OBSTETRICS

Pharmacokinetics and placental transfer of magnesium sulfate in pregnant women

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BACKGROUND: Magnesium sulfate is one of the most commonly prescribed intravenous medications in obstetrics. Despite its widespread use, there are limited data about magnesium pharmacokinetics, and magnesium is prescribed empirically without dose adjustment for different indications.

OBJECTIVE: The aim of this study was to characterize the pharmacokinetics and placental transfer of magnesium sulfate in pregnant women and to determine key covariates that impact the pharmacokinetics.

STUDY DESIGN: This is a prospective pharmacokinetic cohort study of pregnant women who were prescribed magnesium sulfate for preeclampsia, preterm labor, or extreme prematurity. Women received a 4-g loading dose and 2 g/h maintenance dose as clinically indicated. Maternal blood samples were obtained before and at multiple time points during and after magnesium administration. Cord blood also was sampled at delivery. A population pharmacokinetic approach that used a nonlinear mixed–effects modeling was used to characterize magnesium disposition.

RESULTS: Pharmacokinetic profiles of 111 pregnant women were analyzed. Magnesium clearance was 3.98 L/h in preeclamptic women and 5.88 L/h non-preeclamptic women. Steady-state concentration of magnesium was 7.2 mg/dL in preeclamptic women compared with 5.1 mg/dL in non-preeclamptic women. Maternal weight significantly impacted time to steady state. The ratio of the mean umbilical vein magnesium level to the mean maternal serum magnesium level at the time of delivery was 0.94 ± 0.15.

CONCLUSIONS: The study accurately characterizes the pharmacokinetics of magnesium administered to pregnant women. Preeclamptic status and maternal weight significantly impact serum magnesium levels. This pharmacokinetic model could be applied to larger cohorts to help tailor magnesium treatment and account for these covariates.

Key words: magnesium sulfate, neuroprotection, NONMEM, pharmacokinetics, pregnancy

Magnesium sulfate is one of the most commonly prescribed intravenous medications in obstetrics and is used for seizure prophylaxis in preeclampsia, tocolysis in threatened preterm labor, and neuroprotection of the preterm fetus with anticipated delivery before 32 weeks' gestation.[1,2] It is estimated that more than 700,000 newborns in the United States are born each year are exposed to magnesium sulfate after maternal administration. Although many dosing protocols are designed to prevent an untoward outcome, undesirable effects for both mother and neonate have been observed with varying magnesium sulfate dosing regimens during pregnancy.[1,3-16]

Current knowledge of magnesium disposition in pregnant women is limited to studies of women with preeclampsia via the use of minimal blood sampling with limited covariate data available.[17-19] Standard magnesium sulfate treatment protocols (without pharmacokinetic modeling consideration) were proposed by Pritchard in 1955 to provide estimated serum magnesium levels necessary to treat eclampsia.[20] Recent evidence suggests that many magnesium sulfate treatment protocols do not achieve serum levels considered therapeutic.[16] These standardized protocols are administered to all patients, without adjustment for maternal or fetal factors that may affect serum magnesium levels in the mother. Optimal serum magnesium levels for treatment of non-preeclamptic indications also are unknown.[21]

The aim of this study was to develop an accurate pharmacokinetic model, describe the placental transfer of magnesium sulfate in pregnant women, and evaluate the impact of potentially influential covariates (gestational age, presence of preeclampsia, maternal weight, and maternal creatinine) on magnesium pharmacokinetics.

Materials and Methods

Patients, magnesium sulfate dosing, and sampling

After approval from the Stanford University Institutional Review Board, women and their neonates with the potential for magnesium sulfate exposure were enrolled in this prospective study, conducted at Lucile Packard Children's Hospital Stanford. Informed consent was obtained in Labor and Delivery at the time of hospital admission. The mother, or mother and father (if possible), provided written informed consent for the neonates. The study was conducted from October 2012 to May 2014. The study was registered at ClinicalTrials.gov (NCT01709630) before the enrollment of patients began.

Pregnant women aged 18–45 years who were admitted to the hospital with preeclampsia, preterm labor, or extreme prematurity and prescribed magnesium sulfate were included. We excluded pregnant women who were on dialysis. Women received the standardized dosing protocol for magnesium heptahydrate ($MgSO_4 \cdot 7H_2O$) 20 g/500 mL (4%) used at our institution, which is an

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intravenous 4-g loading dose (over 20 minutes) and a 2 g/h maintenance infusion as clinically indicated. Maternal blood samples were obtained for magnesium at baseline before the administration of magnesium sulfate; at 30 minutes, 1 hour, 2 hours, 4 hours, and every 6 hours during the administration of magnesium sulfate; and at 1 hour, 3 hours, 6 hours, 9 hours, and 12 hours after magnesium sulfate was discontinued. Whenever possible, a magnesium level also was obtained from umbilical cord venous blood at delivery. Magnesium levels were measured in Stanford's Hospital Laboratory with a Dimension RxL Max Integrated Chemistry System (Siemens, Berlin, Germany).

