A Novel Mechanism-Based Pharmacokinetic-Pharmacodynamic (PKPD) Model Describing Ceftazidime-Avibactam (CAZ-AVI) Efficacy Against β-lactamase-Producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* Isolates

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Introduction

Background: Several non-β-lactam β-lactamase inhibitors such as the diazabicyclootances (DBOs) are currently in clinical development. Among those, Roche is developing Nacubactam, an inhibitor of class A and C β-lactamases, and is utilizing PKPD modelling in order to explore the exposure response. Comparison with other β-lactam - β-lactamase inhibitor combinations is however hampered due to lack of a published PKPD model for the main comparator avibactam.

Objective: To develop a mechanism-based PKPD model describing the interaction between the diazabicyclootance (DBO) β-lactamase inhibitor avibactam (AVI) and ceftazidime (CAZ) in order to enable comparative evaluation with other β-lactamase inhibitors in clinical development.

Methods

Data: Static in vitro time-kill data (Figure 1, left) was generated for the KPC-3 (*K. pneumoniae* carbapenemase, IC50 AVI 0.042 µg/ml) producing *K. pneumoniae* strain NCTC13438 (MIC CAZ 128 mg/L) over 24h, under the conditions:

- CAZ alone (64-1024 mg/L)
- AVI alone (2-32 mg/L)
- CAZ-AVI (CAZ 1-16 mg/L + 4mg/L AVI)
- growth control

The CFU counts (PD) and the drug concentrations (PK) were measured over the course of the experiment.

Model development:

The model structure was based on a two-subpopulation model for meropenem on *Pseudomonas aeruginosa* [1], where the first subpopulation was assumed to be CAZ susceptible and the second subpopulation CAZ resistant (Figure 2). Each subpopulation consists of an actively growing, drug susceptible state, and a resting drug insusceptible state to which the bacteria transfer at high population densities. The effect of AVI was included as:

1. Inhibition of the β-lactamase activity
2. A direct antibacterial effect on the growing state
3. An enhancement of the CAZ effect on the growing state

The kill rates of AVI and CAZ were combined assuming Bliss independence.

Linear, power, and sigmoidal Emax models were evaluated for the drug effect on both subpopulations.

The modelling was performed in NONMEM7.3 [2], guided by visual predictive checks (VPC) and a p-value of 0.001 for parameter inclusion. Parameter uncertainty was determined by SIR [3], as implemented in PsN [4].

Model structure evaluation:

The model structure was applied on extensive literature PD data of three *P. aeruginosa* strains [5] (MIC CAZ 64-256 mg/L) (Figure 1, right).

In order to explain strain differences, inter strain variability were added on relevant parameters and MIC values investigated as covariates.

Results

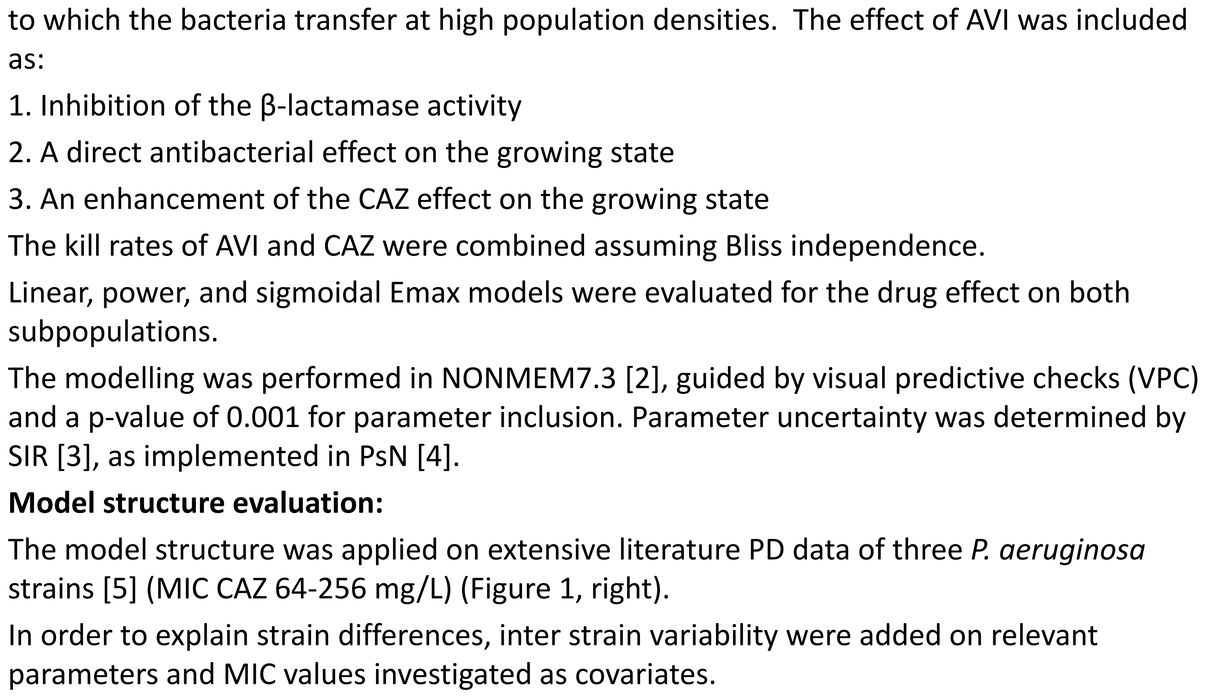

Figure 1. Visual predictive checks (VPCs) of the PD for *K. pneumoniae* NCTC13438 (left) and *Pseudomonas aeruginosa* (right). The 80% prediction interval (PI) of the model is indicated, as well as the initial inoculate (dashed line), and for NCTC13438 the lower limit of quantification (lower dashed line).

