

A Comparison of Phenytoin-loading Techniques in the Emergency Department

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Abstract

Objectives: To compare the effectivenesses of three phenytoin-loading techniques. **Methods:** Patients with subtherapeutic phenytoin concentrations who presented within 48 hours of a seizure were randomized to receive either 20 mg/kg of oral phenytoin (PO), divided in maximum doses of 400 mg every two hours, 18 mg/kg of intravenous phenytoin (IVP) at an initial infusion rate of 50 mg/min, or 18 mg/kg (phenytoin equivalents) of intravenous fosphenytoin (IVF) at an initial infusion rate of 150 mg/min. **Results:** A total of 45 patients were enrolled: 16 in the PO group, 14 in the IVP group, and 15 in the IVF group. The times required to reach therapeutic drug concentrations were (mean \pm standard deviation [SD]) 5.62 \pm 0.28 hours, 0.24 \pm 0.3 hours, and 0.21 \pm 0.28 hours, respectively. A total of 17, 27, and 32 adverse drug events were observed in the PO, IVP, and IVF

groups, respectively, with significantly fewer events in the PO group ($p = 0.02$, $p = 0.01$). No significant difference was found between the numbers of necessary adjustments to the infusions in the two IV groups. The average time to safe emergency department discharge was significantly shorter for the IV groups compared with the PO group ($p < 0.001$). **Conclusions:** Oral loading has fewer adverse drug events than either IV loading method, but its use may be limited when therapeutic concentrations are required quickly. Although IVF loading is faster, from an adverse-drug event perspective, no advantage of IVF over IVP was apparent. **Key words:** phenytoin; anticonvulsants; emergency department; adverse drug events; randomized, controlled trial. *ACADEMIC EMERGENCY MEDICINE* 2004; 11:244–252.

Phenytoin remains one of the most commonly used antiepileptic medications. Patients normally controlled on phenytoin presenting to the emergency department (ED) with a history of recent seizure are frequently found on laboratory analysis to have subtherapeutic serum concentrations. Although they are no longer actively seizing, it is common practice to administer a loading dose of phenytoin to these patients while

they are still in the ED. The rationale behind this practice is that the achievement of therapeutic concentrations will prevent further seizures and make ED discharge safe.

Methods for loading phenytoin both orally and intravenously vary widely from institution to institution, and even within institutions.^{1,2} Differences exist in the pharmacokinetic and adverse-drug event (ADE) profiles of the commonly used methods. The intravenous route provides rapid attainment of therapeutic serum concentrations, but it is associated with significant morbidity related to its propylene glycol vehicle.^{3–5} For this reason, intravenous administration requires close monitoring, and thus significant resources in the ED. The oral route frequently results in delayed achievement of desired therapeutic serum concentrations because of its capacity-limited absorption.^{6–10} Given its delayed absorption when administered in a large single dose,^{7,9,11} many practitioners are concerned that serum concentrations are not attained rapidly or reliably enough for safe ED discharge. It also is unclear what optimal loading dose(s) and interval should be used in the oral loading method. Several regimens have been proposed.^{7,8,12–14}

Fosphenytoin, the recently introduced prodrug of phenytoin, is rapidly converted to phenytoin by plasma and tissue esterases after its intravenous administration.¹⁵ Because it is not formulated in the propylene glycol vehicle, it may be administered more rapidly than intravenous phenytoin.¹⁵ Although

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fosphephenytoin is significantly more expensive than either oral or intravenous phenytoin, some authors have proposed that the faster infusion rate and lower incidence of ADEs make administration of this more expensive drug more cost-effective than either of the two other methods.¹⁶⁻¹⁸ The purpose of our study was to determine the cost-effectiveness of three methods of loading phenytoin in the ED: intravenous phenytoin (IVP), oral phenytoin (PO), and intravenous fosphenytoin (IVF). We determined effectiveness by comparing adverse event rates and by calculating the time to safe ED discharge. The time to safe ED discharge was defined by the time at which therapeutic concentrations of phenytoin (≥ 10 mg/L) were achieved and there was absence of any adverse events that precluded discharge. The cost-effectiveness was determined by comparing the net costs and numbers of adverse events, and the net costs required to achieve the time to safe ED discharge. In this article, we report the effectiveness data. A subsequent article will report the cost-effectiveness data.

METHODS

Study Design. This was a randomized, prospective, controlled trial. The facility's institutional review board approved the study protocol. Signed, written informed consent was obtained from all patients by one of the investigators or the treating physician before enrollment. Patients were enrolled between October 1999 and May 2001.

