Magnesium sulfate pharmacokinetics after intramuscular dosing in women with preeclampsia

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BACKGROUND: Current intramuscular magnesium dosing regimens in low and middle-income countries are based on indirect absorption parameters to inform pharmacokinetic and pharmacodynamic response.

OBJECTIVE: To determine if therapeutic serum magnesium levels are obtained in women with severe preeclampsia receiving intramuscular administration of magnesium sulfate using the Pritchard regimen and to compare the key pharmacokinetic variables to those previously published.

STUDY DESIGN: Serum magnesium levels were obtained at multiple time points at baseline and after magnesium sulfate administration from women with severe preeclampsia receiving the standard Pritchard regimen for seizure prophylaxis at Bayero University, Kano, Nigeria. The pharmacokinetic profiles were constructed for the study cohort and the updated pharmacokinetic model was compared with the one that was previously published.

RESULTS: A total of 80 blood samples were collected from 20 women with severe preeclampsia (45 collected before childbirth and 35 collected after childbirth). After 11.5 hours of magnesium sulfate administration, 63% of women in the cohort had serum magnesium levels of ≥2.0 mmol/L. Data from women receiving the Pritchard regimen combined with data from women previously modeled after the receipt of intravenous magnesium sulfate were adequately described using a 2-compartment model with first-order absorption and linear elimination from the central compartment. All structural pharmacokinetic parameters including clearance, central volume of distribution, peripheral volume of distribution, and intercompartment clearance were adjusted for maternal weight, and the clearance was further adjusted for serum creatinine level and antepartum or postpartum status. The simulated pharmacokinetic profiles of the updated pharmacokinetic model and the previously published pharmacokinetic model are similar. In previously published pharmacokinetic modeling, absorption rate constant=0.32 and absolute bioavailability=0.86. In the updated pharmacokinetic model, absorption rate constant=0.45 and absolute bioavailability=0.91.

CONCLUSION: These data support the use of the Pritchard regimen as acceptable to achieve therapeutic serum magnesium levels and support the reported simulation of serum magnesium levels and eclampsia response associated with different intramuscular regimens.

Key words: intravenous magnesium, low- and middle-income countries, magnesium pharmacodynamics, magnesium sulfate dosing, Pritchard regimen, seizure prophylaxis, severe preeclampsia

Introduction

Magnesium sulfate is 1 of the most commonly prescribed intravenous medications in contemporary obstetrical practice.[1] It is the drug of choice for preventing seizures in women with preeclampsia—a leading cause of maternal morbidity and mortality.[2,3] Adequate serum magnesium levels are

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Why was this study conducted?

To update the key pharmacokinetic characteristics of magnesium sulfate using data from women with severe preeclampsia who received intramuscular magnesium sulfate.

Key findings

Magnesium sulfate given as per the Pritchard regimen resulted in therapeutic serum magnesium levels in 63% of women with little variation in the pharmacokinetic estimates from modeling based on intravenous regimens.

What does this add to what is known?

Simulated pharmacokinetic profiles after intramuscular magnesium sulfate administration support the results of previous modeling that were used to identify serum magnesium levels and predict eclampsia rates associated with different magnesium sulfate regimens.

necessary for seizure prophylaxis and treatment.[4] Serum magnesium levels between 2.0 and 3.5 mmol/L are generally considered therapeutic to prevent recurrent eclamptic seizures, though pharmacokinetic (PK) studies of intravenous (IV) magnesium sulfate suggest that even lower serum levels may confer protection against eclampsia.[5] A review of magnesium PK properties showed that magnesium levels in this range are inconsistently achieved when standard Zuspan (IV) and Pritchard (IV and intramuscular [IM]) regimens are used.[6] A dose-response model previously published by our group and a large randomized trial, have determined, despite often achieving lower serum levels than these targets, that the Zuspan and Pritchard regimens reduce eclampsia rates by 50%.[7,8] It is also recognized that many expectant mothers experience side effects related to antenatal magnesium sulfate administration, and magnesium sulfate may negatively impact obstetrical outcomes and lead to adverse neonatal effects.[9–11] Therefore, optimal dosing strategies are important to maximize efficacy while limiting side effects and maternal and neonatal morbidity.

