PK/PD Indices of Antibiotics Predicted by Mechanism-based PKPD Models

Elisabet I Nielsen[1,2]*, Otto Cars[3], Lena E Friberg[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University; [2]Hospital Pharmacy, University Hospital;
[3]Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden

CONCLUSIONS

- Predictions from PKPD models based on in vitro experiments could identify the previously established PK/PD indices for six commonly used antibacterial agents, with predicted magnitudes for the effect similar to those observed in patients.
- The selection and magnitude of the PK/PD indices were however shown to be sensitive to study design and not always consistent between patient sub-populations with different PK profile. The PK/PD indices might therefore extrapolate poorly.
- This study supports that PKPD models based on in vitro studies are predictive of antibacterial effects observed in vivo and that a model-based strategy may have more predictive value than the PK/PD indices in the development of dosing regimens.

Background and Objectives

Dosing regimens of antibiotics are generally based on summary endpoints such as the PK/PD indices. These indices relates the drug exposure to the minimum inhibitory concentration (MIC) and includes C_{max}/MIC, AUC/MIC and the percent of a 24 hr time period that the drug concentration exceeds the MIC ($T_{>MIC}$).

Lately, mechanism-based PKPD models based on in vitro data have gained increased interest as they provide for a quantitative description of the multiple processes that occurs within a bacterial system. However, before these PKPD models can be fully utilized, it should be confirmed that predictions based on the models are in agreement with previously determined PD characteristics (i.e. the PK/PD indices).

The aim of this study was to perform predictions from PKPD models developed based on in vitro data and evaluate their capability in identifying the currently used PK/PD indices and the magnitudes of the selected PK/PD indices required to achieve a bacteriostatic and bactericidal effect.

Material and Methods

- Six antibacterial drugs were investigated
- For each drug, a dose fractionation study was simulated, using a wide range of total daily doses ($Cu_{ss,av}$ 0.0078-256xMIC) given as intermittent doses (tau 4, 8, 12, 24 hrs) or as a constant drug exposure
- PK models were taken from the literature
- Previously developed PKPD models (Fig. 1, [1-3]) were used to predict the bacterial killing kinetics following the different dosing regimens
- Non-linear least squares regression analyses determined the PK/PD index (C_{max}/MIC, AUC/MIC, or $T_{>MIC}$) being most predictive of the effect, with bacterial count at 24 hrs as default PD endpoint
- The sensitivity in the selection and magnitude of the PK/PD index towards factors such as different PK profiles, study design, uncertainty in MIC, and choice of PD endpoint were also investigated

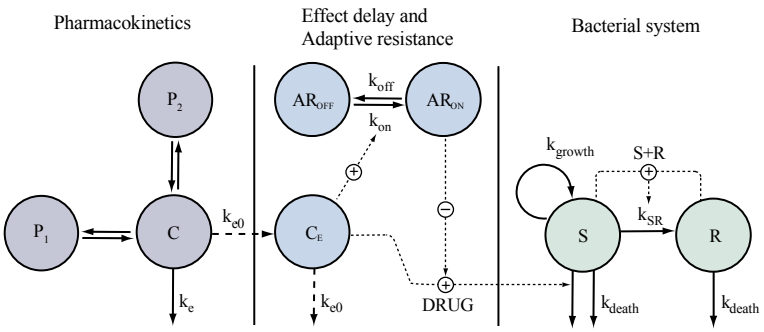

Figure 1. Schematic illustration of the full semi-mechanistic PKPD model.
To explain the biphasic killing behavior and the reduced growth rate and drug-susceptibility at high bacteria levels the total bacterial population was in the model divided into two subpopulations, one growing drug-susceptible population (S) and one resting drug-insensitive population. (R) For gentamicin, the model was modified to also include a binding (inhibitory) component (AR_{OFF} and AR_{ON}) in order to describe the reduced drug sensitivity due to adaptive resistance.

Results

In accordance to previous findings, $T_{>MIC}$ was the PK/PD index identified to be best correlated to the PD endpoint for the two β-lactam antibiotics while AUC/MIC was the best predictor of the effect for the remaining four antibacterial drugs (Fig. 2). Further, the estimated magnitudes of the PK/PD index required for efficacy corresponded well with those earlier observed clinically.

The selection and magnitude of the PK/PD index were shown to be sensitive to:

- **PK profile in the study population**: when decreasing the rate of elimination to mimic patient groups with lower clearances, the AUC/MIC became a universal predictor of the effect (Fig. 3)
- **Study design**: when excluding long dosing intervals (i.e. 12 and 24 hrs), AUC/MIC became a universal predictor of the effect
- **Poor precision in MIC value**: the correlation between the $T_{>MIC}$ and the effect was highly dependent on the MIC

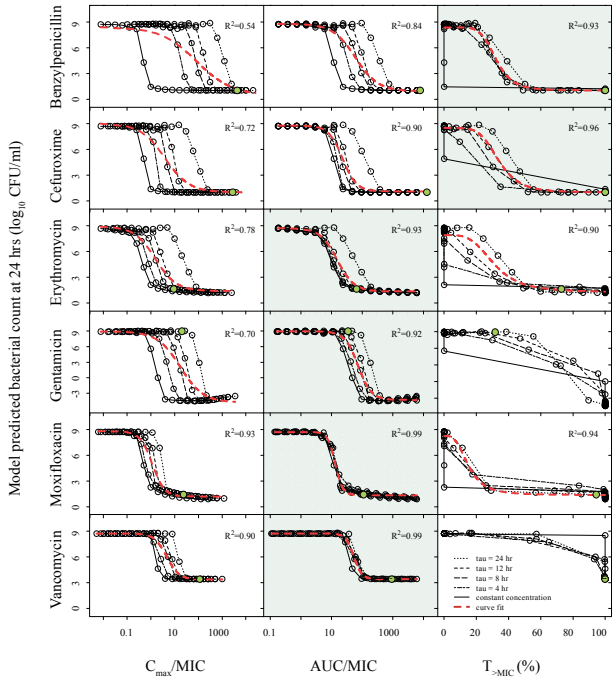

Figure 2. Relationship between model-predicted bacterial count at 24 hrs and the PK/PD indices simulating the **PK profile of adults.**
Shaded area indicates the PK/PD index with the best correlation to the PD endpoint. Predictions for clinically commonly used dosing regimens are indicated in green.

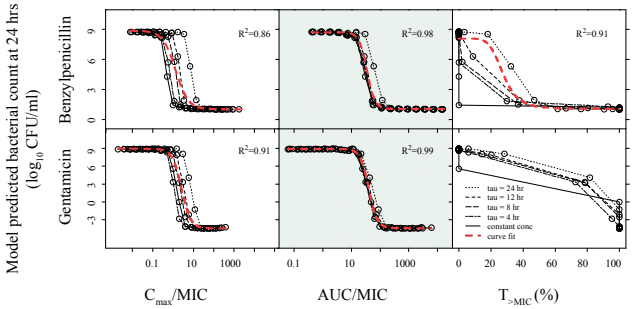

Figure 3. Relationship between the model-predicted bacterial count at 24 hrs and the PK/PD indices simulating the **PK profile of neonates** (GA=30 weeks, PNA=3 days).

References

[1] Nielsen EI et al. *Antimicrob Agents Chemother.* 2007 Jan;51(1):128-36
[2] Mohamed AF et al. PAGE 19 (2010) Abstract 1876
[3] Nielsen EI et al. *Antimicrob Agents Chemother.* 2011 Apr;55(4):1571-9