PK-PD of new broad-spectrum agent BWC0977

[1]L. McEntee, [1]N. Farrington, [1]A. Johnson, [1]A. Stevenson, [1]I. Horner, [1]A. Jimenez-Valverde, [1]J. Unsworth, [2]R. Kolamunnage-Dona, [3]H.K. Kotakonda, [3]V. Balasubramanian, [1]W. Hope, [1]S. Das, [1]A-G. Märtson

[1]Antimicrobial Pharmacodynamics and Therapeutics, University of Liverpool, UK
[2]Department of Health Data Science, University of Liverpool, UK
[3]Bugworks Research India Pvt. Ltd., Bengaluru, Indias

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@anne8rete
University of Liverpool, a.martson@liverpool.ac.uk

INTRODUCTION

New antibacterial agents for drug resistant infections are urgently needed. Novel agent BWC0977 is a potent gyrase-topoisomerase inhibitor with activity against ESBLs, AmpC, KPCs and fluoroquinolone resistant strains. BWC0977 has shown efficacy in lung and thigh infection models. The compound is currently being assessed in a Phase 1 clinical programme and it is aimed at treating patients with serious bacterial infections.

Here we describe the pharmacokinetics and pharmacodynamics (PK-PD) of BWC0977 assessed in the murine thigh infection model.

METHODS

The animal model

A 26-hour neutropenic murine thigh infection model was used for dose ranging and fractionation. Challenge strain *P. aeruginosa* NCTC 13921 was used for dose fractionation studies and PK. A destructive design was employed, with mice dosed subcutaneously 2 hours post-infection and bacterial density (CFU/g) infection compared to a 2h baseline control taken as the endpoint.

Dose ranging and fractionation

For fractionation 160 mg/kg q24h, 80 mg/kg every 12 hours, 40 mg/kg every 6 hours were administered with PD samples taken 2, 8, 14, 26 hours post infection. For dose ranging BWC0977 was administered every 8 hours and Polymyxin B was used as comparator control. In the PK study 10, 40, 80, 120mg/kg administered once and plasma samples taken at 30 minutes and 1, 2, 4, 6, 8, 24 hours post-dose.

PK/PD experiments and analysis

Further isolates of *P. aeruginosa, A. baumannii, K. pneumoniae* and *E. coli* with resistance mechanisms were used for dose ranging (**Table 1**). The population PK modeling and further analysis was done with the non-parametric population analysis software Pmetrics and ADAPT5. The protein binding used for this analysis was 87.4%.

Table 1. Strains tested in the murine model

Species	Strain	Molecular info	BWC0977 MIC (mg/L)	Meropenem MIC (mg/L)
P. aeruginosa	ATCC 27853	WT	0.5	0.25-0.5
P. aeruginosa	NCTC 13921	SPM-1	0.25	>64
P. aeruginosa	NCTC 13437	VIM-10, VEB-1	0.5	>64
A. baumannii	NCTC 13301	OXA-23	0.25	>64
A. baumannii	ATCC 17978	WT	0.125-0.25	0.25-1
K. pneumoniae	NCTC 13465	CTX-M25	0.125-0.25	0.125
K. pneumoniae	ATCC 43816	WT	0.25	
E. coli	ATCC BAA-2523	OXA-48	0.06-0.125	0.5-1
E. coli	NCTC 13462	CTX-M2	0.06	0.5-1

WT, wild-type; SPM-1, Sao Paolo metallo-beta-lacatamse; VIM-10, Verona Imipenemase beta-lactamase; VEB-1, extended spectrum beta-lactamase (ESBL); OXA-23, OXA-48, oxacillinase beta-lactamase; CTX-M25, CTX-M2, cefotaxime-Munich ESBL.

