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Translational pharmacokinetic-pharmacodynamic (PKPD) modelling of apramycin to facilitate prediction of efficacious dose in urinary tract infections

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Background & aim

Apramycin (EBL-1003) is a broad-spectrum aminoglycoside antibiotic for the treatment of gram-negative bacteria infections that is currently under development for human use. Although apramycin has demonstrated best-in-class coverage of resistant isolates and efficacy in preclinical lung infection models [1], its utility in other disease indications needs to be further evaluated. Previous proof-of-concept studies have suggested that apramycin has potential in the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis [2]. In this study, we used pharmacokinetic-pharmacodynamic (PKPD) modelling based on *in vitro* and *in vivo* data in order to predict apramycin efficacy in different mouse models of cUTI for subsequent scaling to humans.

Methods

- Two *E. coli* bacterial strains were investigated: ATCC 700336 (a sulfamethoxazole-trimethoprim (SXT)-resistant UTI isolate) and EN591 (a multidrug-resistant *rmtB* isolate)
- *In vitro* time-kill experimental data at pH6 and pH7.4, as well as *in vivo* PK data of apramycin (studied in healthy and infected mice) were used to develop the PKPD model
- *In vivo* efficacy was evaluated in two cUTI mouse models (ATCC 700336 and EN591) assessing bacterial load in kidney and bladder tissue
- Model was developed using NONMEM v.7.5
- Data management, visualization and simulations were done using R v.4.2.0

Results

PKPD model

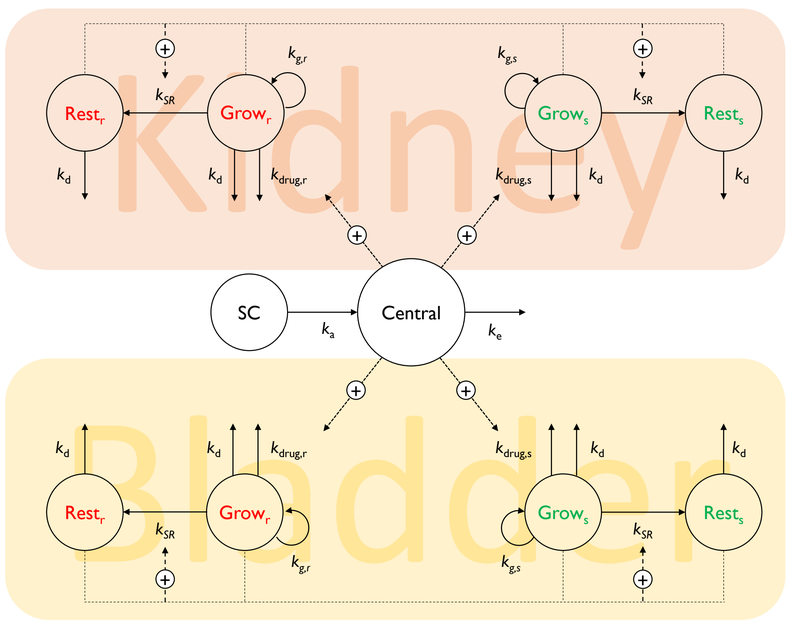

Figure 1. Schematic representation of the final PKPD model to predict apramycin effect *in vivo* in kidney and bladder tissue. The model includes two bacterial subpopulations, one susceptible (right) and one resistant (left). In each subpopulation the bacteria may exist in one of two discrete states: (i) antibiotic susceptible proliferating bacteria (grow), and (ii) non-proliferating bacteria unsusceptible to the antibiotic (rest).

Table 1. Parameter estimates and relative standard errors (RSEs) of the final model

Parameter	Unit	Description	Strain	Value	%RSE
k_{g,s_vitro}	(h^{-1})	Susceptible bacteria growth rate constant (*in vitro*)	EN591	3.16	13.1
			ATCC 700336	2.69	8.9
$k_{g,s\_vivo,kidney}$	(h^{-1})	Susceptible bacteria growth rate constant in kidney (*in vivo*)	EN591	0.451	4.2
			ATCC 700336	0.878	2.6
$k_{g,s\_vivo,bladder}$	(h^{-1})	Susceptible bacteria growth rate constant in bladder (*in vivo*)	EN591	0.153	3.6
			ATCC 700336	0.304	8.2
$Reduk_g$	(%)	Fractional reduction in growth rate for the resistant subpopulation	EN591	40.1	20.3
			ATCC 700336	29.6	32
k_d	(h^{-1})	Natural bacterial death rate constant	Both	0.179	fix
B_{max}	log_{10} CFU/mL	Maximum bacterial density	EN591	9.42	1.3
			ATCC 700336	9.56	0.9
$Slope_s$	(h^{-1})	Rate constant for apramycin effect normalized by MIC in the susceptible subpopulation	EN591	3.79	10.7
			ATCC 700336	3.85	12.4
$Slope_r$	(h^{-1})	Rate constant for apramycin effect normalized by MIC in the resistant subpopulation	EN591	0.238	5.2
			ATCC 700336	0.613	12.3
k_{ada}	(h^{-1})	Rate constant for drug driven phenotypic switch from susceptible to resistant	Both	0.511	fix
RES_{vitro}	log_{10} CFU/mL	Residual error variance on log_{10} scale (*in vitro*)	EN591	0.335	22.2
			ATCC 700336	0.357	14.4
$RES_{vivo,kidney}$	log_{10} CFU/organ	Residual error variance on log_{10} scale (*in vivo* - kidney)	EN591	1.75	19.1
			ATCC 700336	1.91	57.6
$RES_{vivo,bladder}$	log_{10} CFU/organ	Residual error variance on log_{10} scale (*in vivo* - bladder)	EN591	1.95	11.9
			ATCC 700336	3.77	50.9