Although PK modeling of IV magnesium sulfate regimens suggests that smaller doses than those previously thought of, may be effective for eclamptic seizure prophylaxis, PK modeling for IM dosing is sparse. Previous publications have used absorption parameters from the literature and not from direct model-estimation.[12,13] Furthermore, previous PK modeling has been scrutinized for a lack of diversity among participants and a lack of model adjustment for covariates that impacts magnesium disposition (ie, maternal weight). Although current protocols in Western countries most often use IV dosing of magnesium sulfate for eclampsia prophylaxis, IM regimens remain popular in low- and middle-income countries (LMICs) because of the limited availability of health professionals to administer IV regimens. Current IM dosing regimens are based on indirect absorption parameters to inform PKs and the pharmacodynamic drug response.[12,13] Existing PK models have been constructed from serum magnesium levels obtained primarily from women receiving IV-only magnesium sulfate regimens. A brief overview of the IV sampling used in previous studies is described in the methods for context.[14] Given the popularity of IM regimens in LMICs, we sought to construct a comprehensive PK model to estimate the absorption of magnesium sulfate using a commonly prescribed, predominantly IM regimen (Pritchard regimen). The regimen consists of both IM and IV loading doses, followed by a serial IM redosing every 5 hours. Data from the proposed study were needed to validate the previous IM PK model[12] and provide new information regarding the differences in magnesium disposition in this population.[12,14]

The primary aim of the study was to determine if empirical therapeutic serum magnesium levels are achieved in women with severe preeclampsia receiving predominately IM administration of magnesium sulfate using the Pritchard regimen. We aimed to compare the key PK variables (bioavailability, absorption rate constant, maximum drug concentration, and clearance) to those obtained previously by Salinger (absorption rate constant [Ka]=0.32 and absolute bioavailability [F]=0.86)[13] and simulate the serum magnesium levels after the administration of the Pritchard regimen using the updated modeling parameters.

Materials and Methods

Description of intramuscular study

This prospective cohort study was approved by the Kano State of Nigeria Ministry of Health Institutional Review Board (commissioner 08023337417; October 7, 2019). Women with severe preeclampsia who were prescribed the standard Pritchard regimen for seizure prophylaxis at Bayero University, Kano, Nigeria, were approached for participation in the study between October 15, 2019 and December 31, 2019. Each participating woman signed an informed consent for their participation in the study before the receipt of magnesium sulfate. The administered Pritchard regimen consisted of the following: magnesium sulfate 4 g IV administered over 20 minutes and 10 g IM loading dosage, followed by 5 g IM every 4 hours, for 24 hours. To limit the number of blood draws to 5 per participant while still maintaining adequate time points for PK model construction, a convenience sample of women was divided into 2 groups (10 women alternating enrollment into each group). The serum magnesium levels were obtained from Group 1 at baseline and after the administration of magnesium sulfate at 30 minutes, 1.5 hours, 11.5 hours, and 24 hours (a total of 5 samples per participant). The serum magnesium levels were obtained from Group 2 at baseline and after the administration of magnesium sulfate at 3.5 hours, 11.5 hours, 13 hours, and 21 hours. (5 total samples per participant). The PK profiles were

constructed using all 20 women in the study cohort. The timings of the blood draws and magnesium sulfate administration and the serum magnesium levels were recorded, as were the following covariates: woman's age, gestational age, body weight, height, and baseline creatinine level.

Description of intravenous study

A complete study description has been previously published.[14] In summary, pregnant women were prescribed magnesium sulfate for either preeclampsia, preterm labor tocolysis, or neuroprotection of the extremely preterm fetus. A total of 92 pregnant women with preeclampsia were used in modeling analysis (the non-preeclampsia cohort in the original study was not used). All women with preeclampsia received an intravenous infusion loading dosage of 4 g magnesium sulfate over 20 minutes followed by a continuous intravenous infusion maintenance dosage of 2 g per hour of magnesium sulfate. Similar to the IM study regimen, the timings of the blood draws and magnesium sulfate administration, serum magnesium levels, the woman's age, gestational age, body weight, height, and baseline creatinine level were recorded.