Study Setting and Population. Patients were selected from the ED at the Los Angeles County University of Southern California Medical Center, an urban tertiary care facility. The study population was a convenience sample. Patients were considered eligible if the treating physician determined that they required phenytoin loading and the study investigators determined that they met the following inclusion and exclusion criteria. Inclusion criteria were: patient age ≥ 18 years, a history of seizure in the preceding 48 hours, a known history of a seizure disorder, seizures controlled on maintenance (chronic) PO therapy, and a subtherapeutic concentration of phenytoin (< 5 $\mu\text{g}/\text{mL}$) on laboratory determination. Exclusion criteria were: the concurrent use (at time of presentation) of valproic acid, felbamate, or topiramate; the administration of other antiepileptic drugs in the out-of-hospital setting or in the ED before enrollment; the inability to take oral medications; the presence of status epilepticus (either in the out-of-hospital setting or in the ED); the presence of any acute central nervous system pathology (e.g., meningitis, abscess, intracranial hemorrhage, acute head injury); the presence of an acute metabolic derangement that may have caused the seizure (e.g., hyponatremia or hypercalcemia); and the presence of hepatic insufficiency on the basis of

initial history, physical examination, or laboratory data (i.e., total bilirubin > 3.0 mg/dL, prothrombin time > 14 seconds, or albumin < 3.0 mg/dL). Whereas alcoholism itself was not an exclusion criterion, patients in whom seizures were solely a result of alcohol withdrawal were not included.

Study Protocol. After consent was obtained and all clinical care, with the exception of phenytoin loading, was completed, patients were transferred to the General Clinical Research Center (GCRC) for randomization and study-drug administration. Patients were randomized to one of three treatment arms using a predetermined randomization sequence using blocks of six. No delay in necessary care occurred as a result of the study protocol; phenytoin loading was performed directly after randomization. The investigators were not blinded to the randomization arm.

An automated blood pressure cuff was applied to all patients, and patients in the intravenous groups were placed on a cardiac monitor during the infusion. A heparin lock was placed in the upper extremity of all patients, and an intravenous catheter was placed in the contralateral arm of those patients receiving intravenous study medication. The specific location and caliber of these catheters were left to the discretion of the health care providers. Serial heparinized blood samples were collected through the heparin lock.

Study medication was labeled according to the randomization sequence and provided for each patient. Each patient received study medication by one of the following methods: 1) 20 mg/kg of phenytoin sodium in 100-mg capsules orally; 2) a continuous intravenous infusion of 18 mg/kg of phenytoin at the initial rate of 50 mg/min via intravenous pump (Alaris Signature Edition Infusion Pump, Alaris Medical Systems, Inc., San Diego, CA); or 3) a continuous infusion of 18 mg/kg IVF (75 mg/mL phenytoin equivalents) at an initial rate of 150 mg/min via intravenous syringe pump (Baxter Auto Syringe AS40A, Baxter, Inc., Deerfield, IL). The slightly higher doses used for PO were chosen because of the 90% bioavailability of the oral formulation.

To determine the amount of study medication to be administered, patient weight was rounded up to the nearest 5 kg. To maximize absorption in the oral group, the number of capsules administered was divided into intervals of two hours, with a maximum of 400 mg to be given during each interval. IVP and IVF were mixed at the time of administration to standardized concentrations. If the patient did not tolerate the initial infusion rates because of local reactions (e.g., venous irritation, infiltration) and/or systemic complications (e.g., pruritus, hypotension), the infusion was adjusted according to a standardized study protocol (see Table 1) to maximize the likelihood of patient tolerability. A provision was made for rescue benzodiazepine dosing to be administered by the GCRC staff if the patient

TABLE 1. Guidelines for Modification of the Intravenous Loading Protocols

Phenytoin toxicity symptoms (nausea, vomiting, nystagmus)
 Local site irritation
 Hypotension (systolic blood pressure < 100 mm Hg or 20% drop from baseline) or cardiac dysrhythmia*



Stop infusion until symptoms/signs resolve
 Resite intravenous line if any extravasation
 Administer ice packs for local irritation
 Bolus 250 mL normal saline for hypotension
 Decrease infusion rate by 50%

*Discontinue intravenous loading process after third adjustment of infusion rate or for any life-threatening dysrhythmia.

experienced any seizure activity during the loading or the study observation period. The use of benzodiazepines or other anticonvulsant medications remained at the discretion of the study physicians. Any rescue medications as well as their doses and times of administration were recorded on the data-collection sheet. When ADEs related to the loading process were encountered, all modifications, adjustments, and substitutions to the loading protocols were implemented according to standardized guidelines outlined by the investigators in the protocol (see Table 1). All such interventions, along with their times, were recorded on the data-collection forms.

