Optimal dosing regimen design of phenytoin for Korean epilepsy patients: from premature baby to the elderly.

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Objectives: With the development of new effective antiepileptic agents, the use of phenytoin has kept decreasing. Large inter-individual variability and narrow therapeutic range in drug concentration is another reason for decrease in phenytoin use. However, phenytoin is still an essential agent for second-line treatment of status epilepticus. In this study, model-based dose individualization scheme is proposed as a tool to overcome such limitation with phenytoin use, with an application to Korean clinical population.

Methods: A total of 188 concentration samples obtained from 117 patients after i.v. infusion of phenytoin were collected from Electronic Medical Records of Severance Hospital (Seoul, Republic of Korea). One and two compartment models with first-order or Michaelis-Menten elimination were examined. Gender, postmenstrual age (or age), albumin level, AST/ALT ratio, and co-medication history were tested as potential covariates. Then, simulation was performed for each of pediatric and adult patients, using various combinations of dose amounts and covariates selected. All analyses were done using NONMEM 7.3.0 and R 3.2.0.

Results: One compartment model with first-order elimination with weight included via allometric scaling best described the data with reasonable precision of parameter estimates. For the weight of 60kg, volume of distribution and clearance was 68.19 (L) and 0.63 (L/h), respectively. Postmenstrual age (or age) and albumin levels were significant covariates of clearance, which was a physiologically reasonable result. Simulation results suggested shorter dosing interval for neonate to infant, 1.5 to 2.0 fold higher maintenance doses for obese patients, and a loading dose of 19–23mg/kg for adult populations.

Conclusions: For the influence of hypoalbuminemia on the optimal dose, further studies are needed because of insufficient data in this study. Nevertheless, this study will be a good example to illustrate an application of pharmacometrics method to optimal dosage regimen design of phenytoin with routine clinical data.