Abstract for IATDMCT2024, Banff, Canada, September 15-18, 2024

PK/PD modeling of amoxicillin/clavulanic acid *in vitro* effects on bacterial growth and killing and *in vivo* exposure evaluation in young pediatric patients.

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Background: Amoxicillin/clavulanic acid is currently the most effective antimicrobial for the treatment of children with recurrent acute otitis media. A lower dose of clavulanic acid than currently used may be associated with fewer side effects without compromising clinical efficacy. In this study, we employed a model-informed approach to estimate amoxicillin/clavulanic acid exposure in middle ear fluid (MEF) to evaluate the validity of reduced clavulanic acid dose based on *in vitro* exposure-response data.

Methods: Previously developed and qualified pediatric population PK models[1] for oral amoxicillin/clavulanic acid were employed using NONMEM to simulate drug exposures in plasma and MEF for the reduced amoxicillin/clavulanic acid doses (45/1.425 mg/kg) administered every 12 hours. A virtual pediatric population (age range of 3-24 months) was generated for simulations using publically available data from the NHANES database. Drug concentrations in MEF were determined based on plasma concentrations with the penetration ratio of amoxicillin from plasma to MEF (36.9% from the Augmentin ES-600 package insert). Exposure-response analysis was performed using *in vitro* bacterial growth and killing data against five different isolates of *Haemophilus influenzae* to determine effective AUC metrics to be compared with the simulated amoxicillin/clavulanic acid exposures in MEF.

Results: The model-informed simulations provided both plasma and MEF concentration-time profiles for amoxicillin/clavulanic acid. The simulated mean AUC in MEF was 48.0 mg*h/L for amoxicillin and 1.59 mg*h/L for clavulanic acid. With *in vitro* exposure-response analyses, the mean $EAUC_{50}$ ($AUC_{0\text{-}24}$ to reduce bacteria by 50%) and $AUC_{0\text{-}24h}$ achieving 1- and 2-log10 CFU/mL reductions were determined as 0.68, 3.87, and 5.40 mg*h/L, respectively. The simulated mean $AUC_{0\text{-}24h}$ in MEF for the reduced dose exceeds $EAUC_{50}$ for all isolates and exceeds the $AUC_{0\text{-}24h}$, achieving 1-log 10 CFU/mL reduction against the isolate with a minimum inhibitory concentration of 0.5 mg/L.

Conclusions: The combination of model-informed simulations and exposure-response analyses indicates that the reduced clavulanic acid dose could provide effective drug exposure in MEF while mitigating the risk of toxicity.

Reference:

[1]Fukushima K, et al. Pediatric population pharmacokinetic model development for oral amoxicillin and clavulanic: leveraging literature data for model-informed drug exposure analysis in young children. Clin Pharmacol Ther, 113(2), 762-7 (2023).

318/350 words