IV fosphenytoin in obese patients

Dosing strategies, safety, and efficacy

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Abstract

Background: Previous studies evaluated the disposition of IV phenytoin loading doses and found that obese patients had increased drug distribution into excess body weight, larger volumes of distribution, and longer half-lives when compared to their nonobese counterparts. We assess the safety and efficacy of fosphenytoin loading doses in patients with different body mass indices (BMIs). **Methods:** A retrospective chart review was conducted in 410 patients who received fosphenytoin. Patients were divided into 2 groups: BMI <30 (nonobese) and BMI ≥30 (obese). Patient demographics, fosphenytoin dose administered in mg/kg body weight, renal and liver function tests, fosphenytoin drug levels, and pre- and post-fosphenytoin administration vital signs were collected to assess for adverse events. Necessity of additional antiepileptic loading doses was used as a surrogate for clinical efficacy. **Results:** The median dose of fosphenytoin administered was 19 mg/kg (interquartile range 15–20). The most frequently encountered adverse event was hypotension, which occurred in 39% of the cohort. Using a Bonferroni adjustment for multiple comparisons, there were no differences in adverse events between the 2 groups. The need for additional antiepileptic loading doses was not different between the 2 groups ($p = 0.07$). **Conclusions:** The incidence of adverse events and the need for repeat loading antiepileptic medications was similar between the 2 groups. From our findings, the patients in our study did not receive empiric loading dose adjustments and the current method of loading fosphenytoin achieves similar outcomes, regardless of the patient's BMI. *Neurol Clin Pract* 2017;7:45-52

Obesity is a growing worldwide epidemic that affects countries all over the globe. The WHO estimated that in 2014, nearly 1.9 billion adults were overweight (body mass index [BMI] >25), and 600 million of these men and women were obese (BMI ≥30).¹ As the population of obese patients continues to increase, information on the pharmacokinetic and pharmacodynamic properties of medications will play a crucial role in dosing and disease management strategies in all areas of medicine.

Epilepsy is the 4th most commonly encountered neurologic disorder, affecting all ages of life.^{2,3} Status epilepticus (SE) is considered a medical emergency, defined as recurrent seizure activity for 5 minutes or 2 distinct seizures without return to baseline cognition between the

Mayo Clinic, Rochester, MN.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article** at Neurology.org/cp.

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seizures.^{4–8} Risk factors for developing seizures include sleep deprivation, infections, alcohol use or withdrawal, stroke, and brain tumors. Mortality is increased by delay in treatment.⁹ Fosphenytoin, the prodrug of phenytoin, is a first-line antiepileptic drug (AED) used for the management of SE after the administration of a benzodiazepine. Its use has largely replaced IV phenytoin for seizure management based on its favorable safety and side effect profile, administration rate, and availability for intramuscular administration.^{10–18} Previous studies evaluating phenytoin loading doses in obese patients have shown changes in the pharmacokinetic and pharmacodynamic properties of the drug, including greater drug distribution into excess body tissues, increased volumes of distribution (Vd), and prolonged half-lives ($t_{1/2}$) in obese patients.^{18–23} Higher loading doses have been suggested for obese patients based on this finding.¹⁹ Limited clinical data are available on the effects of obesity on the pharmacokinetic and pharmacodynamic properties of fosphenytoin, which are limited to small case series or reports. We evaluated the effects of obesity on the dosing, safety, and efficacy in adults who received IV fosphenytoin loading doses.

