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A translational semi-mechanistic pharmacokinetic-pharmacodynamic framework to design animal studies: Application to linezolid and vancomycin

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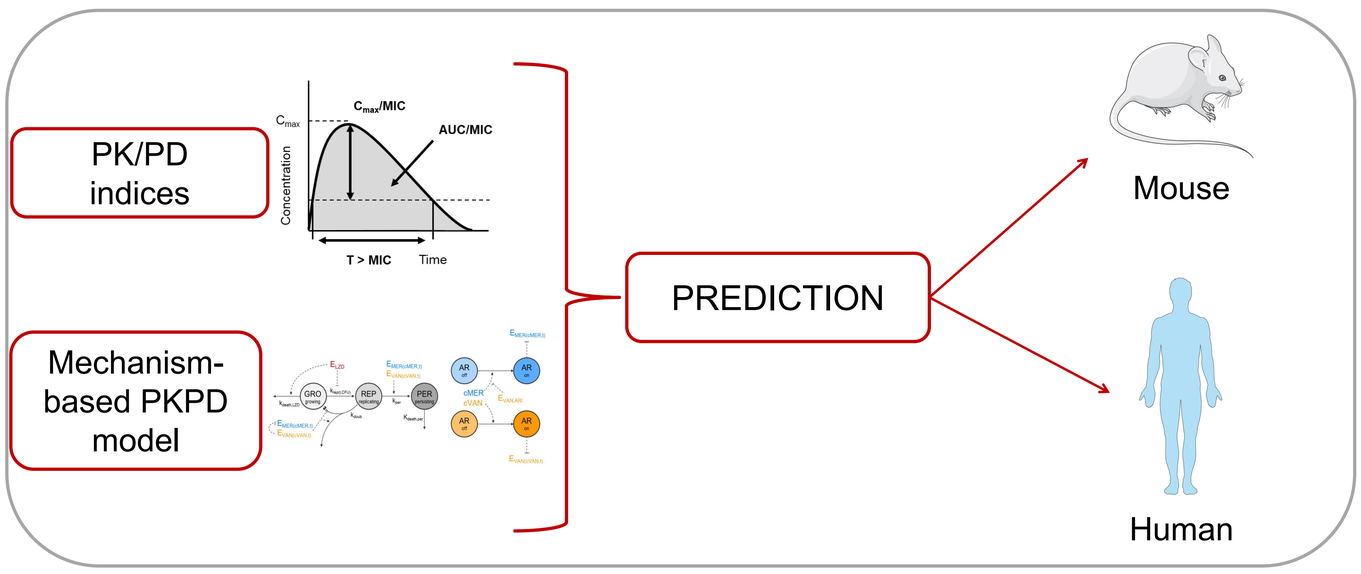
Background

- PK/PD indices are summary metrics of drug exposure related to the minimum inhibitory concentration (MIC). During drug development these are explored for their correlation with antimicrobial response in animal models and fixed targets are defined.
- Translation of antibiotic effects is, by tradition, based on these targets despite advantages of mechanism-based PKPD models that consider bacterial counts over time [1].
- One of the goals of the **COMBINE** project, which is part of the AMR Accelerator, is to improve the **translation** of **drug effects** from **preclinical** to **clinical** development for antibacterial drugs using a pneumonia mouse model which is standardized and will be validated in this project. Clinical data on linezolid (LZD) and vancomycin (VAN) have been made available for this purpose.
- Relevant dosages to be used for translation needs consideration of species differences in PK and its impact on bacterial growth and killing.

AIM: We here aimed to set up a translational framework for LZD and VAN using **PK** and **PKPD models**, which also can be used to facilitate the **design** of pneumonia **mouse studies** that mimic human conditions coming from data of pneumonia clinical studies (i.e. **reverse translation**), considering suggested **PKPD targets** as well as model-based strategies using predictions of **bacterial counts**.

