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In vitro PK/PD modelling of polymyxin B against resistant strain of *A. baumannii* in presence of mucin

Mathilde Lacroix^{1,2}, Alexia Chauzy², Claudia Zampaloni³, Caterina Bissanz⁴, H el ene Mirfendereski^{2,5}, Hamasseh Shirvani¹, Julien Buyck², Sandrine Marchand^{2,5}, William Couet^{2,5}

¹ Institut Roche - Boulogne-Billancourt (France)

² INSERM U1070, University of Poitiers - Poitiers (France)

³ Roche Pharma Research and Early Development, Immunology, Inflammation and Infectious Diseases, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124 - Basel (Switzerland)

⁴ Roche Pharma Research and Early Development, Pharmaceutical Science, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124 - Basel (Switzerland)

⁵ Department of Toxicology and Pharmacokinetics, University Hospital of Poitiers - Poitiers (France)

Background

Pulmonary infections with *Acinetobacter baumannii* are often difficult to treat due to multidrug resistance. Furthermore, the presence of mucin (main component of mucus) in lung has been shown to decrease polymyxin activity (Huang JX *et al.*, 2015 Antimicrob Agents Chemother).

The aim of this study was to characterize the effect of mucin on polymyxin B (PMB) activity against *A. baumannii* *in vitro*, using a PK/PD modelling approach.

Materials and methods

PMB binding on mucin was characterized in cation adjusted Mueller-Hinton broth (MHB) supplemented by 1% mucin, by ultracentrifugation. Unbound PMB concentrations were determined by LC-MS/MS.

Time-kill (TK) experiments were performed in MHB, with 1% mucin or without as control, from exponential phase cultures of a clinical *A. baumannii* strain resistant to PMB (Jaidane N *et al.*, 2018 International Journal of Antimicrobial Agents), with a starting inoculum at 10⁶ CFU/mL. PMB concentrations varied between 8 and 512 mg/L according to MIC (64 mg/L). Bacterial count was determined (3 replicates)(Figure 1), and combined with unbound PMB concentrations in a PK/PD model using NONMEM[®].

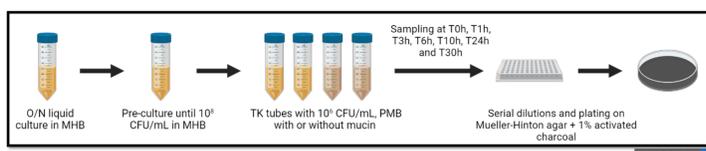
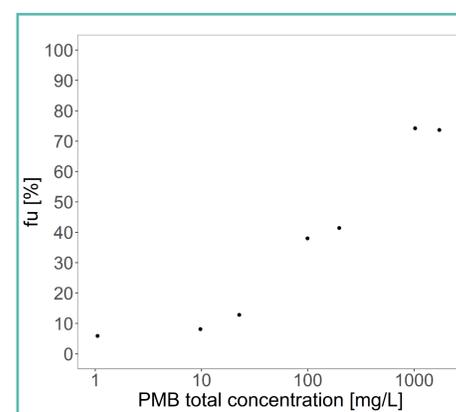


Figure 1 : Time-kill experiment's design

Results

PMB binding to mucin



The following relationship was found between PMB unbound (C_u) and total (C_T) concentration:

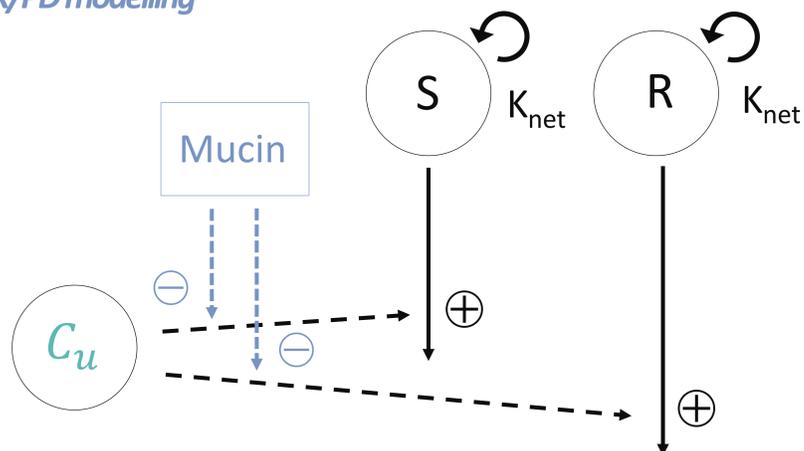
$$C_u = C_T - 1.18 C_T^{0.81}$$

Derived PMB unbound fraction (f_u) increased from ~6% to ~74% when total concentration increased from 1 to 1000 mg/L (Figure 2).