METHODS

We conducted a retrospective chart review on adult patients who received a loading dose of IV fosphenytoin in a large tertiary care hospital setting over a 5-year period from January 1, 2008, to December 31, 2012, at the Mayo Clinic in Rochester, Minnesota. Patients were identified from a pharmacy dispensing database. The charts were analyzed for inclusion criteria. Basic patient demographic information gathered included age, sex, height, weight, and calculated BMI. The presence of renal dysfunction, albumin level, liver function tests, and prior seizure and cardiac history was collected. Other information recorded included currently administered antiepileptic medications, phenytoin concentration prior to fosphenytoin load in patients chronically taking phenytoin, and AEDs administered following fosphenytoin loading. History of cardiac disease was collected to assess if patients with cardiac disease were more susceptible to adverse effects of fosphenytoin. Patients were excluded from the study if they received a fosphenytoin dose of less than 10 mg/kg actual body weight, did not have a serum phenytoin level obtained within 24 hours following the fosphenytoin loading dose, received intramuscular fosphenytoin, were younger than 18 years, or had incomplete information in the medical record. The patients were divided into 2 different groups based on their BMI: <30 (nonobese) and ≥ 30 (obese). Serum phenytoin levels were collected from 1 to 24 hours after the fosphenytoin loading dose was administered, with a total drug level 10–20 $\mu\text{g/mL}$ or free drug level of 1–2 $\mu\text{g/mL}$ considered to be within therapeutic range. Adverse events (AEs) including nystagmus, ataxia, hypotension, bradycardia, and held doses were recorded to assess toxicity parameters. Other laboratory data collected included liver function tests, serum creatinine, and albumin. Liver function tests were recorded as normal or 2 or 3 times the upper limit of normal. Creatinine clearance, which was determined by using Cockcroft-Gault, was used to determine the patient's renal function. Renal dysfunction was described as a creatinine clearance less than 50 mL/min. Albumin level was recorded as low (<3.5 g/dL) or normal (3.5–5 g/dL). Administration of a second AED following the fosphenytoin load was used as a surrogate for lack of efficacy. We allowed for a 2-hour window for another drug needing to be administered, given this is the expected peak time effect for fosphenytoin. Other medications administered beyond 2 hours were not included. Hospital length of stay (LOS) and mortality data were collected and analyzed.

Standard protocol approval, registrations, and patient consents

Consent for research was verified in all patients included in the review. The study was approved by the local institutional review board.

Statistical analysis

For baseline characteristics, means and ranges were calculated for continuous data and analysis of variance F tests were used to compare obesity groups. Frequencies and percentages were

Figure Patient flow diagram

computed for categorical variables and Pearson χ^2 tests were used to compare the groups. LOS and mortality were described using Kaplan-Meier survivorship methods and Cox proportional hazards regression. Logistic regression was used to model the proportion with a subtherapeutic level. The association between obesity (y/n) and drug level, adjusted for the time between drug administration and drug level, was measured using a multiple linear regression model. A Bonferroni type I error level of 0.0083 (0.05/6) was used for AE comparisons between BMI groups, while a p value < 0.05 was considered statistically significant for all other hypothesis tests.

RESULTS

Over 1,400 patients received fosphenytoin during the study period. Of these patients, 410 ($n = 234$ men, 176 women) met inclusion criteria (figure). Median age was 59 years (interquartile range [IQR] 45–71). A total of 280 patients (68.2%) were not obese and 130 patients (31.7%) were obese. The median BMI for the cohort was 26.9 (IQR 23.9–31.6). The median fosphenytoin loading dose between the 2 groups was not different ($p = 0.09$). The median loading dose was 19 mg/kg (IQR 16–20) in the nonobese group and was 18 mg/kg (IQR 15–20) in the obese group. Age, sex, and history of cardiac disease were similar between the 2 groups. Table 1 shows patient demographic data.

