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Evaluation of phenytoin serum levels following a loading dose in the acute hospital setting

Olga Selioutski[a,*], Katherine Grzesik[b], Olga N. Vasilyeva[c], Ágúst Hilmarsson[d], A. James Fessler[a], Lynn Liu[a], Robert A. Gross[a]

[a] Department of Neurology, Strong Epilepsy Center, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[b] Department of Biostatistics, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[c] Department of Pharmacy, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[d] Landspitali University Hospital, Slettuvegi, Reykjavik, Iceland

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ABSTRACT

Purpose: Due to the complex pharmacokinetic profiles of phenytoin (PHT) and fosphenytoin (FOS), achieving sustained, targeted serum PHT levels in the first day of use is challenging.
Methods: A population based approach was used to analyze total serum PHT (tPHT) level within 2–24 h of PHT/FOS loading with or without supplementary maintenance or additional loading doses among PHT-naïve patients in the acute hospital setting. Adequate tPHT serum level was defined as ≥20 μg/mL.
Results: Among 494 patients with 545 tPHT serum levels obtained in the first 2–24 h after the loading dose (LD), tPHT serum levels of either <or ≥ 20 μg/mL were observed along wide and overlapping cumulative dose ranges. Among those receiving 15–20 mg/kg and 20–55 mg/kg weight-based loading dose, 63% and 51% respectively did not attain tPHT serum level of ≥20 μg/mL even within the first 6 h of treatment. For the 393 available concomitant free and total serum PHT levels, correlation was weak, r = 0.36.
Conclusion: Close laboratory surveillance and PHT/FOS dose adjustments are recommended to ensure adequate and sustained tPHT serum levels early in treatment. Free serum PHT level is the preferred method of drug monitoring.

1. Introduction

Phenytoin (PHT) is currently approved for treatment of generalized and focal seizures and to prevent seizures following neurosurgical procedures [1]. Fosphenytoin (FOS) is a phosphate ester prodrug developed as an alternative to parenteral PHT [2]. Rapid intravenous (IV) administration is convenient for the management of acute seizures, status epilepticus and seizure prophylaxis. Following benzodiazepines PHT/FOS are listed as second line agents for management of status epilepticus by the European Federation of Neurological Societies (EFNS) [3], Neurocritical Care Society (NCS) [4] and the American Epilepsy Society (AES) [5] with an initial recommended loading dose (LD) of PHT/FOS ranging between 15 and 30 mg/kg or phenytoin equivalents (PE) [6,7,8,9,10] with the targeted serum PHT level being ≥20 μg/mL. Despite that recommendation, the latest guideline also recommends a single dose of FOS to be capped at 1500 mg PE [5]. Moreover, in spite of widespread PHT/FOS use, there are no comprehensive guidelines on the timing of maintenance dosing (MD) initiation. Cranford et al. (1978) state that "IV administration of a single 18 mg/kg PHT dose was safe and effective in maintaining serum PHT levels above 10 μg/mL for 24 h in most participants after which an oral or IV maintenance PHT dose can be started when convenient, approximately 24 h after the infusion." Published references suggest 5 mg/kg/day dose [6] or 100 mg every six to eight hours [11].

We compared different approaches to PHT/FOS administration in the acute hospital setting by evaluating the total PHT (tPHT) serum levels obtained 2–24 h post LD. We sought to know whether in this time period different medication dosing regimens resulted in sustained tPHT serum levels ≥20 μg/mL during the first day of

Abbreviations: PHT, phenytoin; FOS, Fosphenytoin; tPHT, total serum PHT; *fr*PHT, free serum PHT; IV, intravenous; LD, loading dose; MD, maintenance dose.

* Corresponding author at: Department of Neurology, Strong Epilepsy Center, University of Rochester Medical Center, School of Medicine and Dentistry, 601 Elmwood Ave, Box 673 Rochester, NY 14642, USA.
E-mail address: olga_selioutski@urmc.rochester.edu (O. Selioutski).

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Table 1
Demographics.