After the ten-hour pharmacokinetic sample was drawn, patients were given the option of remaining in the GCRC or leaving and returning for the 24-hour reassessment. A clinical evaluation was performed at 24 hours for all groups, including the drawing of the 24-hour blood concentration and an assessment for any adverse events or further seizure activity.

Measurements. Before patient enrollment, the following data were collected: patient age; gender; race and ethnicity; details of seizure history; and out-of-hospital course, including medications administered, medication history, and a focused history and physical examination. Baseline phenytoin concentrations and albumin concentrations were obtained for all patients.

Sequential blood pressure determinations were made at regular intervals during the loading and specimen collection periods. Pharmacokinetic samples were obtained at the initiation of the intravenous loading regimens and at 5, 15, and 30 minutes, and 1, 2, 4, 6, 8, 10, and 24 hours thereafter. For the PO group, samples were obtained at 1, 2, 3, 4, 6, 8, 10, and 24 hours. The blood samples were centrifuged within 30 minutes and the serum separated and stored at -70°C until they were assayed.

Plasma phenytoin concentrations were determined according to previously published fluorescence polarization immunoassay (FPIA) (TDX, Abbott Laboratories, Chicago, IL) methods. Samples were analyzed in

batch and in duplicate. The assay was linear between 6.75 and 33 mg/L. The interday assay coefficient of variation for the determination of phenytoin was 0.2% (standard deviation [SD] ± 0.571). The root mean squared error for the calibration curves was 0.8. The minimum detectable concentration was 0.02 mg/L. Samples that exceeded the maximum detectable limit were diluted and re-assayed.

Patients in the intravenous groups were formally assessed for the presence of ADEs at 5-minute intervals during intravenous loading and thereafter at each blood draw. Patients in the PO group were assessed for ADEs at each blood draw. These assessments were made by the GCRC research nurses according to training provided by the clinical investigators. ADEs were grouped into local (pain, phlebitis and extravasation, perineal pruritus), cardiovascular (dysrhythmia, hypotension), neurologic (seizure activity, disorientation, nystagmus, and ataxia), and gastrointestinal (nausea, vomiting).

More specifically, pain, phlebitis, and extravasation were grouped together and defined as any redness, swelling, tenderness, or pain around the intravenous site. Hypotension was defined as a systolic blood pressure < 100 mm Hg or a decrease of mean arterial pressure from baseline of 20% or greater. Any dysrhythmia on cardiac monitoring was considered significant. Ataxia was defined as the presence of either truncal or gait instability. Any direction of nystagmus was considered abnormal. Disorientation was defined as any impairment in the standard orientation questions. Any seizure activity was considered abnormal. Nausea and perineal pruritus were subjectively identified by patients.

Data Analysis. Sample size calculations were performed by the Department of Biostatistics at LAC+USC Medical Center. These calculations were based on the parameters required to conduct a cost-effectiveness study. The pharmacoeconomic parameters used in the determination of sample size included the costs of drug and other products used in the loading process, the costs of nursing and medical personnel time, and the rates of ADEs as estimated from a chart review. Based on the total estimated costs for each arm, the sample size was calculated to detect a minimum difference of 30% in cost between the three groups with 80% power. A total sample size of 180, with 60 patients per group, was conservatively chosen on the basis of this analysis. An interim analysis was performed after the enrollment of the first 45 patients, at which time a significant difference in cost-effectiveness was found among the three groups.

Peak plasma concentration (C_{max}) and time to peak concentration (T_{max}) of phenytoin were derived directly from measured values. The area under the plasma phenytoin concentration-time curve (AUC) was calculated by use of the linear trapezoidal method

(AUC₀₋₂₄). The noncompartmental analysis was performed using Microsoft Excel (PK Functions for Microsoft Excel, Joel I. Usansky, PhD, Atul Desai, MS, and Diane Tang-Liu, PhD, Department of Pharmacokinetics and Drug Metabolism Allergan, Irvine, CA).

In each group, the mean time to therapeutic concentration was calculated by averaging the time at which the serum phenytoin concentration reached 10 µg/mL or greater for each patient. ADEs were itemized by type and then added together to obtain a total number in each group. For the two intravenous groups, calculations included the mean number of times the infusion rate was adjusted and the mean time required to administer study medication. The average time to safe ED discharge was calculated in each group. This was defined as the time at which therapeutic concentrations were achieved and the patient was free of ADEs precluding discharge.