In vitro time-kill data

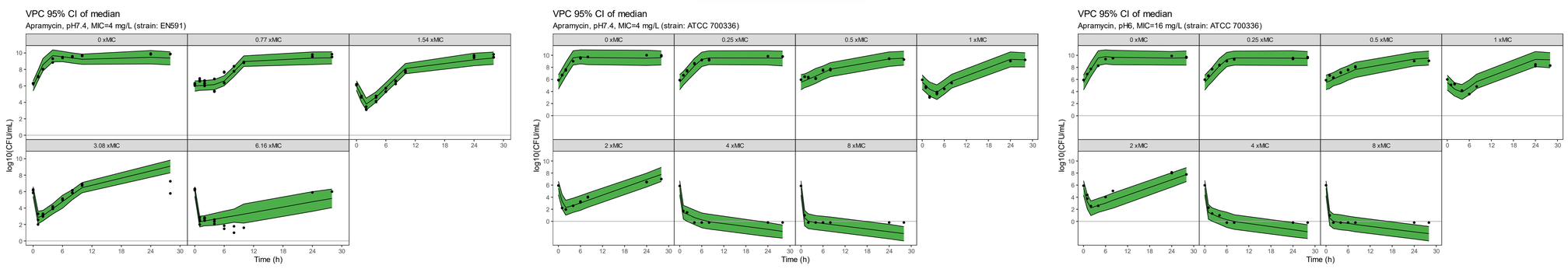

Figure 2. Visual predictive checks (VPC) of the final model. Dots represent observed data, lines and area represent 95% confidence interval (CI) of the median. Each panel represents data for a specific bacterial strain , namely, EN591 (left panel) and ATCC 700336 (mid and right panels) under different pH conditions (pH6 or pH 7.4 – pH differences were only examined for ATCC 700336 bacterial strain). Subpanels represent different apramycin concentrations (xMIC). Data below the limit of detection are plotted as -0.2.

In vivo PD data

EN591 cUTI mouse model

ATCC700336 cUTI mouse model

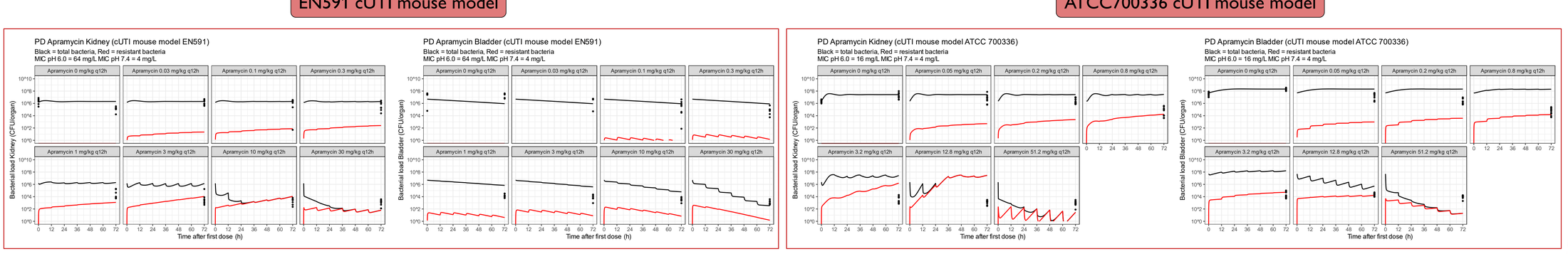

Figure 3. Predicted (lines) and observed (points) kidney and bladder CFU with the newly estimated k_g values. Each panel represents data for a different organ (i.e. kidney or bladder) in the two studied cUTI mouse models. Subpanels represent different apramycin concentrations.

Conclusions

- *In vitro* estimated effect parameters are similar under different pH (pH6 and pH7.4) after adjusting for MIC differences
- PKPD modelling integrated data from different sources: plasma PK, *in vitro* time-kill data, *in vivo* CFU data in kidney and bladder tissue
- PKPD model predictions of apramycin effect in kidney and urine were (up to certain extent) comparable to the measured effect
- k_g estimation suggested that bacterial growth is slower *in vivo*, as previously observed in a mouse thigh infection model [3]. Nevertheless, k_g estimation is associated to uncertainty due to the scarcity of data
- Slower k_g explained the larger reductions in bacterial count estimated in bladder as compared to kidney.
- Further dynamic PK and PD data both in kidney and bladder would be desirable for a better understanding and prediction on the tissue effect of apramycin in cUTIs
- This study holds promise to enable dosing recommendations for future clinical trials in patients with cUTI and to support the development of apramycin for human use

References:

[1]Aranzana-Climent V et al. *Clin Microbiol Infect* (2022) 28(19):1367-1374
[2]Becker K et al. *EBioMedicine* (2021) 73, 103652
[3]Sou T et al. *Clin Pharm Ther* (2021) 109(4):1063-1073

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