Methods

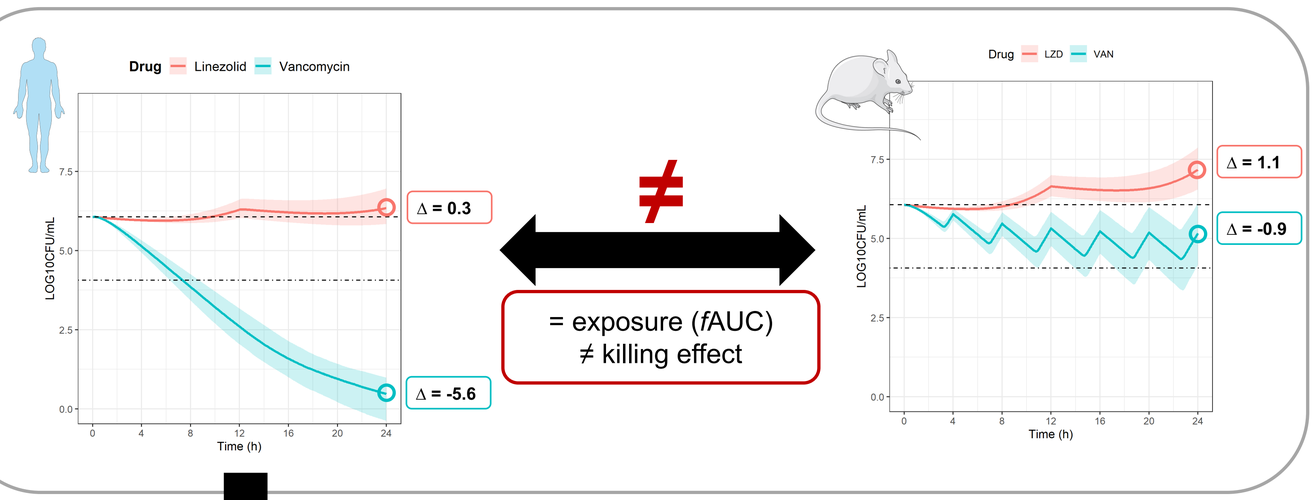
- PK models on LZD and VAN: From literature for mice and humans [2-5]
  - Simulation: typical profiles for a 25 g mouse (f_u: 0.76 and 0.83 for LZD and VAN) and a 70 kg subject (f_u: 0.69 and 0.45 for LZD and VAN)
- PKPD model for LZD and VAN: From literature, developed from *in vitro* data [6]
  - Simulation: colony-forming units (CFU)/mL over 24h
  - Initial inoculum: 6.06 $\log_{10}$CFU/mL. MICs: 4 mg/L (LZD), 2 mg/L (VAN)
  - Parameter uncertainty (RSE%) included in PK/PD simulations
- PK/PD indices: free AUC to minimum inhibitory concentration (*f*AUC/MIC)
  - Based on clinical data: 55-83 (LZD), 180 (VAN) [7]
- Software: R + packages
  - Model simulations: *mrgsolve.* Data processing, plots: *tidyverse*



Translation: PK/PD indices

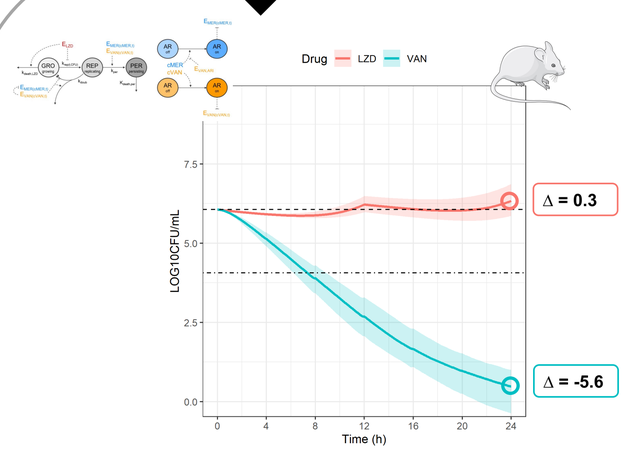
1. Predicted concentration-time profiles in humans were driving predictions of bacterial counts in the PKPD model for doses of 600 mg b.i.d. 1h i.v. infusion (LZD) and 15 mg/kg b.i.d i.v. infusion of 600 mg/h (VAN).
   - LZD: $\Delta\log_{10}$(CFU/mL) = 0.3; *f*AUC/MIC = 27
   - VAN: $\Delta\log_{10}$(CFU/mL) = -5.6; *f*AUC/MIC = 55
2. Exposure in mice resulting in same *f*AUC as in humans after standard dosing:
   - LZD: 12 mg/kg IV bolus q12h → bacterial growth ($\Delta\log_{10}$(CFU/mL) = 1.1)
   - VAN: 17 mg/kg q4h → modest killing effect ($\Delta\log_{10}$(CFU/mL) = -0.9).