Baseline demographic data among the three groups were compared using a three-way chi-square test. The individual ADEs in each group were compared using the chi-square test. The total numbers of ADEs among the groups were compared using the Kruskal-Wallis test and Mann-Whitney tests. The numbers of adjustments to the infusion in each of the intravenous arms were compared using the Mann-Whitney test. One-way analysis of variance (ANOVA) using the Kruskal-Wallis test and Dunn's multiple-comparison test was used to compare pharmacokinetic parameters for phenytoin between the three treatment arms. The graphs and statistical analysis were performed using GraphPad Prism Version 3.03 (GraphPad Software, San Diego, CA). The ANOVA test was used to compare the times to therapeutic concentrations and safe ED discharge. Data are reported as means ± SDs or proportions, as appropriate. The statistical tests were two-tailed and were considered significant at an alpha level of 0.05.

RESULTS

A total of 45 patients were enrolled in the study between October 1999 and May 2001. Significant

differences were found in the primary outcome measures at the time of the interim analysis. Patient recruitment was hampered because of difficulties with the identification of patients by rotating ED housestaff and shortages in nursing staff to administer the study protocol. All patients enrolled remained in the GCRC for the initial ten-hour study period. Two patients did not return for the 24-hour evaluation.

Baseline demographic information of the study population is given in Table 2. A total of 16 patients (35.6%) were randomized to receive PO, 14 (31.1%) to receive IVP, and 15 (33.3%) to receive IVF.

Pharmacokinetic Analysis. Table 3 depicts the mean (± SD) and median (interquartile range) of the doses administered as well as the AUC₀₋₂₄, C_{max}, and T_{max} for each study group. The higher dose of orally administered phenytoin was intended by design to account for the lower bioavailability when compared with the parenteral formulation. The AUC₀₋₂₄ for IVP is significantly greater than that of IVF and PO. There is no difference in AUC₀₋₂₄ between IVF and PO. In the IVF group, the C_{max} was significantly greater and the T_{max} significantly shorter than for IVP and PO, and was predictable given the faster administration of IVF despite the frequent changes in infusion rates required in the majority of patients. There is a large variability in the C_{max} and T_{max} for IVF (Figure 1), given the frequent changes in infusion rate relative to the short total administration time of the infusion.

Time to Therapeutic Concentration. The mean times to therapeutic concentration (phenytoin ≥10 mg/L) were 5.62 ± 0.28 hours, 0.24 ± 0.3 hours, and 0.21 ± 0.28 hours in the PO, IVP, and IVF groups, respectively (Table 4).

Seizures and ADEs. There were a total of five seizures observed after patients were randomized. One seizure occurred in the PO group. At the time of this seizure, which occurred during the loading process, the phenytoin concentration was found to

TABLE 2. Characteristics of Patients in Intravenous Phenytoin (IVP), Intravenous Fosphenytoin (IVF), and Oral Fosphenytoin (PO) Study Groups

Characteristic	IVP	IVF	PO	p-value*
Total number (45) (100%)	14 (31.1)	15 (33.3)	16 (35.6)	NS
Male (37) (82%)	14 (100)	12 (73)	11 (69)	NS
Ethnicity				
Hispanic (29) (64%)	10	9	10	NS
African American (12) (26%)	2	6	4	NS
White (4) (8%)	2	0	2	NS
Age (yr) (mean ± SD)	35.8 ± 10.6	40.7 ± 10.0	38.4 ± 10.0	NS
Weight (kg) (mean ± SD)	70.4 ± 12.5	76.4 ± 18.1	71.0 ± 10.4	NS
Time since seizure (hr) (mean ± SD)	9.8 ± 13.7	14.7 ± 20.0	14.7 ± 16.7	NS

NS = not significant; SD = standard deviation.

*p-value calculated by chi-square (collapsed categories for small expected frequencies) for nominal data and analysis of variance (ANOVA) for continuous variables.

TABLE 3. Summary of Pharmacokinetic Parameters

	IVP	IVF	PO
Dose (mg/kg)			
Mean (SD)	17.7 (0.4)	18.1 (0.5)	19.9 (0.6)
Median (25%–75%)	17.6 (17.4–18)†	18.1 (17.6–18.4)‡	19.8 (19.7–20.25)†‡
AUC _{0–24}			
Mean (SD)	486.8 (56.5)	405.8 (103)	357.1 (84.4)
Median (25%–75%)	493.7 (474.5–515.0)*†	375.8 (347.9–460.2)*	369.3 (302.5–420.2)†
C _{max}			
Mean (SD)	35.2 (5.5)	89.1 (27.5)	19.9 (4.9)
Median (25%–75%)	36.3 (33.2–39.0)*‡	77 (71–120)*‡	20.6 (16.8–23.4)†‡
T _{max}			
Mean (SD)	0.7 (0.3)	0.2 (0.2)	12.4 (7.2)
Median (25%–75%)	0.5 (0.5–1)*§	0.1 (0.1–0.1)*†	10 (8–17)†§

Kruskal-Wallis with Dunn's multiple comparison test.

