Prediction accuracy of amikacin population pharmacokinetic models in Japanese pediatric patients. Okada K, Ikari Y, Kobayashi Y, Yoshikado T, Oka M, Chiba K, Laboratory of clinical pharmacology, Yokohama University of Pharmacy

Background: Therapeutic drug monitoring is widely recommended for determining amikacin (AMK) serum concentrations in patients. Although many population pharmacokinetic (PPK) models have been reported for monitoring AMK serum concentrations, no studies have used such models in Asian pediatric patients. The purpose of this study was to conduct a comprehensive search for previous, clinically useful, PPK models for the monitoring of AMK concentrations in Japanese pediatric patients. As part of this study, we used Bayesian estimation to evaluate the applicability and the predictive accuracy of three AMK pediatric PPK models reported by Alqahtani (*Paediatr Drugs.*, 2018), Amponsah (*Curr Ther Res Clin Exp.*, 2017), and Alhadab (*Antimicrob Agents Chemother.*, 2018) , in which weight was the only covariate.

Methods: Serum concentrations of AMK were obtained from 45 Japanese pediatric patients at 228 timepoints from previous reports (Iwai N, *Jpn J Antibiot.*, 1987). The three AMK pediatric PPK models were reconstructed using NONMEM. Alqahtani's and Amponsah's models were developed according to a 1-compartment model while Alhadab's model was developed according to a 2-compartment model. Empirical Bayesian estimation was performed to evaluate the accuracy of the models for predicting AMK serum concentrations. A prediction-corrected visual predictive check was performed and prediction accuracy was calculated.

Results: The AMK serum concentrations at 228 timepoints were generally within the 90 percentile interval in Alqahtani's model, indicating that the Alqahtani's model was the most applicable for modeling AMK serum concentrations in Japanese pediatric patients. Of the three models, Alhadab's model had the smallest relative mean square error (%) (20.5%), suggesting that it had the best predictive accuracy. Conversely, in the higher concentration region, Alqahtani's and Amponsah's PKK models predicted values that were different from the reported values. A peripheral compartment was considered necessary to describe the distribution characteristics of AMK in young pediatric patients. For neonates, infants and children, Alhadab's method appears to have better predictive accuracy, while for school-age children, Alqahtani's model is better.

Conclusion: The Alhadab model is a clinically useful model for predicting AMK serum concentrations in Japanese pediatric patients.

Key Words; amikacin, pediatric, neonate, infant, population pharmacokinetic