Hypotension was the most frequently reported AE. For the entire cohort, 39% of the patients experienced hypotension (43% in the obese and 37% nonobese groups). A difference was observed between the groups in the incidence of postdose nystagmus (6 [5%] obese vs 31 [11%] nonobese, $p = 0.03$). There were no differences in the incidence of hypotension, ataxia, held doses, bradycardia, or need for blood pressure augmentation between the obese and nonobese groups following fosphenytoin administration. Using a Bonferroni multiple comparison procedure, none of the AE comparisons were significant at the comparison-wise type I error level of 0.0083 (0.005/6). Only a minority of patients needed to have subsequent

Table 1 Patient demographics

	BMI <30	BMI ≥30	p Value
Male, n (%)	161 (58)	73 (56)	0.80
Age, y, mean (range)	58 (18–93)	56 (18–89)	0.42
Seizure history, n (%)	86 (31)	33 (25)	0.27
Cardiac history, n (%)	48 (17)	26 (20)	0.48
Fosphenytoin dose, mg/kg, mean (range)	18 (10–32)	17 (10–25)	0.09

Abbreviation: BMI = body mass index.

fosphenytoin doses held due to supratherapeutic drug levels. Tables 2 and 3 list the incidence of AEs observed in the study.

After adjusting for administration time, the frequency of subtherapeutic drug levels was similar between patients with and without renal dysfunction (odds ratio [OR] 1.34, $p = 0.53$). There was no difference in the frequency of subtherapeutic drug levels comparing obese patients with and without renal dysfunction (OR 1.92, $p = 0.38$). The median total drug level for the nonobese group was 17.3 (IQR 13.7–20.9) and 15.7 (IQR 12.8–18.9) in the obese group ($p = 0.002$, adjusted for administration time). A free or unbound drug level was obtained in 331 patients. The median free drug level was 2.1 (IQR 1.7–2.5) in the obese group and 2 (IQR 1.7–2.5) in the nonobese group ($p = 0.26$, adjusted for administration time). The majority of the patients had a therapeutic phenytoin level observed after the fosphenytoin load, with only 25 patients (6.1%) having a supratherapeutic level $>20 \mu\text{g/mL}$. The median time from the fosphenytoin administration to serum drug level was 11 hours (IQR 6–16) in the nonobese group and 11 hours (IQR 7–15) in the obese group. These results were not different between the groups ($p = 0.89$). Liver dysfunction did not influence the fosphenytoin level observed following the loading dose ($p = 0.43$).

The frequency of patients requiring a second AED or an additional fosphenytoin load for continued seizure activity was also assessed. Overall, 103 patients required 2 or more additional AEDs for seizure management, excluding the initial benzodiazepine dose. Patients in the obese group were more likely to receive a second AED than the nonobese groups (31% vs 23%, $p = 0.07$). Thirty-three (12%) patients in the nonobese group and 19 (15%) patients in the obese group required an additional fosphenytoin dose for seizure control. Levetiracetam was the most frequently used AED apart from a second dose of fosphenytoin, with 38 patients (9%) receiving an additional levetiracetam load. Other additional AEDs used included midazolam infusion (24 patients), valproic acid (16 patients), propofol infusion (11 patients), phenobarbital (7 patients), diazepam (3 patients), and lacosamide (1 patient). Sixty-two patients had a final diagnosis of SE during their hospitalization.

Table 2 Adverse events, n (%)

	BMI <30	BMI ≥30	p Value
Nystagmus	31 (11.1)	6 (4.6)	0.03
Ataxia	4 (1.4)	1 (0.8)	1.00
Hypotension	104 (37.1)	56 (43.1)	0.25
Bradycardia	19 (6.8)	7 (5.4)	0.59
Vasopressor use	65 (23.2)	33 (25.4)	0.63
Held doses	11 (3.9)	3 (2.3)	0.56

Abbreviation: BMI = body mass index.

Inconclusive evidence exists on the effects of obesity on the pharmacokinetics of medications.

The median (IQR) LOS in the obese and nonobese groups was 8 (4–24) and 7 (4–15) days, respectively ($p = 0.02$). Forty-six patients died during the hospitalization. In-hospital mortality rates did not differ between the obese and nonobese groups (hazard ratio 1.63, $p = 0.11$). Nine patients with SE died while hospitalized; only one of these deaths was directly due to uncontrolled SE.