SD = standard deviation; AUC = area under the curve; C_{max} = peak plasma concentrations; T_{max} = time to C_{max}.

*p < 0.05; †p < 0.001; ‡p < 0.05; §p < 0.01; ||p < 0.001.

be in the therapeutic range. There were four seizures recorded in the IVF arm. One of these seizures occurred immediately following randomization, before the initiation of the loading protocol, and the remaining three occurred after the completion of the loading protocol. Serum phenytoin concentrations were therapeutic in each of these cases. No seizure was observed in the IVP group.

In total, 76 ADEs were recorded: 17 in the PO group, 27 in the IVP group, and 32 in the IVF group (p = 0.015). The lower incidence of ADEs in the PO group compared with the two IV groups was statistically significant (IVP vs. PO, p = 0.02; IVF vs. PO, p = 0.01). There was no significant difference between the two IV groups (p = 0.55). The numbers of patients experiencing at least one ADE were 10, 14, and 15 in the PO, IVP, and IVF groups, respectively (p = 0.002). For each type of ADE, significant differences between the groups were found only for pain and phlebitis at the infusion site (11 patients in the IVP group vs. 3 in the IVF group, p < 0.001) and perineal pruritus (12 patients in IVF group vs. 0 in the IVP group, p < 0.001). There was no significant difference in the incidence of hypotension (two patients in the IVP group and one patient in the IVF group). One patient in the IVF group experienced a brief episode of sinus tachycardia during the IV infusion that could not be otherwise explained. After 5 minutes, the tachycardia resolved spontaneously and did not recur. Table 5 summarizes the ADEs in the three groups.

Total Time of Intravenous Loading and Number of Adjustments to Intravenous Infusion. The IVP group required a significantly longer duration of infusion than the IVF group (60.7 ± 50.6 minutes vs. 20.1 ± 23.6 minutes, p = 0.01). Seven of 14 (50%) patients receiving IVP and six of 15 (40%) patients receiving IVF required at least one adjustment of the intravenous infusion because of ADEs. The total numbers of adjustments to the infusion rate required during the loading process were not significantly

different between the IVP and IVF groups. These data are summarized in Table 6.

Average Time to Safe ED Discharge. The average times to safe ED discharge were 6.4 ± 2.2 hours, 1.7 ± 0.8 hours, and 1.3 ± 1.0 hours, in the PO, IVP, and IVF groups, respectively (p < 0.01; IVP vs. PO, p < 0.001; IVF vs. PO, p < 0.001). Table 4 outlines the time to reach therapeutic concentration and average time to safe ED discharge in the three groups.

DISCUSSION

There remains no standard for the loading of phenytoin in the ED patient. Although the choice of loading technique may vary depending on the circumstances of each case, the factors involved in this decision remain the same. These include the time to therapeutic phenytoin concentrations, ADEs, and cost of administration.

The primary pharmacokinetic endpoints used in our analysis were C_{max} and T_{max}. The AUC_{0–24} reflects the 24-hour exposure of the patient to phenytoin. Higher concentrations were observed in the IVP group compared with the IVF and PO groups. Two explanations deserve mention. First, the higher C_{max} in the IVP group compared with the PO group is expected. For this reason, we gave a higher dose to the PO group (20 mg/kg) compared with the IVP (18 mg/kg) and IVF (18 mg/kg phenytoin equivalents) groups. However, despite the greater dose in the PO group, the absorption still was lower in the oral group. As is standard in studies evaluating pharmacokinetics, we had patients remain fasting until two hours after the last dose of the PO regimen to ensure uniformity in absorption. The PO absorption may have been greater had we fed patients a fatty meal, because phenytoin is lipid-soluble.

