Poster

[P26-1] P26-1: Anticonvulsant drugs

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[P26-1-9] Population pharmacokinetic analysis of phenytoin after intravenous administration of fosphenytoin in Japanese epileptic patients

Daiki Yamashita[1], Departmentof Hospital Pharmacy[2], Makoto Kakara[3], Yushi Kashihara[4], Takeshi Hirota[5], Masaaki Hirakawa[6], Ichiro Ieiri[7] (1.Fukuoka Tokushukai Medical Center, 2.Kyushu University, 3.Kyushu University, 4.Kyushu University, 5.Kyushu University, 6.Fukuoka Tokushukai Medical Center, 7.Kyushu University)

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Background

Fosphenytoin was developed as a phenytoin pro-drug to improve the low solubility of phenytoin injection, which is used for the treatment of seizures, such as those in status epilepticus. Although many population pharmacokinetic (PPK) analyses have been done for phenytoin itself, there have been few reports regarding phenytoin converted from fosphenytoin in Japanese patients. The aim of this study was to perform a PPK analysis of phenytoin after intravenous administration of fosphenytoin in Japanese epileptic patients.

Methods

Patients (n = 173), who received fosphenytoin (Fostoin®, Nobelpharma) intravenously, were enrolled. Information on patient backgrounds, laboratory tests, and prescribed medicines was collected retrospectively from electronic medical records available at the Fukuoka Tokushukai Medical Center (Fukuoka, Japan). Patients backgrounds (gender, age, and body weight), laboratory tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, albumin, blood urea nitrogen, and serum creatinine), and co-administered medicines (valproate, carbamazepine, warfarin, zonisamide, amiodarone, allopurinol, diltiazem, and clobazam) were selected as candidates for the covariates. The significant levels for forward inclusion and backward elimination were set at 0.01 and 0.001, respectively. The adequacy of the constructed PPK model was assessed using goodness-of-fit (GOF) plots and a bootstrap analysis. The PPK analysis was performed using NONMEM 7.3 with the first-order conditional estimation method with interaction (FOCE-INTER). The study protocol was approved by the Fukuoka Tokushukai Ethics Committee (ethics approval number 280307).

Results

A linear one-compartment model with conversion of fosphenytoin to phenytoin described the pharmacokinetics of phenytoin after intravenous administration of fosphenytoin. The pharmacokinetic parameters of phenytoin such as total clearance (CL) and central volume of distribution (Vd) were influenced by body weight. The regression equations for each parameter in the final model were CL (liter/h) = 2.17 × (body weight/52.4)$^{0.826}$ and Vd (liter) = 72.2 ×(body weight/52.4)$^{1.10}$. The rate constant of conversion of fosphenytoin was estimated as 0.814 /h. GOF plots showed good predictive performance of the final model, and systematic deviations were not observed.

Conclusions

The pharmacokinetics of phenytoin after intravenous administration of fosphenytoin could be described using a linear one-compartment model.