Descriptive analysis of intramuscular study

We assessed the proportion of women with therapeutic serum magnesium levels 11.5 hours after administration of the Pritchard regimen. This was the single overlapping time point between the groups for PK sample collection among participating women. For the purposes of this study, we considered serum magnesium levels of ≥2.0 mmol/L as therapeutic for eclamptic seizure prophylaxis, and serum levels >3.5 mmol/L as approaching the range associated with side effects and magnesium toxicity.[15]

Population pharmacokinetic modeling of intramuscular and intravenous studies

Population PK analysis was performed using the nonlinear mixed-effects modeling approach for a change from the baseline in the magnesium concentration. A detailed description of the software, modeling of fixed effects and random effects, covariate analysis, and model simulations has previously been published.[12]

Results

Descriptive findings of intramuscular study

The concentration time profiles for 20 enrolled women are detailed in Figure 1. It demonstrates the individual change from the baseline after the administration of the Pritchard regimen. Serum magnesium levels rapidly increased after the loading dosage and the maintenance dosage for most women up to 11.5 hours after magnesium administration. Although the serum magnesium levels remained above the baseline during magnesium sulfate administration, they were relatively decreased in the postpartum period when compared with the antepartum measurements for the cohort examined.

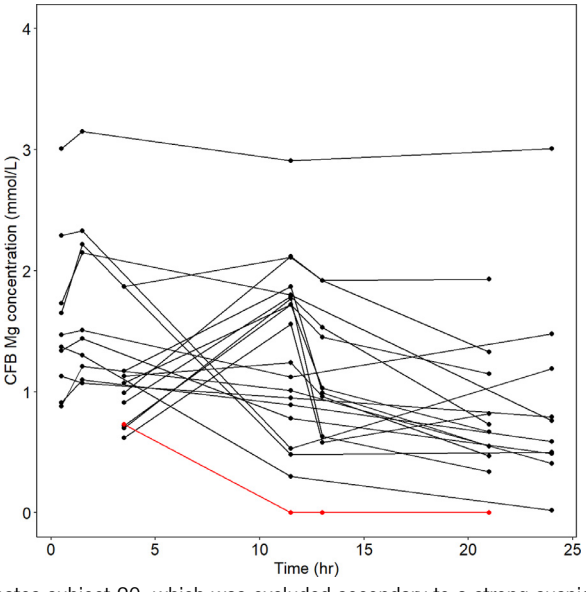
The analysis data set included 80 blood samples (45 collected antepartum and 35 collected postpartum). Data from participant number 20 were excluded owing to recorded serum magnesium levels below the baseline level after magnesium sulfate administration, which is indicative of sampling error. The baseline characteristics of the 2 groups are summarized in Table 1. There were no statistically significant differences between Group 1 and Group 2 with respect to the maternal age at delivery, maternal weight, gestational age at delivery, mean baseline serum magnesium, and the mean baseline serum creatinine. The mean serum magnesium level after 11.5 hours of magnesium sulfate administration was 1.9 mmol/L for Group 1 and 2.6 mmol/L for Group 2 (P=.03).

At 11.5 hours after magnesium sulfate administration (the single overlapping collection time point for the 2 groups), 12 of 19 women in the cohort had reached serum magnesium levels of ≥2.0 mmol/L.

Population pharmacokinetic modeling of intramuscular and intravenous studies

A 2-compartment model with first-order absorption and linear elimination

FIGURE 1
Individual CFB magnesium concentration—time profiles in preeclamptic Nigerian women study cohort



The *red line* indicates subject 20, which was excluded secondary to a strong suspicion for sampling error.

CFB, change from baseline.

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TABLE 1
Baseline characteristics

Characteristics	Group 1 (n=10)	Group 2 (n=10)
Mean maternal age, y	28.4±6.0	26.9±6.7
Mean maternal weight, kg	83.5±6.1	79.0±6.8
Mean gestational age, wk	37.4±1.4	38.8±0.9
Mean baseline magnesium, mmol/L	0.86±0.1	0.88±0.10
Mean baseline creatinine, μmol/L	52.4±18	46.0±12.0
Mean serum magnesium level at 11.5 h, mmol/L	1.9±0.6	2.6±0.3
Postpartum (n)	5	7

Data are presented as mean±standard deviation, unless stated otherwise. Group 1=blood sampling at baseline, 0.5 hours, 1.5 hours, 11.5 hours, and 24 hours after administration of magnesium. Group 2=blood sampling at baseline, 3.5 hours, 11.5 hours, 13 hours, and 21 hours after administration of magnesium.