RESULTS

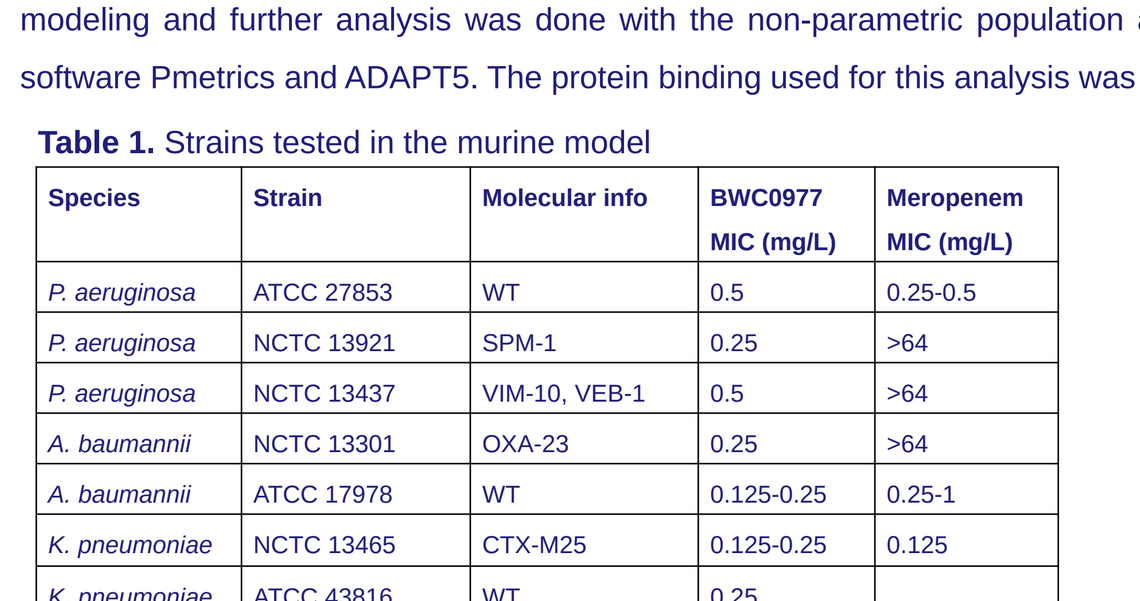

Figure 1. Murine plasma PK of BWC0977 (LLQ = 0.05 mg/L)

RESULTS

Dose fractionation studies

The different doses showed dose-proportional PK **(Figure 1)**. Dose range studies with *P. aeruginosa* strain NCTC 13921 were repeated 3 times to gain several data sets for modelling the ED_{50}. ED_{50} was approximately 58mg/kg q8h (or 174mg/kg q24h). The highest possible dose (given solubility and volume constraints) was 160mg/kg q24h, which was fractionated – 160mg/kg q24h, 80mg/kg q12h, 40mg/kg q6h (**Figure 2**).