Figure 2 : PMB unbound fraction versus PMB total concentration in presence of 1% mucin in Mueller-Hinton broth.

Results

PK/PD modelling



$$\begin{aligned} \text{Drug effect}_S &= \text{Slope}_S \times C_u & \text{Drug effect}_{S_{\text{mucin}}} &= \text{Slope}_{S_{\text{mucin}}} \times C_u \\ \text{Drug effect}_R &= \text{Slope}_R \times C_u & \text{Drug effect}_{R_{\text{mucin}}} &= \text{Slope}_{R_{\text{mucin}}} \times C_u \end{aligned}$$

Figure 3 : PK/PD model representation

Time-kill data showed an initial rapid CFU decay followed by regrowth, which was described by a two bacterial sub-populations model: susceptible (S) and resistant (R), with a bactericidal effect of PMB (Figure 3). The selected PK/PD model based on C_u , provided good data fitting (Figure 4) with estimated parameters values presented in Table 1.

Furthermore, independently of binding, mucin appeared to decrease the antibiotic efficacy, with reduction of kill rates by 77% and 65% for respectively the S and R sub-populations, in the presence of mucin.

Parameter	Description	Estimate (RSE%)
LGINOC	Initial bacterial density for 10 ⁶ CFU/mL inoculum (log ₁₀ CFU/mL)	5.38 (1)
Knet	Apparent growth rate constant (h ⁻¹)	2.99 (11)
Bmax	Maximum bacterial population size (log ₁₀ CFU/mL)	8.08 (1)
Slope _S	Maximum kill rate constant without mucin for susceptible population	0.113 (19)
Slope _{S_{mucin}}	Maximum kill rate constant with mucin for susceptible population	0.0256 (11)
Slope _R	Maximum kill rate constant without mucin for resistant population	0.0215 (11)
Slope _{R_{mucin}}	Maximum kill rate constant with mucin for resistant population	0.0076 (11)
Mucin _a	Factor of PMB binding equation ax^b	1.18 (Fixed)
Mucin _b	Factor of PMB binding equation ax^b	0.81 (Fixed)
σ	Additive residual error on log ₁₀ scale for total bacteria count (log ₁₀ CFU/mL)	0.422 (27)

Table 1: PK/PD parameter values

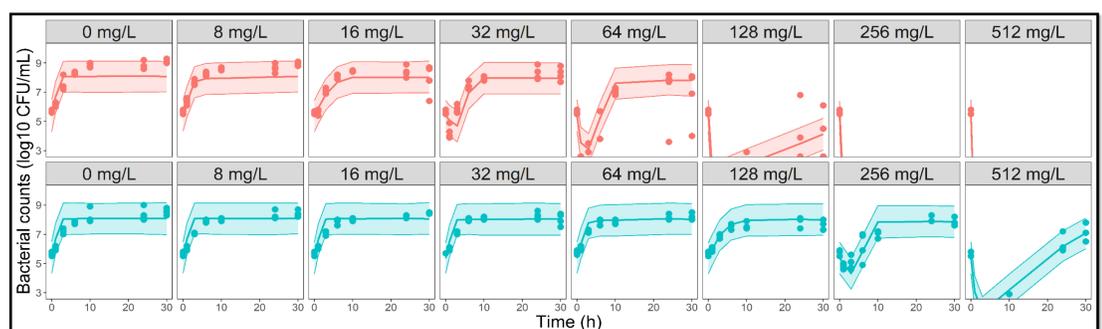


Figure 4 : Visual predictive checks (VPC) for the final model. Circles represent experimental data, solid lines depict the median of simulated data and colored areas depict the 90% prediction interval for 1,000 simulated profiles. Blue graphs represent data with 1% mucin and the reds without. The PMB concentrations indicated represent PMB total concentrations in Time-kill tubes.

Note that with this strain, active *in vitro* concentrations are much higher than most of concentrations found in clinic (between 1 and 10mg/L).

Conclusion

This study has shown for the first time that mucin may decrease the apparent PMB antimicrobial activity via two distinct mechanisms: a concentration dependent binding of the antibiotic and a proper inhibitory effect.

However, at concentrations observed in clinical practice PMB is extensively (more than 90%) bound to mucin, which would contribute mostly to the reduced antimicrobial activity. Experiments are being conducted with a susceptible strain to complement these observations.