Pharmacostatistical analysis

Detailed pharmacokinetic model development and covariate analysis is described in the Supplemental Materials and Methods (Appendix A). To summarize in brief, population pharmacokinetic modeling seeks to measure the physiologic sources of variability within a population that affects drug disposition while maintaining and accounting for the individuality of each patient. NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD) was used for population pharmacokinetic analysis and RStudio Version 0.97.320 (RStudio, Inc, Boston, MA) was used for goodness-of-fit diagnostics. One- and 2-compartment models were evaluated. Selection between models was based on successful NONMEM minimization with at least 3 significant digits in each parameter estimate, decrease in objective function of >3.84 ($P < .05$), visual inspection of diagnostic scatter plots (observed vs individual and population predicted concentrations, residual/conditional weighted residual vs predicted concentration or time), the precision of the parameter estimates measured by the percent SEM, and changes in the interindividual and residual variability. The population pharmacokinetic analysis allowed for investigation of the following covariates in the model: gestational age, presence of preeclampsia, maternal weight at the time of magnesium sulfate administration, antepartum or postpartum status, and maternal creatinine.

Once infused, magnesium sulfate dissociates to Mg^{++} (magnesium ion). The half-life ($t_{1/2}$) of magnesium was calculated with the following formula: $t_{1/2} = 0.693$*volume/ clearance (CL). Final pharmacokinetic model evaluation occurred with a bootstrap analysis to evaluate parameter uncertainty and estimate 95th percentile confidence intervals. One thousand replicates of the dataset were created through repeat sampling with replacement. Model parameters were estimated for each of the 1000 datasets.

Simulation

A simulation study that used NONMEM was performed to determine expected magnesium plasma concentrations of the study population. Simulated magnesium sulfate dose was 4-g loading dose administered over 20 minutes followed by an infusion of 2 g/h for >60 hours. A second simulation was performed with the same dosing to determine time to reach a serum magnesium level of 4.8 mg/dL. One thousand Monte Carlo simulation replicates were performed that incorporated the final population model parameter estimates of fixed effects, interindividual, and residual random variability.

Serum magnesium concentration at steady state was calculated with simulation for a 70-kg pregnant woman receiving a 4-g magnesium sulfate bolus administered over 20 minutes, followed by a 2 g/h infusion. The steady-state concentrations (C_{ss}) of magnesium in preeclamptic and non-preeclamptic women were calculated via the following formulas: (1) For intravenous infusion, C_{ss}=infusion rate/CL; and (2) For intravenous bolus, C_{ss}=dose/(CL*dosing interval).

Correlation with umbilical cord magnesium levels

Via the final model, maternal serum magnesium levels were predicted at the time of delivery for each umbilical cord sample obtained. The ratio of the mean umbilical vein magnesium level at the time of delivery to the mean maternal serum magnesium level at the time of delivery was calculated to determine the transfer ratio.

Results

All pregnant women who consented to the study, received magnesium sulfate, and had at least 1 magnesium level recorded while receiving magnesium sulfate were included in the data analysis (Figure 1). A total of 111 maternal subjects with 687 magnesium levels and 66 umbilical cord blood magnesium levels were available for analysis. Baseline characteristics of subjects are shown in Table 1. Preeclamptic women were significantly heavier, delivered at a later gestational age, and had greater baseline creatinine levels compared with non-preeclamptic women who were administered magnesium sulfate.

Individual concentration-time profile data are outlined in Appendix B. Magnesium disposition in pregnant women was best fit by the use of a 1-compartment model, because magnesium rapidly equilibrates between highly perfused organs and peripheral tissues. In our covariate pharmacokinetic analysis, the effect of maternal weight on the volume of distribution of magnesium, and the effect of preeclampsia on the clearance of magnesium, were statistically significant ($P < .001$). Gestational age at the time of magnesium sulfate administration, antepartum or postpartum status, and maternal creatinine were not significant in the final model.

Final parameter estimates and interindividual variability, including standard errors of the point estimates, are represented in Table 2. Observed vs. individual and population predicted concentrations are shown in Figure 2. On the basis of our pharmacokinetic model, the mean population parameter estimate for magnesium clearance was 5.88 L/h in non-preeclamptic women and 3.98 L/h in preeclamptic women. Volume of distribution of magnesium was 22.5 L. The residual (unexplained) variability that existed after the data were fitted to the population model was 18%. The half-life ($t_{1/2}$) of magnesium was 2.7 hours in non-preeclamptic women and 3.9 hours

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