Second, there was an unexpected difference in the AUC_{0–24} between the IVP and IVF groups. One possible explanation for this observation is a difference in metabolizing capacity between the two

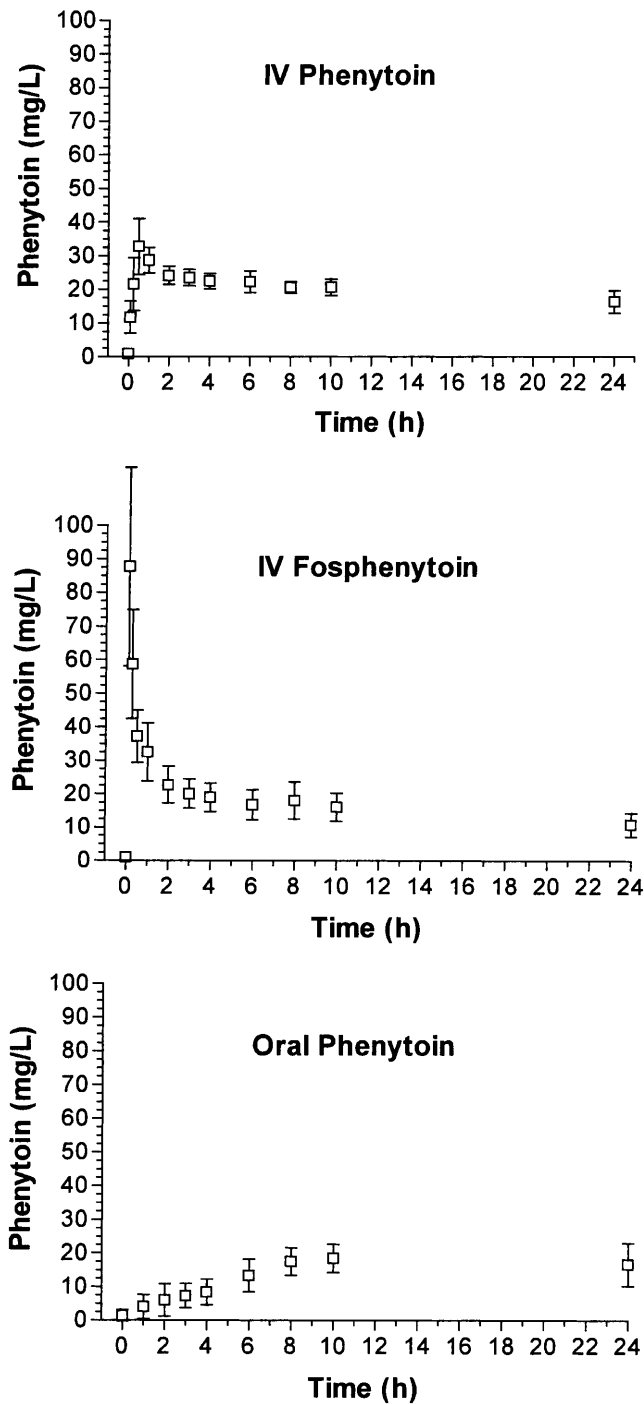


Figure 1. Serum concentration–time profiles for intravenous (IV) phenytoin, IV fosphenytoin, and oral phenytoin. h = hours.

groups. We do not believe (or have any evidence to suggest) that this difference could be attributed to differences in plasma esterase activity. This is in contrast to published Food and Drug Administration registration trials for fosphenytoin, in which the AUC was not different from that for phenytoin. However, these initial studies were performed in a crossover fashion, by which the same patient receives each drug such that no difference in metabolism is apparent. Patients in our study were different in each group. Another possible explanation for the difference in

AUC_{0–24} between the IVP and IVF groups is that there may have been residual enzyme induction from drugs that patients may have taken up to a week before study but were no longer taking (undetectable serum drug concentrations) (e.g., carbamazepine, phenobarbital). However, only two patients in the IVP group had taken phenobarbital in the past. One was noncompliant for at least three weeks before, and the other had discontinued the medication six months before the ED visit. In the IVF group, one patient had taken phenobarbital and carbamazepine but had not been compliant with either medication for an unknown length of time.

The C_{max} was significantly higher and the T_{max} was significantly shorter in the IVF groups compared with the IVP and PO groups. This is explained by the faster infusion rate for IVF (maximum, 150 mg/min) than for IVP (50 mg/min) (see Table 5). The T_{max} for the PO arm was expectedly variable, given its poor dissolution and high lipid solubility. The analysis of the plasma concentration–time curves was performed using a noncompartmental approach. Upon inspection of the IVP and IVF time–concentration curves (Figure 1), a biexponential decline in concentrations was present, suggesting that perhaps a two-compartment model may be necessary to describe the disposition following a single dose of phenytoin administered in this study. Upon inspection of the time–concentration curve for the PO arm, the distribution phase is not distinguished but may be obscured by the prolonged absorption phase.