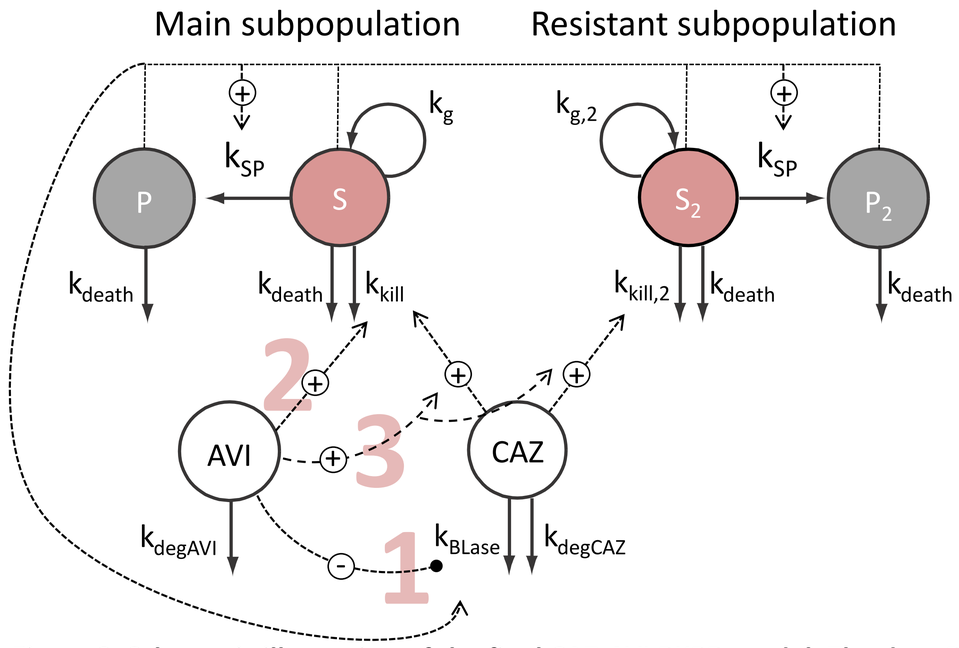

Figure 2. Schematic illustration of the final CAZ-AVI PKPD model. The drug PK is modelled as first order degradation ($k_{deg,X}$) and is for CAZ augmented by the β-lactamase activity modelled by k_{BLase} driven by the total bacterial population. The PD is described by a two subpopulation model (main and resistant) where each subpopulation consists of an actively growing drug susceptible (S), and a resting, drug insusceptible, (P) state. The effect of AVI was incorporated as: 1. inhibition of k_{BLase}, 2. kill of the main population (*K. pneumoniae* only), 3. enhancement of the CAZ effect.

PK: The AVI and CAZ dynamics were modelled for NCTC13438: the CFU count influenced β-lactamase activity by an sigmoidal Emax-function, and AVI inhibition of β-lactamase activity was modelled by an Imax-function with IC50 fixed to a measured value:

$$k_{BLase} = k_{BLasemax} \times \left(\frac{BN^{\gamma_{BN}}}{BN50^{\gamma_{BN}} + BN^{\gamma_{BN}}}\right) \times \left(1 - \left(\frac{C_{AVI}}{C_{AVI} + IC50_{AVI}}\right)\right)$$

where $k_{BLasemax}$ is the maximum, CFU driven, degradation rate, and BN is the bacterial density. For *P. aeruginosa* no IC50 was available, and instead the reported half-lives of CAZ were used [1].

PD: The final PKPD model is shown in Figure 2, and described the data for for *K. pneumoniae* NCTC13438 well (Figure1, left). The CAZ effect was described by a sigmoidal Emax-function , and regrowth was explained by a higher EC50 for the second subpopulation. For AVI a direct antibacterial effect was evident , and modelled by a slope function affecting the main subpopulation, and fast regrowth explained by the lack of AVI effect on the second subpopulation. In addition, as described for aztreonam [6], a potentiation of CAZ by AVI was observed and modelled by an Emax-function affecting the CAZ EC50:

$$EC50_{CAZ,SYN,i} = EC50_{CAZ,i}^{\gamma_{CAZ}} \times \left(1 + \frac{SYNmax \times C_{AVI}}{C_{AVI} + SYN50}\right)$$

where the maximum achievable synergy $SYNmax$ was fixed to -1, $SYN50$ is the AVI concentration where half $SYNmax$ was achieved, and i = {1,2} for the two subpopulations.

The developed model structure described the *P. aeruginosa* data well (Figure1, right), except that no direct antibacterial effect of AVI was found. In addition a 28% inter strain variability was found on the $SYN50$ was required to fit the data adequately and the EC50 could be expressed as a function of the CAZ MIC: $EC50_{CAZ} = 0.56*MIC_{CAZ}$.

Conclusions

A novel PKPD model for the DBO- β-lactam combination CAZ-AVI was successfully developed to describe the longitudinal effect on *K. pneumonia* and *P. aeruginosa*. The model enables comparison of the effect of AVI with other DBO- β-lactam inhibitors in simulation, and may provide aid in translating PKPD results from in vitro to animal and human.

References

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