Population Pharmacokinetics of Phenytoin in Patients with Traumatic Brain Injury

Kansinee Srisaeng[1,2*], Juntip Kanjanasilp[1], Peeraya Sriphong[1], Chumlong Kittivaravach[3] and Prawatwong Wongsrikaew[3]

[1]Faculty of Pharmacy, Mahasarakham University, Maha Sarakham 44150, Thailand
[2]Pharmacy Department, Sunpasitthiprasong Hospital, Ubon Ratchathani 34000, Thailand
[3]Neurosurgery Department, Sunpasitthiprasong Hospital, Ubon Ratchathani 34000, Thailand

**Corresponding author. E-mail: yingkans@gmail.com*

ABSTRACT

This study investigated the pharmacokinetic parameters of intravenous phenytoin in patients with early traumatic brain injury. Routine clinical pharmacokinetic data were obtained from 122 patients, aged 12-79 years old, admitted to the neurotrauma ward, at Sunpasitthiprasong Hospital, Thailand. Three plasma samples per patient were collected during Days 3-7 after receiving phenytoin. We investigated the factors influencing the pharmacokinetics of intravenous phenytoin, including demographic, clinical, pathological, and surgical treatment data. The data were analyzed using NONMEM and the final model was validated using a nonparametric bootstrap technique and a visual predictive check (VPC). A one-compartment model with Michaelis-Menten elimination adequately described the data. Actual body weight (ABW) was the only variable that affected the Michaelis-Menten constant (Km). The final model parameters were: Km = 4.34 mg/L*(1-0.026*(ABW-57)), Vmax = 8.76 mg/kg/day and Vd = 0.719 L/kg; the bootstrap and VPC results were satisfactory.

Keywords: Phenytoin, NONMEM, Traumatic brain injury, Population pharmacokinetics, Post-traumatic epilepsy

INTRODUCTION

Post-traumatic seizure causes secondary brain injury, contributing to morbidity and mortality after traumatic brain injury. Post-traumatic epilepsy is defined as a recurrent seizure disorder due to traumatic brain injury (Khan and Benerjee, 2010). It has become an important clinical problem related to head injury in many countries (Beghi, 2003). Post-traumatic epilepsy can be divided into three groups: immediate seizure, occurring within 24 hours of injury; early seizure, occurring within 7 days of injury; and late seizure, occurring more than 7 days after injury (Garga and Lowenstein, 2006; Gupta and Gupta, 2006; Khan and Benerjee, 2010). Immediate and early seizures are believed to have a different