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Raphaël Saporta
raphael.saporta@farmaci.uu.se

Pharmacokinetic-pharmacodynamic modelling of afabicin *in vitro* activity against *Staphylococcus aureus*

Raphaël Saporta [1], Elisabet I. Nielsen [1], Valérie Nicolas-Métral [2], David R. Cameron [2], Annick Menetrey [2], Lena E. Friberg [1]

[1] Department of Pharmacy, Uppsala University, Sweden [2] Debiopharm International SA, Lausanne, Switzerland

Background

- Afabicin is a novel class antibiotic targeting the FabI enzyme in staphylococci, in development for:
  - Bone and joint infections due to staphylococci (currently in Phase II clinical trials)
  - Staphylococcal acute bacterial skin and skin structure infections (Phase II completed [1])
- Static *in vitro* time-kill experiments were performed for various *Staphylococcus aureus* strains, to evaluate the antimicrobial activity of the active moiety of afabicin, afabicin desphosphono (Debio 1452).
- **Aim:** Build a model characterizing afabicin desphosphono pharmacokinetics-pharmacodynamics (PK/PD) based on the time-kill data to support further development of afabicin.

Conclusions

- The developed model successfully described the effect of afabicin desphosphono over time *in vitro* in the majority of the experiments:
  - Against 21 *S. aureus* strains
  - In a 250-fold concentration range
- The strains' MICs were successfully used to scale drug effect, allowing for prediction of efficacy in other *S. aureus* strains. The relationship between MIC and EC_{50} was however estimated to be less than proportional - a doubling of the MIC resulted in a ~12% increase in EC_{50}.
- The *in vivo* predictability of this PK/PD model will be further evaluated using data from mouse infection models. The model will also be used to explore the impact of the immune system on *in vivo* PK/PD.

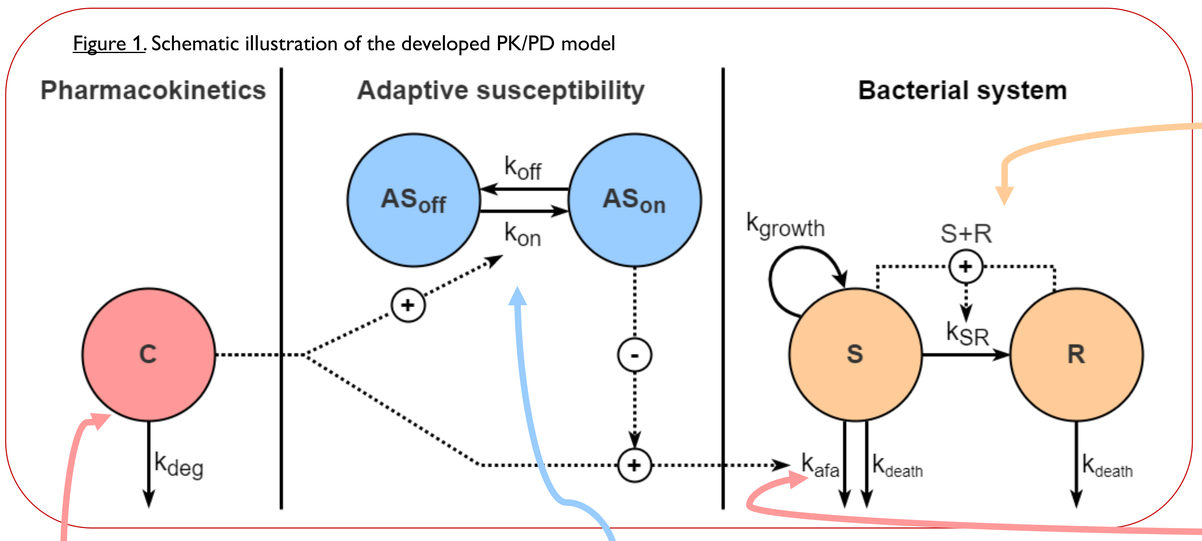
Methods

- 162 individual time-kill curves were available for model building:
  - A total of 21 *S. aureus* strains, with minimum inhibitory concentrations (MIC) ranging from 0.004 to 0.03 µg/ml
  - Afabicin desphosphono concentrations ranging from 0.004 to 1.0 µg/ml
  - Colony forming unit (CFU) counts determined up to 48 hours
- Model was developed using NONMEM 7.5.
  The PK/PD model assumed that bacteria could be in a drug-susceptible and growing state (S) or a resting state (R) [2].
- Different additions to the model were evaluated.
  Kept in the developed model:
  - Scaling of afabicin desphosphono effect by MIC to account for strain differences
  - Additional compartments characterizing observed regrowth [3]

  Not supported by the data:
  - Lag in drug effect to describe a delay before initiation of bacterial killing
  - Different proportions of bacteria in the S and R states in the initial inoculum

Results

Figure 1. Schematic illustration of the developed PK/PD model



- Susceptible bacteria (S state) are assumed to grow with a first order growth rate k_{growth}.
- Resting bacteria (R state) are assumed to not grow, and not be affected by afabicin desphopshono.
- Both S and R states share the same first order natural death rate k_{death}.
- The total amount of bacteria in the system (S+R) stimulates transfer from susceptible to resting state.

Afabicin desphosphono concentration was constant in the model (k_{deg} = 0).

The adaptive susceptibility (off at the start of experiments) turns on (As_{on} state) with a concentration-dependent rate k_{on} when exposed to afabicin desphosphono, inducing a reduction of the maximal drug effect. Susceptibility returns to baseline through the k_{off} rate.