Sex – Female (%)	50%
Age (years): Median (IQR; min/max)	58 (29; 6/96)
Weight (kg) Median (IQR; min/max)	75 (27; 22/159)
PHT vs. FOS used for loading dose	41(8%)/453(92%)
Loading dose (mg)	
Median (IQR; min/max)	1378 (629; 500/2614)
Mean	1356
Loading dose (mg/kg)	
Median (IQR; min/max)	19 (5; 4/31)
Mean	18
Maintenance dose (MD), Mean (mg)	112
Weight adjusted maintenance dose, Mean (mg/kg)	1.5
Additional Loading dose, Mean (mg)	931
Weight adjusted additional Loading dose, Mean (mg/kg)	11
Timing in hours of the serum lab draw following a loading dose, Mean (Min/Max)	
LD Only	7 (2/24)
LD + MD(s)	16 (5/24)
Multiple LDs	13 (2/24)
Timing in hours of the serum lab draw following last PHT dose, Mean (Min/Max)	
LD + MD(s)	5 (2/13)
Multiple LDs	7 (2/21)
Diagnoses on admission	
Known seizure disorder/Epilepsy	158
Altered mental status	42
Traumatic brain injury/Trauma	35
Intracerebral hemorrhage	34
Subdural hematoma	24
Brain mass (primary or secondary)	24
Acute stroke	19
Subarachnoid hemorrhage	15
Infectious meningitis/Encephalitis	8
Cardiac arrest	5
Epidural hematoma	4
Other medical conditions[a]	93

[a] Other conditions registered as the primary diagnosis included urinary tract infections, asphyxiation, long bone fractures, pseudo-seizure, gunshot to the abdomen, etc. See *Supplemental data* for further details and the list of secondary and tertiary diagnoses.

use. A level greater than 20 μg/mL was chosen, as it is typically desired in urgent hospital situations.

2. Methods

The study was approved by the University of Rochester Research Subjects Review Board. A retrospective automated electronic medical record (Epic) search identified 1361 PHT-naïve patients admitted between March of 2011 and August of 2015 who received a PHT/FOS dose of 500 mg or more and subsequently had a tPHT serum level drawn. Five hundred milligram cut off dose was used to include children into the analysis. The laboratory analysis of tPHT serum levels was not performed at predetermined time points but was obtained as clinically indicated pending availability of a laboratory technician. Patients were excluded if they did not have tPHT serum levels within 24 h of dosing, were on PHT prior to admission, or had tPHT serum levels measured within the first two hours of medication administration. Patients with extreme outlying laboratory values or those with clear documentation errors were also excluded (tPHT levels >70 μg/mL or undetectable levels, multiple simultaneously recorded LDs, PHT LD not recorded, or clinically obvious errors such as an adult patient with a weight listed as <4 kg). When a patient had more than one tPHT[1] serum level drawn within a 24 h period, the laboratory values were included for analysis only if maintenance or a second loading dose was given prior to the second tPHT serum level draw. There were a total of 494 patients with 545 available tPHT serum level measurements for the primary end point analysis. The laboratory data were divided into three groups based on the PHT/FOS dosing regimens. The first group consisted of patients with tPHT serum levels drawn following a single Loading Dose (LD only, N = 355). The second group consisted of patients with tPHT serum levels drawn following a LD and supplemented by a Maintenance Dose(s) [LD+MD(s)], (N = 137). The last group consisted of patients with tPHT serum levels obtained after an additional LD (defined as at least 350 mg of PHT/FOS) (N = 53).

We hypothesized there would be a strong relationship between the cumulative weight-adjusted PHT/FOS dose and the tPHT serum level. To test this hypothesis we further subdivided each group into [3-15) mg/kg, [15-20) mg/kg, or [20- 55) mg/kg subgroups based on the cumulative weight-based PHT/FOS dose administered prior to the blood draw. Three hundred and ninety-three concomitant free and total serum PHT levels were available from 344 patients for an additional analysis.

The weight on admission was converted to kilograms (kg). Timing of obtaining serum tPHT level is presented in hours (h) following the first LD administration. The medication loading dose was calculated based on recorded weight and presented in mg/kg for PHT and mg/kg PE for FOS. The serum PHT levels were reported in micrograms per milliliter (μg/mL). ANOVA supplemented by the Tukey's test for differences and correlation analysis were applied for statistical assessment of numerical data. The Kruskal-Wallis Rank Sum test was performed to analyze the association of ordinal

[1] Total serum phenytoin level (tPHT).