;36(6):572-578.
20. Johnson MD, Zorc JJ, Nelson DS, et al. Intravenous magnesium in asthma pharmacotherapy: variability in use in the PECARN registry. *J Pediatr*. 2020;220:165-174. e2.
21. Schuh S, Zemek R, Plint A, et al. Magnesium use in asthma pharmacotherapy: a Pediatric Emergency Research Canada study. *Pediatrics*. 2012;129(5):852-859.
22. Schuh S, Macias C, Freedman SB, et al. North American practice patterns of intravenous magnesium therapy in severe acute asthma in children. *Acad Emerg Med*. 2010;17(11):1189-1196.
23. Gray CS, Xu Y, Babl FE, et al. International perspective on research priorities and outcome measures of importance in the care of children with acute exacerbations of asthma: a qualitative interview study. *BMJ Open Respir. Res*. 2023;10(1):e001502.
24. Johnson MD, Barney BJ, Rower JE, Finkelstein Y, Zorc JJ. Intravenous magnesium: prompt use for asthma in children treated in the emergency department (IMPACT-ED): protocol for a multicenter pilot randomized controlled trial. *JMIR Res Protoc*. 2023;12(1):e48302.
25. Becker SM, Job KM, Lima K, et al. Prospective study of serum and ionized magnesium pharmacokinetics in the treatment of children with severe acute asthma. *Eur J Clin Pharmacol*. 2019;75:59-66.
26. Egelund TA, Wassil SK, Edwards EM, Linden S, Irazuzta JE. High-dose magnesium sulfate infusion protocol for status asthmaticus: a safety and pharmacokinetics cohort study. *Intensive Care Med*. 2013;39:117-122.
27. Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed July 10, 2023, www.ginasthma.org
28. Rower JE, McKnite A, Hong B, et al. External assessment and refinement of a population pharmacokinetic model to guide tacrolimus dosing in pediatric heart transplant. *Pharmacotherapy*. 2023;43(7):650-658.
29. Rower JE, Stockmann C, Linakis MW, et al. Predicting tacrolimus concentrations in children receiving a heart transplant using a population pharmacokinetic model. *BMJ Paediatr Open*. 2017;1(1):e000147
30. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. *J Pediatr*. 2000;137(6):762-768.
31. Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr*. 2008;152(4):476-480. e1.
32. DeMers D, Wachs D. Physiology, mean arterial pressure. *StatPearls*. StatPearls Publishing LLC; 2024.
33. Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: Pediatric advanced life support. *Circulation*. 2010;122(18_suppl_3):S876-S908.
34. Curry JN, Yu ASL. Magnesium handling in the kidney. *Adv Chronic Kidney Dis*. 2018;25(3):236-243.

35. Gürkan F, Haspolat K, Bosnak M, Dikici B, Derman O, Ece A. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children nonresponding to conventional therapy. *Eur J Emerg Med*. 1999;6(3):201-205.
36. Euser AG, Cipolla MJ. Magnesium sulfate for the treatment of eclampsia: a brief review. *Stroke*. 2009;40(4):1169-1175.
37. Alexander JM, McIntire DD, Leveno KJ, Cunningham FG. Selective magnesium sulfate prophylaxis for the prevention of eclampsia in women with gestational hypertension. *Obstet Gynecol*. 2006;108(4):826-832.
38. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. *Clin Pharmacokinet*. 2000;38:305-314.
39. Juibari HM, Eftekharian HR, Arabion HR. Intravenous magnesium sulfate to deliberate hypotension and bleeding after bimaxillary orthognathic surgery; a randomized double-blind controlled trial. *J Dent*. 2016;17(3 Suppl):276.
40. Elsharnouby N, Elsharnouby M. Magnesium sulphate as a technique of hypotensive anaesthesia. *Br. J Anaesth*. 2006;96(6):727-731.
41. Mireskandari SM, Karvandian K, Jafarzadeh A, et al. The effectiveness of intravenous magnesium sulfate for deliberate hypotension in rhinoplasty. *Arch Anesthesiol. Crit Care*. 2015;1(4):112-115.
42. Rosanoff A, Costello RB, Johnson GH. Effectively prescribing oral magnesium therapy for hypertension: a categorized systematic review of 49 clinical trials. *Nutrients*. 2021;13(1):195.
43. Camargo CA, Jr., Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev*. 2003;2003(4):Cd001115.
44. Wisecup S, Eades S, Hashmi SS, Samuels C, Mosquera RA. Diastolic hypotension in pediatric patients with asthma receiving continuous albuterol. *J Asthma*. 2015;52(7):693-698.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.