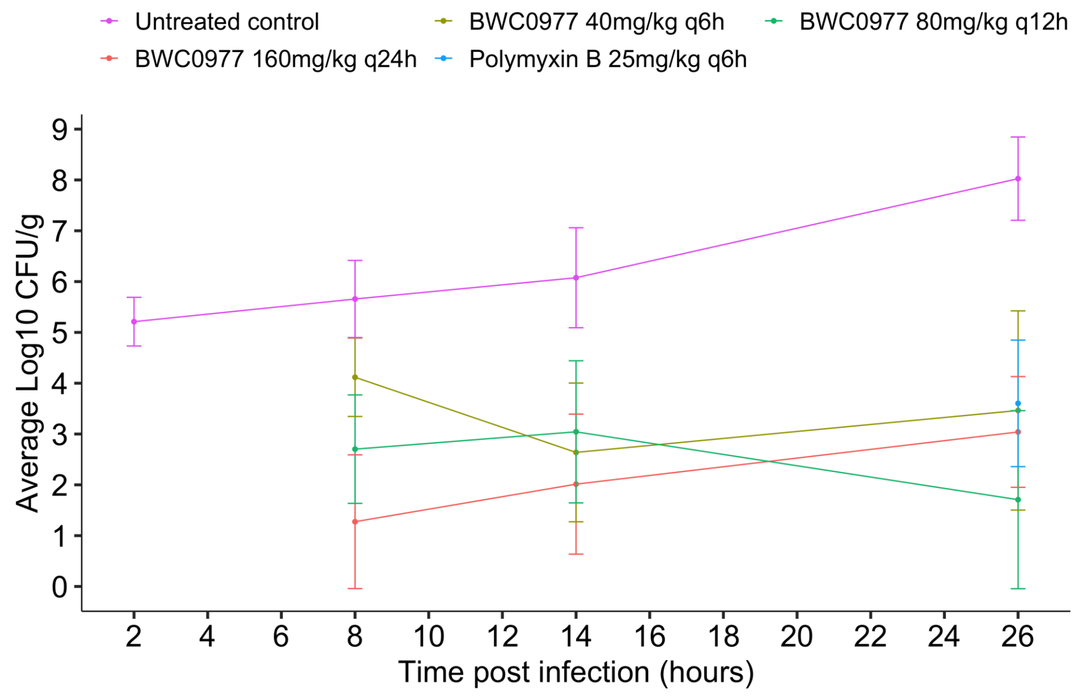

Figure 2. Dose fractionation studies with BWC0977

PK/PD index

Linear mixed effects modelling showed significant reduction between all the dosing groups in bacterial burden compared to control, but no differences between the single dose and any of the fractionated regimens. The preliminary results suggest the PK-PD driver to be *f*AUC/MIC.

PK/PD analysis

A population PK model was fit for the PK/PD analysis. The fitted PK model was a 2-compartment model with linear clearance. The absorption rate constant was 18 h^{-1}, total clearance 0.1 L/h, volume of distribution 0.03 L, the rate constant for BWC0977 distribution from the central to the peripheral compartment 0.4 h^{-1}, rate constant for the BWC0977 distribution from the peripheral to the central compartment 0.6 h^{-1}. The goodness of fit of the population PK was r^2 of 0.99.

There was an excellent dose response to the tested bacterial isolates (**Figure 3**). *K. pneumoniae* and *A. baumannii* strains showed the highest variability in the CFU decline.

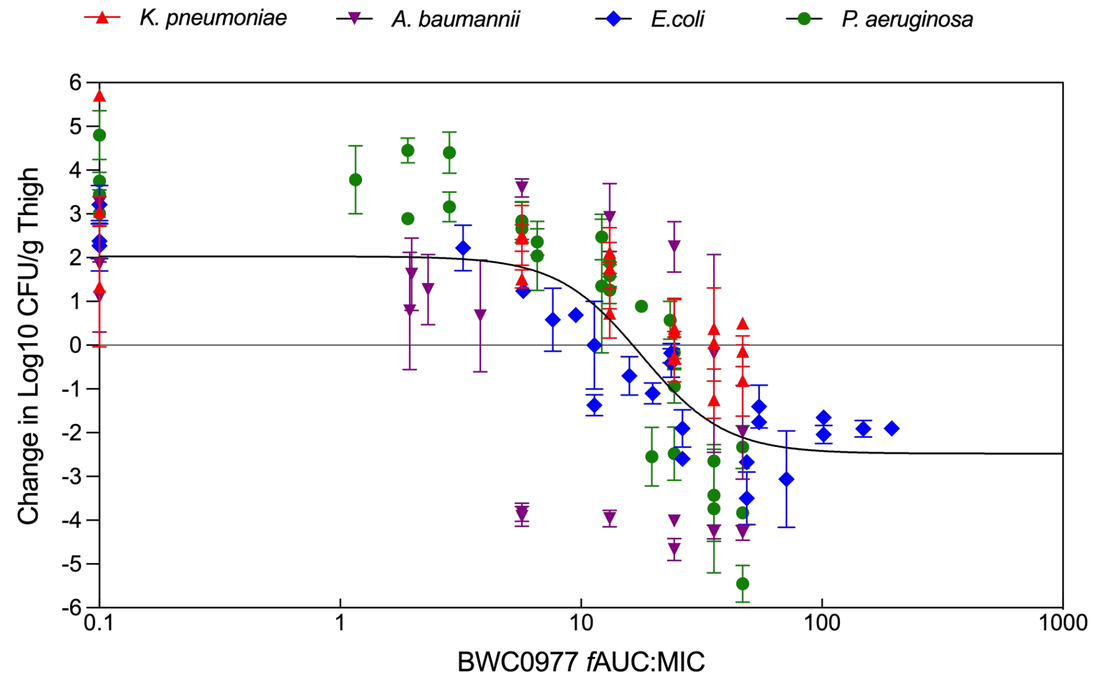

Figure 3. Strains co-modelled and fitted to the Sigmoid E_{max} model in ADAPT5

CONCLUSIONS

The novel drug BWC0977 shows excellent activity against various bacterial strains and the defined PK/PD index for efficacy is *f*AUC/MIC.