DISCUSSION

In this analysis of adult patients receiving a loading dose of fosphenytoin, similar outcomes were observed between obese and nonobese patients. The incidence of AEs was similar in both groups, with the exception of nystagmus, which occurred more often in the nonobese group. Because the Vd increases in obese patients, fosphenytoin is distributed into a greater volume in these patients when given in equal weight-based dosing. Fosphenytoin is more hydrophilic than phenytoin, which makes it more readily distributed into the serum. We postulate these differences have led to more observed nystagmus in the nonobese group. The requirement of additional AED loading doses was similar in both groups.

Bradycardia, ataxia, and nystagmus are AEs that can be observed following fosphenytoin administration.^{12,24} Hypotension can occur following administration of AED loading and can negatively affect patients. In one study, fosphenytoin loading doses were associated with a significant decrease in systolic blood pressure (BP), diastolic BP, and mean arterial pressure compared to patients given IV levetiracetam loading doses.²⁵ Hypotension was the most commonly encountered AE in our study.

The recommended administration rate of fosphenytoin by the manufacturer is 150 mg phenytoin equivalents per minute.^{23,26} The rate of administration can influence the frequency of AEs, with the faster infusion rates being associated with more frequent AEs, especially in patients with hepatic or renal disease, and those with hypoalbuminemia.²³ The administration rate could not be determined in the majority of the patients in our study. Most patients received fosphenytoin loading doses as a slow IV infusion rather than IV push. Transient paresthesias and pruritus have been reported more commonly with fosphenytoin loading than with phenytoin IV loading, independent of rates of administration.^{14,26,27} We did not note any paresthesias or cases of thrombophlebitis following drug administration in our patient population. There were no reports of purple glove syndrome, which is a serious but rare

Table 3 Adverse events and free drug concentration^a

	Odds ratio	95% CI	p Value
Nystagmus	1.036	1.003–1.071	0.0341
Ataxia	1.089	1.033–1.149	0.0016
Hypotension	1.023	0.998–1.049	0.0737
Bradycardia	1.027	0.984–1.072	0.2142
Vasopressor use	1.103	0.985–1.041	0.3750
Held dose	1.115	1.067–1.165	<0.0001

Abbreviation: CI = confidence interval.

^aOdds of having the adverse event for every 0.1 increase in the free drug level.

The majority of the patients in our study had a therapeutic fosphenytoin serum level at 24 hours, regardless of BMI.

adverse reaction noted with the administration of IV phenytoin.¹⁷ Overall, the adverse drug reactions reported in our study are similar to those reported in other studies.^{14,23,25–29}

More than half of our patients received the fosphenytoin loading dose in an intensive care unit (ICU) or the emergency department. Critically ill patients may be more prone to medication AEs also because of physical changes in renal function, fluid status, albumin stores, and other hemodynamic parameters. Critically ill patients are typically exposed to a greater number of medications that in themselves have effects on hemodynamic parameters. Because of these physiologic and pharmaceutical effects, therapeutic drug monitoring is essential for medications with a narrow therapeutic index, especially in the ICU patient.^{30,31}

The metabolism and elimination of medications that undergo extensive CYP1A2, 2C9, 2C19, and 2D6 metabolism may see increased elimination in the obese patient. In one study, the elimination of phenytoin was increased in the obese patients when compared to nonobese patients.¹⁹ Fosphenytoin has been shown to have different clearance rates between obese and nonobese people, as it is largely metabolized by CYP2C9 and 2C19.^{32,33}

Medication clearance is often determined by human physiology and not by obesity. Because obesity is associated with multiple medical comorbidities, including hypertension and type 2 diabetes mellitus, which can negatively affect renal function, the changes in drug clearance are unpredictable. Calculating renal function using standard formulas often overestimates CrCl in obesity.