   Same fAUC/MIC resulted in different bacterial killing for both drugs



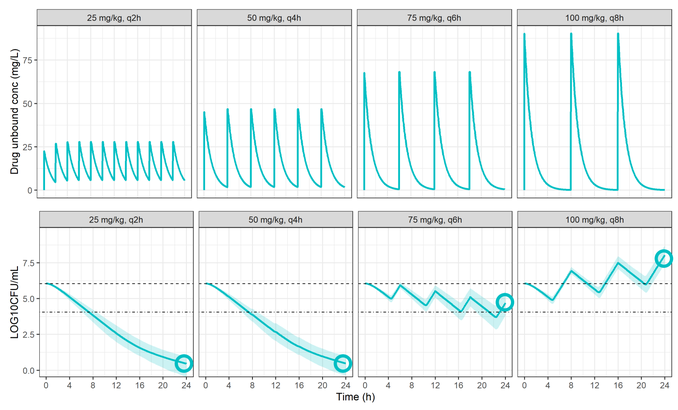
Translation: Bacterial counts

- Mouse doses with same bacterial killing effect as observed in humans:
  - LZD: 18 mg/kg q12h, *f*AUC/MIC = 42 (1.5 times the value in humans)
  - VAN: 50 mg/kg q4h, *f*AUC/MIC = 167 (3 times the value in humans)
- Since VAN was not predicted to have a concentration-dependent killing effect, a dose-fractionation study *in silico* was performed:
  - Total dose (300 mg/kg) was fractionated into different dosing intervals (2 h, 4 h, 6 h and 8 h)
  - Bacterial killing at 24 h ranged from $\Delta\log_{10}$(CFU/mL) = -5.6 if administered q2h to $\Delta\log_{10}$(CFU/mL) = 2.0 if administered q8h.
  - VAN's antimicrobial effect might not be only concentration-dependent, but also time-dependent. For LZD, antimicrobial response was comparable across dosing regimens.



To achieve the **same killing effect** as in humans, **1.5 - 3x** higher drug **exposure** is needed

Vancomycin effect in mice depended on the **dosing interval** with same total dose (300 mg/kg)
- 24h $\Delta\log_{10}$(CFU/mL):
  - q2h: -5.6
  - q4h: -5.6
  - q6h: -1.4
  - q8h: 2.0



Conclusion

- A **PKPD modelling framework,** coupling PK and PKPD models, has been set up to make use of different types of data *(in vitro*, *in* vivo, clinical) of value in the design of mouse pneumonia experiments for LZD and VAN.
- Achieving the **same exposure** (*f*AUC) in mice as in humans was **not** predicted to result in **identical bacterial killing** effect despite being described as AUC-dependent drugs
- This work highlights that the **PK/PD index** approach may **not translate well** between mice and humans for VAN. For LZD the species-difference was smaller.
- The generated data from the pneumonia infection model will be correlated to the clinical data on LZD and VAN.
- The study supports the need for **bacterial PKPD** models to describe and **predict** the **effect** of current and new antibiotics **across different species**.

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