*Population Pharmacokinetic Modelling*

To describe tobramycin concentrations, various compartmental models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the freely available Pmetrics software package for R (Los Angeles, CA).(1, 2) Distribution and elimination parameters were modelled as first-order processes. Discrimination between different models used comparison of the -2 log likelihood (-2LL). Error=SD\*gamma was the structure of the error model, where SD is standard deviation of each observed concentration, and gamma is the unexplained process noise related to the observed concentrations. A p-value of <0.05 was considered statistically significant. Goodness- of- fit was assessed by linear regression, with an observed-predicted plot, coefficients of determination, and log-likelihood values. Predictive performance was evaluated based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models. The internal validity of the population pharmacokinetic model was assessed by the bootstrap resampling method (n=1000) and normalized prediction distribution errors (NPDE). (3) Using a visual predictive check (VPC) method, parameters obtained from the bootstrap method were plotted with the observed concentrations. NPDE plots were examined for normal distribution characteristics and trends in the data errors.

Using the posterior parameter estimates from the final model, area under the concentration time curve (AUC) was calculated in the plasma, epithelial lining fluid (ELF) and interstitial fluid (ISF) compartments. Drug penetration into ELF and ISF of lung was then estimated relative to AUC of the central (plasma) compartment.

References

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