

Title: Population Pharmacokinetics of Unbound Phenytoin after Administration of IV Fosphenytoin And Oral Phenytoin in Pediatric Patients.

Author:

Saikumar Matcha¹

Surulivelrajan Mallayasamy¹

Vijay Ivaturi²

Brady S Moffett^{3,4}

1. Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India.
2. Department of Pharmacy Practice and Science, Center for Translational Medicine, University of Maryland School of Pharmacy, Baltimore, Maryland, USA.
3. Department of Pharmacy, Texas Children's Hospital, Houston, Texas, USA.
4. Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA.

Introduction:

Phenytoin is a widely used narrow therapeutic window anti-epileptic drug (1). Total and unbound plasma concentrations of phenytoin have to be maintained within 10 – 20 mcg/ml and 1 – 2 mcg/ml range (2). Published pharmacometric models used total phenytoin concentrations for dosage regimen decisions (3, 4). It is important to consider unbound phenytoin concentrations, as free drug describes pharmacological effects better (5,6). However, very few models based on unbound concentrations are available in the literature.

Objectives:

- I. To build a population pharmacokinetic model using total and unbound phenytoin concentrations.
- II. To externally validate the developed model with the previously published models and data.

Methods:

A retrospective longitudinal observational study was performed in Texas Children's hospital, U.S.A. to collect pharmacokinetic data from routine clinical care. A total of 167 subjects who matched the inclusion criteria were recruited into the study. Fosphenytoin IV and Phenytoin oral doses were given as loading and maintenance doses. Blood samples were collected at random times as part of routine clinical care that cover most of the time points between C_{max} and C_{min}. Potential demographic & clinical covariates were collected and tested in PopPK model. Pumas 2.0 (Pumas-AI, Baltimore) was used to model the data (7).

Results:

A total of 356 unbound phenytoin concentrations from 134 subjects were used for model building. Subject's age and body weight ranged from 1 day to 18 years and 2.5 kgs to 86 kgs respectively. A one-compartment open model best described pharmacokinetics of unbound phenytoin. The following covariate effects were evaluated using a full covariate model

approach: body weight and albumin levels on volume of distribution, body weight and serum creatinine, age, and gender on clearance. $P < 0.03$ was considered as significant value to consider the covariate effects. Log likelihood ratio test was used to consider the better model. Allometrically scaled weight was found to impact clearance (CL) and volume (V) parameters based on posterior distribution of covariate effects. Absorption rate constant (K_a) and bioavailability (F) were fixed to literature values. The estimates of the PK parameters were $V = 157.34 \text{ L/15kg}$; $CL = 3.83 \text{ L/hr/15kg}$; $K_a = 0.225/\text{hr}$, $F = 0.63$. Between subject variability (BSV) on V and CL was estimated as 46 % & 60 %. Proportional residual error was 33%. Correlation factor between total and unbound phenytoin concentrations was estimated as 8.15. BSV an residual error of correlation factor was estimated as 14% and 29%. Estimated PK parameters were comparable with the published literature of total and unbound phenytoin PK. Current model has been successfully validated with the external data & publications of total and unbound phenytoin with a mean prediction error of less than 20%.

Conclusion:

One compartmental open model with allometric scaling best described the pharmacokinetics of unbound phenytoin and total phenytoin. This model was validated with external data.

Reference:

1. Patocka J, Wu Q, Nepovimova E, Kuca K. Phenytoin—An anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. *Food and Chemical Toxicology*. 2020 May 4;111:393.
2. Phenytoin drug information, IBM Micromedex. Available at : [Drug Result Page - Quick Answers - Medication Safety - Monitoring \(micromedexsolutions.com\)](https://www.micromedex.com/quickanswers/medication-safety-monitoring/micromedexsolutions.com). accessed on 17th April 2021.
3. Tanaka J, Kasai H, Shimizu K, Shimasaki S, Kumagai Y. Population pharmacokinetics of phenytoin after intravenous administration of fosphenytoin sodium in pediatric patients, adult patients, and healthy volunteers. *European journal of clinical pharmacology*. 2013 Mar;69(3):489-97.
4. Moffett BS, Weingarten MM, Schmees LR, Galati M, Erklauer J, Riviello JJ. Fosphenytoin population pharmacokinetics in the acutely ill pediatric population. *Pediatric Critical Care Medicine* | Society of Critical Care Medicine. 2018 Aug 1;19(8):748-54.
5. Burt M, Anderson DC, Kloss J, Apple FS. Evidence-based implementation of free phenytoin therapeutic drug monitoring. *Clinical chemistry*. 2000 Aug 1;46(8):1132-5.
6. Hennig S, Norris R, Tu Q, van Breda K, Riney K, Foster K, Lister B, Charles B. Population pharmacokinetics of phenytoin in critically ill children. *The Journal of Clinical Pharmacology*. 2015 Mar;55(3):355-64.
7. Rackauckas, Chris, Yingbo Ma, Andreas Noack, Vaibhav Dixit, Patrick Kofod Mogensen, Simon Byrne, Shubham Maddhashiya, et al. "Accelerated Predictive Healthcare Analytics with Pumas, a High Performance Pharmaceutical Modeling and Simulation Platform." *BioRxiv*, November 30, 2020, 2020.11.28.402297. <https://doi.org/10.1101/2020.11.28.402297>