Inconclusive evidence exists on the effects of obesity on the pharmacokinetics of medications. The individual pharmacokinetic and pharmacodynamic properties of each medication need to be assessed when dosing medications in people with obesity.^{20,34–36} The Vd varies greatly in the obese and the clinical effect of these medications is difficult to assess.³⁷ The Vd may be more clinically important for those medications requiring a rapid onset and for those medications that are more lipophilic. Volume of distribution is also affected by tissue and protein binding. In the critically ill patient population, these are concerns given that fosphenytoin is water soluble and is 93%–98% bound to albumin.^{11,19,35}

There are a number of strengths to our study. Little data are available on the safety and efficacy of fosphenytoin loading in obese patients, which are limited to a few case reports. This study provides additional information to the literature on fosphenytoin loading doses in obese patients. This study is one of few to assess the outcomes of a large heterogeneous group of adult patients receiving fosphenytoin that compares people with different BMIs. A similar study was conducted on a cohort of pediatric patients, age 2–19 years, who received fosphenytoin loading doses.³⁸ In those findings, body habitus was not a major factor in determining the subsequent serum fosphenytoin concentration. The majority of the patients in our study had a therapeutic fosphenytoin serum level at 24 hours, regardless of BMI. The AEs observed were similar to other studies evaluating the safety of fosphenytoin. The recommended loading dose of fosphenytoin for patients in SE is 20 mg/kg.^{13,39} The patients in our study received a median loading dose of 19 mg/kg.

Limitations to this study include its retrospective design. Results of this study reflect one institution's clinical practice with fosphenytoin administration. Other institutions may have different practices. Some patients did not have complete medical records (such as height or weight), which excluded them from the study. Other patients were missing full laboratory assessments (e.g., 251 patients did not have a serum albumin value), which may have influenced the incidence of supratherapeutic levels. We excluded patients (n = 449) who did not have a serum phenytoin level within 24 hours of the loading dose. While directly monitoring ongoing seizure activity would be the most accurate indicator for efficacy, these data

were not available due to the retrospective nature of the study; thus, repeat doses were used as a marker for efficacy and not the serum drug level. Using repeat AED doses as a surrogate marker for efficacy directly reflects those patients with SE and is likely less reflective of efficacy in the entire study group; however, we potentially excluded patients who could have affected the outcome of the study. It is also possible that nystagmus and ataxia may have been overlooked or simply not documented, thus potentially underestimating the incidence of these adverse effects.

As the rate of obesity continues to increase worldwide, clinicians have the responsibility of knowing and understanding how the body metabolizes medications in all ages and body types. Although there are sparse data available for dosing medication in the obese population, we found that our current management of administering fosphenytoin using standard weight-based dosing without empiric dose adjustment to account for drug distribution effects did not affect clinically relevant AEs or outcomes.

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Received May 16, 2016. Accepted in final form September 6, 2016.

AUTHOR CONTRIBUTIONS

Sarah L. Clark: study concept and design, acquisition of data and interpretation, critical evaluation of the manuscript for intellectual content. Megan R. Leloux: acquisition of data and interpretation, critical evaluation of the manuscript for intellectual content. Ross A. Dierkhising: study concept and design, data interpretation, critical evaluation of the manuscript for intellectual content. Gregory D. Cascino: study concept and design, data interpretation, critical evaluation of the manuscript for intellectual content. Sara E. Hocker: study concept and design, data interpretation, critical evaluation of the manuscript for intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

S.L. Clark, M.R. Leloux, and R.A. Dierkhising report no disclosures. G.D. Cascino serves as an Associate Editor for *Neurology*[®] and receives royalty payments for Mayo Foundation-Mayo Clinic Ventures patent re: High frequency nerve stimulation to treat lower back pain (Nevro, 2013). S.E. Hocker serves on a scientific advisory board for SAGE Therapeutics; has received speaker honoraria from the AAN and honoraria from *Continuum*; and serves as an Associate Editor for *Frontiers in Neurology Education*, on the editorial board of *Journal of Stroke and Cerebrovascular Diseases*, and as Review Editor for *Frontiers in Stroke* and *Frontiers in Neurocritical and Neurohospitalist Care*. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.