Afabicin desphosphono induces killing in susceptible bacteria through a first order rate constant k_{afa}. This rate is concentration-dependent, can vary over time (as exposure induces a reversible reduction in susceptibility) and depends on the strain's MIC:

$$k_{afa}(t) = \frac{E_{max}(t) \cdot C^{hill}}{C^{hill} + EC_{50}^{hill}} \quad \text{with} \quad E_{max}(t) = E_{max} \cdot \left(1 - \frac{AS_{on}(t)}{AS_{on}(t) + AS_{50}}\right) \quad \text{and} \quad EC_{50} = MIC^{\gamma}$$

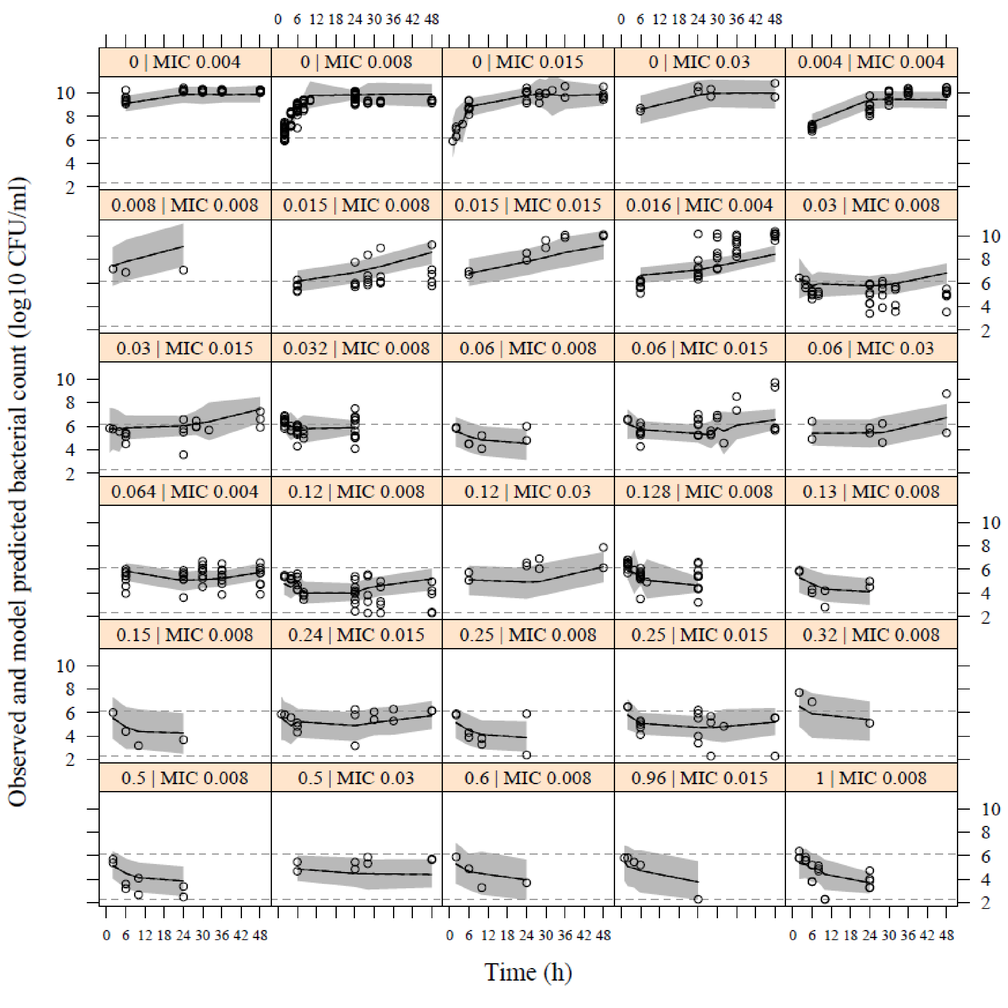


Figure 2. Visual predictive checks of the final model. Shown are the observed bacterial counts (circles), the simulated bacterial counts median (solid line) and its 95% confidence interval (grey area). Grey broken lines are the median starting inocula from all experiments (top line) and the limit of detection (bottom line).
Each panel presents data for an afabicin desphosphono concentration (in µg/ml) for strains with a given MIC.

- Estimated concentration required to reach half of the maximal drug effect (EC_{50}) by MIC, based on the final parameter estimates:

MIC (µg/ml)	0.004	0.008	0.015	0.03
EC_{50} (µg/ml)	0.413	0.462	0.511	0.571

- With an estimated AS_{50} of 0.861, the maximal possible reduction of the maximum effect (E_{max}) by the adaptive susceptibility compartments is ~54%.

Table 1. Parameter estimates from the final model and the relative standard error (RSE) of the estimates. "Fix" values were fixed in the estimation.

Parameter	Unit	Description	Value	RSE (%)
k_{growth}	h^{-1}	Growth rate constant	1.13	2.0*
k_{death}	h^{-1}	Natural death rate constant	0.179	Fix
B_{max}	log_{10} CFU/ml	Maximum bacterial count in the system	9.85	1.0*
E_{max}	h^{-1}	Maximum afabicin desphosphono killing rate constant	4.10	7.0
γ	—	EC_{50} scaling by MIC factor	0.160	36
hill	—	Sigmoidicity factor in the E_{max} model	0.360	6.4
k_{on}	ml/(µg•h)	Diminution in susceptibility rate constant	0.406	24
k_{off}	h^{-1}	Return to susceptibility rate constant	0.0139	Fix
AS_{50}	—	Fraction needed to reach 50% of reduction in susceptibility	0.861	13
RES	log_{10} CFU/ml	Residual variability, additive on the log scale	0.755	10

* k_{growth} and B_{max} values were fixed in the full model based on estimates from a model with growth control data only.

References:

[1] Wittke, F et al. Antimicrobial agents and chemotherapy vol. 64,10 (2020):e00250-20.
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