Brookfield. Magnesium sulfate pharmacokinetics. Am J Obstet Gynecol Glob Rep 2021.

from the central compartment adequately described the data. All structural PK parameters, viz. clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), and intercompartment clearance (Q), were adjusted for the maternal weight, and the CL was further adjusted for serum creatinine level and antepartum or postpartum status. The maternal and gestational ages were examined as covariates in model development but the effects were not statistically significant. The final model parameter estimates are provided in Table 2, and the previous final model parameters are displayed in Appendix 1.

A comparison between the updated model and the published model of the Pritchard regimen is shown in Figure 2. The simulated PK profiles across a wide range of body weights and creatinine levels are similar between these 2 models. Notably, the use of the Pritchard regimen rapidly resulted in serum magnesium levels of ≥2 mmol/L for most average weight women with normal or elevated creatinine. Only those participants with greater obesity (body mass index ≥30 kg/m^2) in simulations from modeling, did not obtain the accepted therapeutic serum magnesium levels for the prevention of eclampsia.

TABLE 2
Pharmacokinetic parameters of the updated model

PK parameters	Estimates	RSE (%)	Shrinkage (%) (%)(%)
CL (L/h)	3.52	2.9	—
Vc (L)	16.9	2.8	—
Q (L/h)	3.62	18.9	—
Vp (L)	14.3	4.6	—
Ka (hr^{-1})	0.451	21.1	—
F	0.91 (fixed)		
WT exponent for CL and Q	0.75 (fixed)	—	—
WT exponent for Vc and Vp	1 (fixed)	—	—
Serum creatinine exponent for CL, θ	−0.73	15.5	
Random effects			
IIV on CL (CV%)	30.3	22.0	15.4
IIV on Vc (CV%)	42.8	43.2	37.3
IOV on CL: antepartum or postpartum (CV%)	24.9	53.0	50.4
IIV on Ka (CV%)	68.5	39.5	76.3
Residual error			
Proportional (CV%)	32.0	49.5	12.0
Additive (mg/L)	5.96	11.9	

CL, clearance; *CV*, coefficient of variation; *F*, bioavailability; *IIV*, interindividual variability; *IOV*, interoccasion variability (antepartum vs postpartum); *Ka*, absorption rate constant; *PK*, pharmacokinetic; *Q*, intercompartmental clearance; *RSE*, relative standard error; *Vc*, central volume of distribution; *Vp*, peripheral volume of distribution; *WT*, body weight.

