Poster

## [P26-2] P26-2: Central nervous system drugs (1)

Chair: Atsushi Yonezawa, Japan

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# [P26-2-3] Population pharmacokinetic modeling and simulation of topiramate using the routinely monitored data for the individualized dosage adjustment

Masato Takeuchi[1], Ikuko Yano[2], Satoko Ito[3], Mitsuhiro Sugimoto[4], Shota Yamamoto[5], Atsushi Yonezawa[6], Akio Ikeda[7], Kazuo Matsubara[8] (1.Kyoto University Hospital, 2.Kobe University Hospital, 3.Kyoto University Hospital, 4.Kyoto University Hospital, 5.Kyoto University Hospital, 6.Kyoto University Hospital, 7.Kyoto University Graduate School of Medicine, 8.Kyoto University Hospital)

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### Background

Topiramate is a second-generation antiepileptic drug used as monotherapy and adjunctive therapy in adults and children with for partial seizures, and the usefulness of topiramate TDM has not been established. In this study, we aimed to identify potential covariates for the individualized therapy of topiramate by population pharmacokinetic (PPK) modeling and simulation approach using routinely monitored serum concentration data.

and to develop a PPK model of topiramate using routinely monitored serum concentration data from patients with epilepsy of different ages (including pediatric and adult patients). In addition, to improve the individualized dose regimen of topiramate, a simulation study based on the obtained PPK model was conducted.

### Methods

Japanese pediatric and adult pPatients whose steady-state serum concentration of topiramate was routinely monitored at Kyoto University Hospital from April 2012 to March 2013 were included in the model-building data. A nonlinear mixed effects modeling program (NONMEM) was used to evaluate the influence ofextract significant covariates on topiramate pharmacokinetics. The obtained population pharmacokinetic PPK model was evaluated by internal validation as well as goodness-of-fit plots, prediction corrected visual predictive check and external validation using validation data from January 2015 to December 2015. Effects of each covariate were evaluated by the simulation study.
, and then the simulation for dosage adjustment was performed based on the final model.

### Results

A total of 177 steady-state serum concentrations from 93 patients were used for the model-building analysis analysis. The patients’ age ranged from 2 to 68 years, and body weight ranged from 8.6 to 105 kg. The median serum concentration of topiramate was 1.7 g/mL, and half of the patients received carbamazepine co-administration. Based on a one-compartment model with first order absorption and elimination, the apparent volume of distribution was 1.505 L/70 kg, and the apparent clearance was allometically related to the body weight as 2.25 L/h/70 kg with interindividual variability of 28.3%. Combination treatment therapy with carbamazepine or phenytoin increased the apparent clearance by by 1.56 times3.51 L/h/70 kg. Goodness-of-fit plots, prediction corrected visual predictive check, and external validation confirmed an

appropriateness of the final model. The sSimulations based on the final model showed that dosage adjustments considering based on the allometrically scaled body weight and concomitant antiepileptic drug are effective to reach a similar concentration range in each individual.was necessary.

## Conclusions

The pPPK opulation pharmacokinetic modeling and simulation approach using routinely obtainable data is valuable to know pharmacokinetic characteristics and dosage adjustment indexes in real clinical settings. using the power scaling of body weight effectively elucidated the topiramate serum concentration profile ranging from pediatric to adult patients. Dosage adjustments based on body weight and concomitant antiepileptic drug (AEDs) help obtain the dosage of topiramate necessary to reach an effective concentration in each individual.