Oral

[O25-8] O25-8: Infections in pediatrics

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[O25-8-3] Population pharmacokinetic-pharmacodynamic modeling and simulation of imipenem for dosing optimization in pediatric patients

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Background

Imipenem has been used since 1980s as the first carbapenem antibiotic. However, its pharmacokinetic (PK)-pharmacodynamic (PD) profiles in neonates and children populations has not yet been characterized. This study performed population PK-PD target attainment analysis of imipenem in pediatric patients to rationalize and individualize dosing regimens.

Methods

PK data were obtained from 15 study reports. Population PK models were separately developed in neonates and children by simultaneously fitting plasma and urine data from 60 neonates (0–0.0932 years) and 39 children (3.00–16.2 years). The developed models were then used to estimate the probability of attaining the PD target (40% of the time above the minimum inhibitory concentration [40% free T >MIC]) against MIC distribution data obtained from European Committee on Antimicrobial Susceptibility Testing. Another PD simulation with an *in vitro* dynamic model was conducted to verify the target-attainment-probability results.

Results

The PK data were best described by a 1-compartment model in neonates (335 plasma and 108 urine data) and a 2-compartment model in children (230 plasma and 155 urine data), respectively. Renal clearance in children (0.187 L/h/kg) was double that of neonates (0.0783 L/h/kg), whereas the volume of distribution at steady-state was approximately 1.8-fold larger in neonates (0.466 L/kg) than in children (0.260 L/kg). Age was not a statistically significant covariate in the PK of both groups. Infusions (0.5 h) of 15 mg/kg every 8 h (45 mg/kg/day) and 25 mg/kg every 12 h (50 mg/kg/day) were shown to be sufficiently bactericidal against common clinical isolates of *Escherichia coli*, *Haemophilus influenza*, methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae*. However, 1.5-h infusions of 25 mg/kg every 8 h (75 mg/kg/day) in neonates and 25 mg/kg every 6 h (100 mg/kg/day) in children were needed to be effective against *Pseudomonas aeruginosa* isolates. These PK-PD results were supported by the simulation with *in vitro* dynamic model.

Conclusions

The results of this study explain the changes in imipenem PK profiles during the human growth process. The results also provide guidance for optimizing imipenem regimens in each pediatric age group, according body weight of a patient and susceptibility of a presumed pathogen.