O157

1-hour Oral Session

Simulation-based evaluation of PK/PD indices for meropenem across patient groups and experimental designs

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Objectives

PK/PD indices are commonly used to set dosing of antibiotics. An underlying assumption is that the type and magnitude of the index is stable across widely different pharmacokinetic (PK) profiles. Additionally, the results are generally assumed to be non-critical to experimental design and uncertainty in the MIC. This work aims to evaluate the appropriateness of these assumptions by simulating PK/PD indices for meropenem in different patient groups and experimental settings using mechanism-based pharmacokinetic-pharmacodynamic (PKPD) -models.

Methods

A mechanism-based PKPD-model for meropenem and *Pseudomonas aeruginosa* (ATCC27853, MIC 1.6 mg/L and L0603761, MIC 16 mg/L) was developed based on 45 static time-kill curve experiments and used in the simulations. A previously published pre-clinical dose fractionation study1 was replicated in simulations using a mouse PK model2. The sensitivity towards uncertainty in the MIC value (MIC x 0.5 and 2), differences in experimental design (dose range and dosing intervals) and the type and magnitude of the PK/PD index to different human PK profiles (adult3, renal failure3 (RF) and neonatal4) was investigated.

Results

The final PKPD model described the data well and explained regrowth after antibiotic exposure by a pre-existing resistant subpopulation. The stationary phase was modelled as a transfer to a non-growing resting state at high bacterial densities5. As expected, *f*T>MIC was the index with highest predictive value when replicating a murine dose fractionation study. However, when the dosing frequency was increased in the design, the *f*AUC/MIC was found to be more predictive than *f*T>MIC. Furthermore, the magnitude of the index was highly sensitive to uncertainty in MIC with around 7 % greater T>MIC required for 2-log kill when simulated with 0.5 x MIC compared with 2 x MIC. For a typical human PK profile (terminal half-life (t1/2) = 0.6h), *f*T>MIC was selected as the best predictor, however, with extended t1/2 (1.5 h) for RF and neonatal PK the predictive value of *f*AUC/MIC was greater.

Conclusion

A mechanism-based PKPD model successfully predicted the previously determined pre-clinical *in vivo* PK/PD index for meropenem. The type and magnitude of the index was sensitive to experimental design and to misspecification of the MIC. In addition, based on the simulations, the PK/PD index in humans is expected to be PK dependent. In conclusion, using mechanism-based PKPD models in dose selection may offer increased robustness and better extrapolation potential, especially for special patient populations.

References

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