The mean time to therapeutic concentrations using PO loading are substantially longer than either IV technique, both in the current study and as reported by others.^{7–9,12–14} In previous studies, where accelerated oral loading regimens were used (using doses higher than those recommended by the manufacturer), only in one were therapeutic concentrations achieved faster than in the current study. The slower and incomplete absorption that occurs with larger single doses is presumably the result of the capacity-limited absorption of phenytoin.^{6–9,13} In addition, some authors have reported a higher incidence of ADEs when using higher-than-recommended doses.^{7,8,11}

To the best of our knowledge, this study is the first to prospectively evaluate ADEs using three common loading techniques of phenytoin in the nonseizing ED patient. In the current study, PO loading was associated with a significantly lower incidence of ADEs than either IV group. Of five studies that have directly compared ADEs from intravenous loading of phenytoin and fosphenytoin, four have found significantly fewer ADEs using fosphenytoin,^{16,19–21} whereas one found no significant difference.²² Our study did not find a reduced incidence of ADEs using fosphenytoin. In fact, the total number of ADEs was greater in the IVF group, with the high incidence of perineal pruritus counterbalancing the lower

TABLE 4. Serum Phenytoin Concentrations in the Intravenous Phenytoin (IVP), Intravenous Fosphenytoin (IVF), and Oral Phenytoin (PO) Study Groups

Parameter	IVP	IVF	PO	p-value
Time to therapeutic concentration* (h) (mean ± SD)	0.24 ± 0.3	0.21 ± 0.28	5.6 ± 0.28	p < 0.001 IVP vs. PO, p < 0.001 IVF vs. PO, p < 0.001 IVP vs. IVF, p = 0.55
Time to safe ED discharge† (h) (mean ± SD)	1.7 ± 0.8	1.3 ± 1.0	6.4 ± 2.2	p < 0.001 IVP vs. PO, p < 0.001 IVF vs. PO, p < 0.001 IVP vs. IVF, p > 0.2

SD = standard deviation; ED = emergency department.

*Therapeutic concentration defined as serum phenytoin concentration >10 µg/mL.

†Time to safe ED discharge is the projected time at which there is a therapeutic serum phenytoin concentration and the absence of adverse drug events precluding discharge.

incidence of pain and phlebitis at the infusion site. Moreover, perineal pruritus was not a trivial reaction in the IVF group; it necessitated a reduction of the infusion rate in many patients. Perineal and generalized pruritus, as well as paresthesia, previously have been reported with IVF infusions, with an incidence as high as 64%. Although the exact mechanism of this ADE is not clear, it appears to be related to the rate of infusion, and often requires an interruption or slowing of the loading process.²³

Probably the most concerning ADEs that are reported with intravenous phenytoin loading involve hemodynamically significant cardiac events. Because of reports of adverse cardiovascular events with IVP, it has been suggested that IVF loading is a safer choice for

a certain subset of patients, such as elders or those with significant coronary artery disease.^{24,25} Most reports of adverse cardiovascular events are before the standardization of the maximum rate of IVP loading (not greater than 50 mg/min).^{26–29} In our study, there were only two minor, transient episodes of hypotension in the IVP group and one minor episode of each hypotension and sinus tachycardia in the IVF group.

The incidence and significance of serious soft-tissue reactions such as purple glove syndrome are unclear. The purple glove syndrome is defined as progressive edema, discoloration, and pain in a distal extremity following IVP loading. Some authors have reported an incidence of such reactions as high as 25.2% in retrospective analyses, although there is no report of

TABLE 5. Adverse Drug Events (ADEs) during the Loading and Observation Periods in the Intravenous Phenytoin (IVP), Intravenous Fosphenytoin (IVF), and Oral Phenytoin (PO) Study Groups

Type of ADE	Incidence in Study Arm			p-value*
	IVP	IVF	PO	
Total number of patients	14	15	16	
Number of patients with ≥1 ADE (total = 39)	14	15	10	0.002
Number of ADEs (total = 76)	27	32	17	0.015 IVP vs. PO, 0.02 IVF vs. PO, 0.01 IVP vs. IVF, 0.55
Neurologic (n)				
Ataxia (6)	2	0	4	0.12
Disorientation (6)	2	2	2	0.99
Dizziness (12)	2	4	6	0.36
Headache (4)	2	2	0	0.30
Nystagmus (12)	6	3	3	0.26
Gastrointestinal (n)				
Nausea/vomiting (6)	0	4	2	0.11
Cardiovascular (n)				
Hypotension (3)	2	1	–	0.29
Arrhythmia† (1)	0	1	–	0.36
Local reaction (n)				
Phlebitis (14)	11	3	–	< 0.001
Pruritus (12)	0	12	–	< 0.001

NS = not significant.

