In vivo pharmacokinetic-pharmacodynamic modelling of Acinetobacter baumannii inoculum effect on polymyxin B in a murine thigh infection model

Alexia Chauzy 1, Grace Akrong 1, Isabelle Lamberge 1, Hélène Mifredenereski 1,2, Julien Buyck 1, William Couet 1,2 and Sandrine Marchand 1,2

1 INSERM U1070, Université de Poitiers - Poitiers (France)
2 Laboratoire de Toxicologie et Pharmacocinétique, CHU de Poitiers - Poitiers (France)

Background

• The reduction in antimicrobial activity at high bacterial densities is a microbiological phenomenon known as inoculum effect (IE).
• A significant IE was recently observed in vitro for polymyxin B (PMB) against a clinical isolate of Acinetobacter baumannii (CS01), and well described by a new pharmacokinetic-pharmacodynamic (PKPD) model (Akrong et al, AAC 2021).
• The aim of this study was to confirm this IE in vivo in a murine thigh infection model.

Materials and methods

Ethics

• This study was approved by the local ethics committee (COMETHEA) and registered by the French Minister of High Education and Research (authorization n° 2017072415099072).

Study design (Fig.1)

• Colistin-susceptible A. baumannii clinical isolate CS01 was studied (MIC PMB = 0.25mg/L).
• A neutrophic murine thigh infection model using inocula of 10^6, 10^7 or 10^8 CFU/thigh was developed.

PKP analysis

• A PKPD model, derived from the model developed after in vitro time-kill experiments, was developed using NONMEM®.
• A sequential PK/PD analysis was performed : in vivo PK data were first analyzed, then PK parameters were fixed to fit PD data.

Results

PK modelling

• PMB PK was well described by a two-compartment model including saturable absorption from the subcutaneous injection site and linear elimination (Fig.2).
• PMB plasma protein binding was concentration independent within the observed range of total concentrations (0.20–14.56 mg/L) and the unbound fraction was estimated to be 17%.
• Unbound concentrations in mice receiving a subcutaneous dose of 1 mg/kg were all below LOQ (Fig.3).

PKPD modelling

• The structural model for the bacterial population included one compartment representing drug-susceptible growing bacteria (Fig.2).
• Predicted unbound plasma concentrations were linked to the bacterial sub-model using a power function to characterize PMB antimicrobial effect (k30).
• IE was modelled by a decrease of the PMB killing rate constant (k30) when the initial inoculum increases using a linear function.
• Modelling suggests that the in vivo IE is moderate and not concentration dependent with a mean PMB killing effect 32% lower at 10^7 CFU/thigh compared with 10^8 CFU/thigh inoculum (Fig.4, Table 1).

Table 1. PMB killing rate constant (h^{-1}) derived from in vitro and in vivo model at various PMB concentrations and starting inocula.

<table>
<thead>
<tr>
<th>Inoculum (CFU/mL or CFU/thigh)</th>
<th>PMB concentration (mg/L)</th>
<th>In vitro</th>
<th>In vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>10^6</td>
<td>6.14</td>
<td>6.94</td>
<td>7.56</td>
</tr>
<tr>
<td>10^7</td>
<td>3.27</td>
<td>4.26</td>
<td>5.27</td>
</tr>
<tr>
<td>% decrease at high inoculum</td>
<td>47</td>
<td>39</td>
<td>30</td>
</tr>
</tbody>
</table>

• By contrast, in vitro model suggested that the IE was attenuated at high PMB concentration (30% decrease of killing effect at 4 mg/L and 47% at 1 mg/L between 10^6 and 10^7 CFU/mL) (Table 1).

Conclusion

A PKPD model has been successfully developed to characterize the in vivo IE of A. baumannii on PMB, which confirms the IE observed in vitro despite some slight differences between the two models.
Comparisons between model parameters demonstrated that the IE of A. baumannii on PMB activity was attenuated in vivo but could still have a real impact on in vivo PMB activity.