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Comment

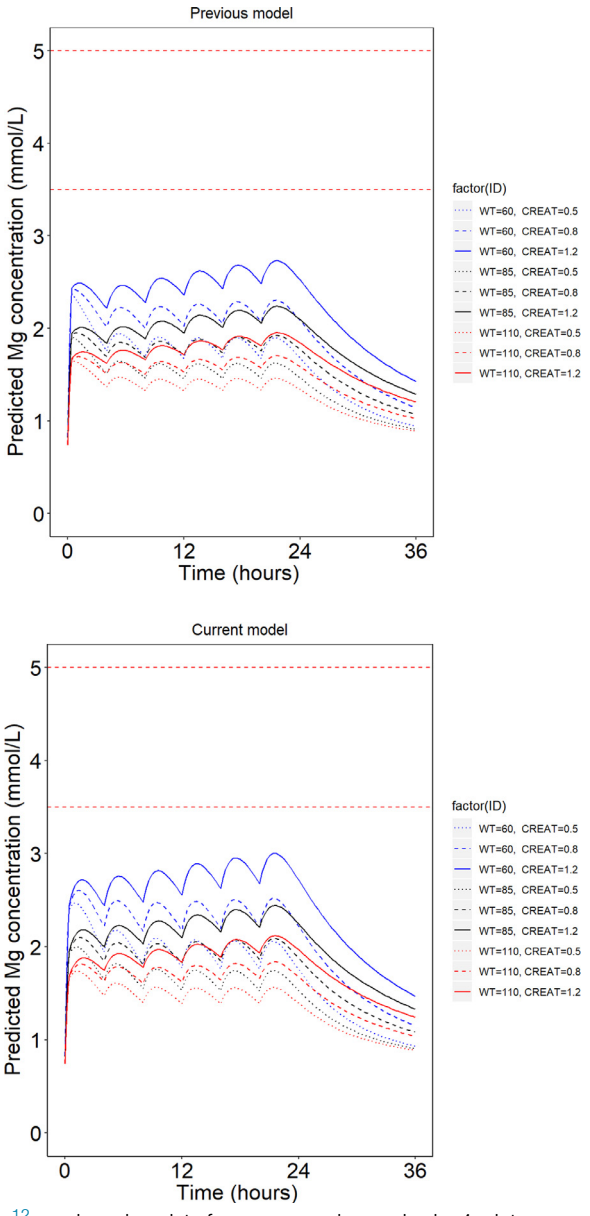
Principal findings

The current study sought to examine whether the IM Pritchard regimen resulted in serum magnesium levels typically accepted as therapeutic for eclamptic seizure prevention. In fact, we found that most of the women of average body weight and normal serum creatinine reached therapeutic serum magnesium levels without magnesium toxicity and did not experience eclampsia. These results suggest that women treated with the Pritchard regimen consistently receive adequate treatment for eclamptic seizure prophylaxis.

Results

The updated PK model including women who received the Pritchard regimen in this study showed little variation from the previously published PK model based on women who received IV magnesium sulfate. In the previous PK model,[12] the PK parameters specific for IM dosing, viz. the Ka and F, were obtained from Salinger et al[13] and were reported to be Ka=0.32 and F=0.86 in a low-resource population in India. In the current study including a cohort of preeclamptic Nigerian women, the estimated values were Ka=0.45 and

FIGURE 2
Simulation comparison for model predictions for the Pritchard regimen



Previous modeling[12] was based on data from women who received a 4 g intravenous loading dosage of magnesium sulfate followed by a 2 g per hour infusion[14] (no samples from women who received intramuscular dosing; the absorption rate constant and the bioavailability are based on the Salinger study).[13] The current model is updated to include women who received the Pritchard regimen, sampled prospectively from the cohort described.

CREAT, serum creatinine level; *ID*, identification; *WT*, body weight.
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F=0.91. The current modeling based on the Pritchard regimen obtained very similar Ka and F values to those published by Salinger et al[13] despite differences in the structural models. The Salinger study used a 1-compartment model, likely owing to the sampling of only a single serum magnesium from each randomized woman. The current study includes multiple samples from each woman and a 2-compartment model is used.

More women in Group 2 had a therapeutic serum magnesium level after 11.5 hours of magnesium administration. It is to be noted that the weight of this group is smaller, which can impact magnesium disposition.[14,16] In addition, preeclampsia may have worsened in this group, resulting in a worsening of renal function and a reduced clearance of magnesium sulfate over time. Only a single creatinine level was obtained at baseline, limiting the ability to explore this possibility further for this magnesium sampling group. However, the interpretation of therapeutic levels at the overlapping time point should be interpreted in the context of the small sample size and patient-to-patient differences, as indicated under "random effects" in Table 2. Irrespective of the assigned sample collection group, all observed magnesium concentrations were captured by modeling analysis, which is more comprehensive than the descriptive analysis.

Clinical implications

Both the Salinger study and the current model suggest that the Pritchard regimen results in serum levels historically considered to be therapeutic for eclamptic seizure prophylaxis (as defined by serum concentration ≥2 mmol/L). These levels are rapidly achieved after the loading dosage is administered in average-weight and below-average-weight women with preeclampsia. Data from women living in 2 different LMICs is reassuring and add to the literature on magnesium pharmacokinetics and pharmacodynamics, as previous modeling has been scrutinized for a lack of diversity among participating subjects, concerns over race-based differences in magnesium sulfate metabolism, and the impact of maternal weight.