*The Kruskal-Wallis and Mann-Whitney tests were used to compare the total number of ADEs among groups. The Pearson chi-square test with Yates' correction was used to compare the number of patients with one or more. The chi-square test was used for comparison of individual ADEs among groups.

†An isolated episode of sinus tachycardia occurred in the IVF group.

TABLE 6. Adjustments to Infusion Rates in the Intravenous Phenytoin (IVP) and Intravenous Fosphenytoin (IVF) Study Groups

Type of Adverse Drug Event	Incidence in Study Arm		p-value
	IVP	IVF	
Infusion duration (min)	60.7 ± 50.6	20.1 ± 23.6	0.01*
Number of patients requiring at least one change of infusion rate	6	7	0.84†
Total number of changes of infusion rate	17	11	0.516‡

*Determined by Student's t-test.

†Determined by Pearson chi-square test with Yates' correction.

‡Determined by Mann-Whitney test.

this phenomenon before the introduction of IVF.^{30,31} A large prospective study conducted in the ED setting found no case among 279 consecutive loading doses of IVP.²² We, likewise, found no case.

Although five seizures occurred during the course of the study, none was considered to be an ADE, because no patient seized secondarily to subtherapeutic phenytoin concentrations once loading was begun.

It is recognized that not all ADEs are the same; some may be more costly or bothersome to patients and caregivers. In the current study, many of the ADEs in the PO group were considered minor enough that several patients in this arm were considered safe for ED discharge despite the persistence of ADEs. For the two IV groups, the comparison of the numbers of changes to the infusion rate by the nursing staff may give a more accurate reflection of the relative severity of the ADEs recorded. From an ADE perspective, it appears difficult to justify the replacement of IVP with IVF for routine loading in the nonseizing ED patient. The analysis to determine which of the three loading methods studied here is superior from a pharmacoeconomic point of view will be reported separately.

The average times to safe ED discharge were calculated by determining the time at which therapeutic serum phenytoin concentrations were achieved and the time at which there were no ADEs that precluded ED discharge. However, in our study, patients were not actually discharged at these times because they remained for completion of the protocol. The derived times most closely reflect actual practice. Patients loaded using the PO technique may be discharged before completion of the entire protocol provided that therapeutic concentrations have been achieved. In contrast, patients receiving IV phenytoin must remain in the ED until the loading protocol is finished, because patients are unable to complete IV loading after discharge and also because measured concentrations achieved during IV loading may be transient and are less reflective of central nervous system (CNS) concentrations.

LIMITATIONS

One limitation of the current study may be a relatively small sample size. Another important limitation was

that although the patients were enrolled from the ED, the actual loading took place in a separate research ward. It is possible that administration of the loading doses in a more controlled setting improved the technique of loading and consequently decreased the number of ADEs. However, this argument is counterbalanced by the previous finding that ADEs with IVP are vastly underreported outside of controlled studies.³² We would not have been able to accurately quantify the full range of ADEs without the use of dedicated nursing staff.

The study was not blinded. Blinding of either the subjects or the investigators would have been difficult, if not impossible, because the three different loading techniques involve different routes of administration, and different equipment is used to administer the loading doses in the two intravenous groups. In addition, most ADEs encountered during the loading process are specific to the technique used. Bias on the part of the investigators was minimized by having the GCRC nursing staff record ADEs according to a standardized protocol.

There are other methods of loading phenytoin not included in this trial. For example, we did not use intramuscular fosphenytoin, which can be used when intravenous access is not available. Moreover, the addition of benzodiazepines to the loading protocol in patients who present with a recent seizure may further minimize the risk of a subsequent seizure before attainment of therapeutic phenytoin concentrations.

Although CNS concentrations of phenytoin might be a more accurate reflection of drug activity, these are neither available nor practical in the clinical setting. Typically, approximately 10% of the total phenytoin concentration is unbound (free fraction) and penetrates the CNS to cause clinical effects. Because the major factor influencing the percentage of free phenytoin is albumin concentration, patients with hypoalbuminemia were excluded from this study, ensuring that the serum concentrations approximate those in the CNS.

CONCLUSIONS

This study demonstrates that although therapeutic concentrations are achieved more slowly using PO

loading of phenytoin, PO loading has fewer ADEs than either IVP or IVF. The decision to use a PO or IV route, however, may involve several factors, including the need to achieve therapeutic concentrations rapidly, the availability of resources in the ED, and the cost of administration.

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