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Paper Poster Session
Late breaker session: Other

Pharmacokinetic-pharmacodynamic modelling of meropenem in plasma and cerebrospinal fluid (CSF) in infants with late-onset sepsis and/or bacterial meningitis

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Background: Meropenem is used off-label in the treatment of neonatal late-onset sepsis (LOS) and bacterial meningitis. We aimed to develop a population PK model of meropenem in plasma and CSF, and then use it to investigate the influence of different dosing regimens by performing simulations and examining the probability-of-target-attainment (PTA) curves in infants aged <3 months.

Material/methods: Data were collected from infants aged <90 days with LOS and/or meningitis (trial: NCT01551394). Meropenem was given at 20mg/kg (LOS) or 40mg/kg (meningitis) as a 30-minute infusion every 8 hours, or every 12 hours in infants <32 weeks gestational age (GA) and <2 weeks postnatal age (PNA). Plasma/CSF concentrations were determined using UHPLC-MS/MS. PK data were modelled using non-linear mixed-effects (NONMEM 7.3). A CSF compartment was added and CSF penetration was estimated as a model parameter. Monte Carlo simulations (n=1000) for several dosing regimens (i.e. different infusion lengths, and dosing frequency) and 8 MIC values (range: 0.25-32 mg/L) were used to generate the PTA curves for 40%, 70%, and 100% time above MIC (t>MIC).

Results: PK samples (401 plasma and 78 CSF) were obtained from a total of 167 infants, with median (range) GA of 33.3 (22.6-41.9) weeks, and PNA of 13 (1-90) days at enrolment. The final model was a one-compartment model, where allometric weight scaling with a postmenstrual-age-driven maturation function was used a priori. Serum creatinine proved a significant covariate on clearance (CL), but PNA was not significant. CSF protein concentration significantly affected meropenem CSF penetration. The values of meropenem CL and central volume of distribution for a typical infant were 0.48 L/h and 1.18 L, respectively; and meropenem CSF/blood concentration ratio was 0.1. Monte Carlo simulations showed that bolus administration (i.e. a 1-minute infusion) gave the same percentages of t>MIC as the 30-minute infusion, regardless of the PTA target. Using longer infusion times or continuous infusion resulted in improved target attainment in plasma (for 40% and 70% t>MIC), but the PTA for CSF decreased. Conversely, when inspecting the cumulative t>MIC at 24 hours, bolus given more frequently (i.e. 4- or 6-times daily) resulted in increased PTA in both plasma and CSF, for 20mg/kg and 40mg/kg regimen. Simulating decreased renal function (expectedly) resulted in higher PTA.

Conclusions: Simulations showed that dosing regimens used in the study for LOS and meningitis in infants aged <3 months are appropriate if MIC <4mg/L (LOS) or <1mg/L (meningitis), for a target of 40% t>MIC. However, to achieve higher t>MIC targets for higher MIC values (using the same unit dose), dosing intervals should be shortened.

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