Research implications

Finally, the similarities of the model parameters (Table 2) and the simulation predictions between the previously published model and the currently described updated model for the Pritchard regimen (Figure 2) support the conclusions published previously.[12] The simulation of serum magnesium levels using PK sampling after IV magnesium

sulfate administration in the previous model suggested that alternative IM dosing regimens likely result in serum magnesium levels sufficient for eclamptic seizure prophylaxis. The inclusion of participants who directly received IM magnesium dosing in this updated model improves model precision in identifying simplified IM regimens that result in similar serum magnesium levels as those obtained with the Pritchard regimen and presumed eclampsia prophylaxis when these serum levels are obtained.[8]

Strengths and limitations

Limitations in PK research include errors in the sampling of serum magnesium owing to incorrect recording of the timing of magnesium administration or blood draw, sampling from a catheter with intravenous magnesium or other medications being administered in close proximity, and laboratory error. Participant number 20 is suspected to have had mislabeled samples. Sampling after magnesium administration yielded serum magnesium levels at or below the recorded baseline for this study participant, and laboratory re-evaluation of these samples demonstrated the same serum magnesium levels consistently. The previously noted differences in the therapeutic serum magnesium levels at 11.5 hours between Group 1 and Group 2, may have been explained by weight differences, worsening of renal function or preeclampsia, or the time of sampling after delivery. Unfortunately, limitations in the level of granularity of the data prohibit drawing definitive conclusions.

The remainder of the data from study participants resulted in PK parameters consistent with the limited data that have previously been published with IM magnesium regimens. This updated PK model is now strengthened by the robust prospective sampling of multiple serum levels from women who received the Pritchard regimen.

Conclusions

These data together with the Salinger study[13] support the use of the Pritchard regimen in LMICs to achieve therapeutic serum magnesium levels. The data support the simulation of serum magnesium levels associated with different IM regimens and the simulation of eclampsia response when alternate regimens are utilized. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2021.100018.

REFERENCES

1. Pryde PG, Mittendorf R. Contemporary usage of obstetric magnesium sulfate: indication, contraindication, and relevance of dose. Obstet Gynecol 2009;114:669–73.

2. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev 2010;2010: CD000025.

3. Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev 2010: CD000128.

4. Pritchard JA. The use of magnesium sulfate in preeclampsia-eclampsia. J Reprod Med 1979;23:107–14.

5. Sibai BM, Lipshitz J, Anderson GD, Dilts Jr. PV. Reassessment of intravenous MgSO4 therapy in preeclampsia-eclampsia. Obstet Gynecol 1981;57:199–202.

6. Okusanya BO, Oladapo OT, Long Q, et al. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. BJOG 2016;123:356–66.

7. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002;359:1877–90.

8. Du L, Wenning LA, Carvalho B, et al. Alternative magnesium sulfate dosing regimens for women with preeclampsia: a population pharmacokinetic exposure-response modeling and simulation study. J Clin Pharmacol 2019; 59:1519–26.

9. Greenberg MB, Penn AA, Thomas LJ, El-Sayed YY, Caughey AB, Lyell DJ. Neonatal medical admission in a term and late-preterm cohort exposed to magnesium sulfate. Am J Obstet Gynecol 2011;204. 515.e1–7.

10. Riaz M, Porat R, Brodsky NL, Hurt H. The effects of maternal magnesium sulfate treatment on newborns: a prospective controlled study. J Perinatol 1998;18:449–54.

11. Yokoyama K, Takahashi N, Yada Y, et al. Prolonged maternal magnesium administration and bone metabolism in neonates. Early Hum Dev 2010;86:187–91.

12. Du L, Wenning L, Migoya E, et al. Population pharmacokinetic modeling to evaluate standard magnesium sulfate treatments and alternative dosing regimens for women with preeclampsia. J Clin Pharmacol 2019;59:374–85.

13. Salinger DH, Mundle S, Regi A, et al. Magnesium sulphate for prevention of eclampsia: are intramuscular and intravenous regimens equivalent? A population pharmacokinetic study. BJOG 2013;120:894–900.

14. Brookfield KF, Su F, Elkomy MH, Drover DR, Lyell DJ, Carvalho B. Pharmacokinetics and placental transfer of magnesium sulfate in pregnant women. Am J Obstet Gynecol 2016;214. 737.e1–9.

15. Pritchard JA. The use of the magnesium ion in the management of eclamptogenic toxemias. Surg Obstet Gynecol 1955;100: 131–40.

16. Brookfield KF, Tuel K, Rincon M, Vinson A, Caughey AB, Carvalho B. Alternate dosing protocol for magnesium sulfate in obese women with preeclampsia: a randomized controlled trial. Obstet Gynecol 2020;136:1190–4.