Poster

# [P26-1] P26-1: Anticonvulsant drugs

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## [P26-1-7] A population pharmacokinetic-pharmacodynamic analysis of valproic acid in pediatric patients with epilepsy

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### Background

Valproic acid (VPA) is one of the most widely prescribed antiepileptic drugs (AEDs) for the treatment of both generalized and partial seizures because of its multiple mechanisms of action and acceptable safety profile. Although it is well known that the doses of VPA and its plasma concentrations are highly correlated, the plasma concentrations do not correlate well with the therapeutic effects of the VPA. In this study, we developed a population-based pharmacokinetic (PK)-pharmacodynamic (PD) model of VPA in pediatric patients with epilepsy.

### Methods

This retrospective study included 77 VPA treated Japanese pediatric patients with epilepsy. A nonlinear mixed-effects model best represented the relationship between the trough concentrations of VPA at steady-state and an over 50% reduction in seizure frequency.

### Results

The model was fitted using a logistic regression model, in which the logit function of the probability was a linear function of the predicted trough concentration of VPA. The model showed that the age, seizure locus, the sodium channel neuronal type I alpha subunit rs3812718 polymorphism and co-administration of carbamazepine, clonazepam, phenytoin or topiramate were associated with an over 50% reduction in the seizure frequency. We plotted the receiver operating characteristic (ROC) curve for the logit(Pr) value of the model and the presence or absence of a more than 50% reduction in seizure frequency, and the areas under the curves with the 95% confidence interval from the ROC curve were 0.823 with 0.793–0.853. A logit(Pr) value of 0.1 was considered the optimal cut-off point (sensitivity = 71.8% and specificity = 80.4%), and we calculated the optimal trough concentration of VPA for each patient.

### Conclusions

This study makes it possible to evaluate the optimal concentration of VPA to achieve reductions in the seizure frequency for each patient using a population PK-PD modeling approach. The procedure may be useful to determine the recommended therapeutic concentration of AEDs for each patient, and may contribute to the further development of personalized pharmacological therapy, although a prospective study in a larger patient cohort is necessary to evaluate the predictive capacity of this model.