Pharmacokinetic/Pharmacodynamic Modelling of Antibiotic Efficacy

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Introduction

Pharmacokinetic/pharmacokinetic (PK/PD) modelling is critical in the development of therapeutics including antibiotics. The data generated is vital for dose prediction through to Phase 2 to enable more efficient dose-response study designs in addition to identifying optimal dosing regimens that can possibly suppress drug resistance. Animal model studies aim at recapitulating the infectious diseases experienced by humans, to allow for robust and validated PK/PD studies to explore drug exposures that may lead to therapeutic success. Recently preclinical PK/PD modelling has become pivotal in the regulatory process due to the difficulty in recruiting patients and the need for smaller faster trials. Traditionally rodent PK/PD models require large studies (using up to 120 mice) and carry a significant risk of failure due to poor study design. In this poster, we present the assessment of the in vivo PK/PD relationship of a novel antibiotic in a neutropenic murine model of Escherichia coli thigh muscle infection. Prior to running the study a large set of in vitro and in vivo data were mathematically modelled to generate a rational design that would be accepted by regulators but using the minimum number of mice to determine the PD driver and magnitude of efficacy. The objective was to use mathematical modelling to generate a rational study design using fewer animals and lower risk of failure to determine the PD driver of a novel antimicrobial agent with a view to optimising the clinical dose regimen in Phase 2 studies.

In silico modelling and rational design resulted in 40% reduction in the number of animals compared to a PK/PD study without applying mathematical modelling techniques

Dose fractionation

To determine the drug exposure associated with optimal effect, a formalised dose-response curve is generated based on experimental results (see Figure 1). Microbial kill is measured by the change in total microbial burden between drug-treated and untreated animals. Mice were treated with the test aricle administered intravenously at five dosing levels (Q4h): 3.75mg/kg, 7.5mg/kg, 15mg/kg, 30mg/kg and 60mg/kg. In addition, vehicle control mice were treated with test article formulation vehicle only.

Dose fractionation studies are used to determine the PK/PD driver, dose level and/or interval to inform clinical regimens. In addition, such studies provide information on maintenance regimen performance. Mice were treated with the test article delivered at fractionated dose levels as shown in Table 1.

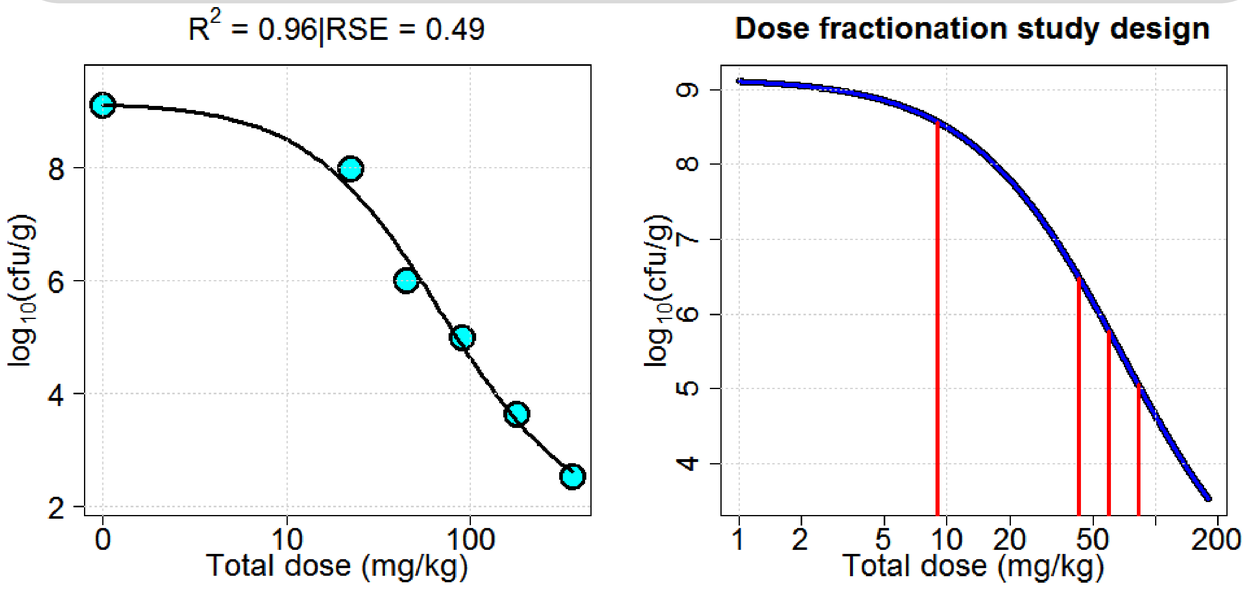


Figure 1: Hill curves. Left: dose-response curve. Right: simulated model and dose fractionation study design.

Table 1: Dose fractionation study design.

Total dose	Dosing regimen
9mg/kg	Q24h, Q12h, Q6h and Q4h
43mg/kg	Q24h, Q12h, Q6h and Q4h
60mg/kg	Q24h, Q12h, Q6h and Q4h
83mg/kg	Q12h, Q6h and Q4h

Pharmacokinetic modelling

The pharmacokinetics (PK) of the antibiotic was evaluated in mice. The compound was administered intravenously (IV); the doses and regimens used were based on the dose-response and the dose fractionation study. The PK study design is summarised in Table 2.

Table 2: PK study design.

Dose
2.5mg/kg
10mg/kg
13.83mg/kg
20.75mg/kg
41.5mg/kg
60mg/kg

A two-compartment model (shown in Figure 2) was used to fit the PK data. The mathematical expression that best describes that best describes the two-compartment IV bolus is:

$$C(t) = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t}$$

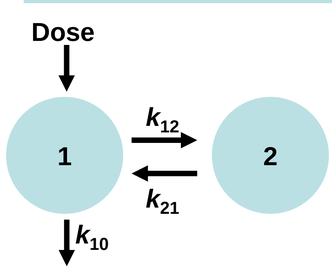


Figure 2: The two-compartment model.

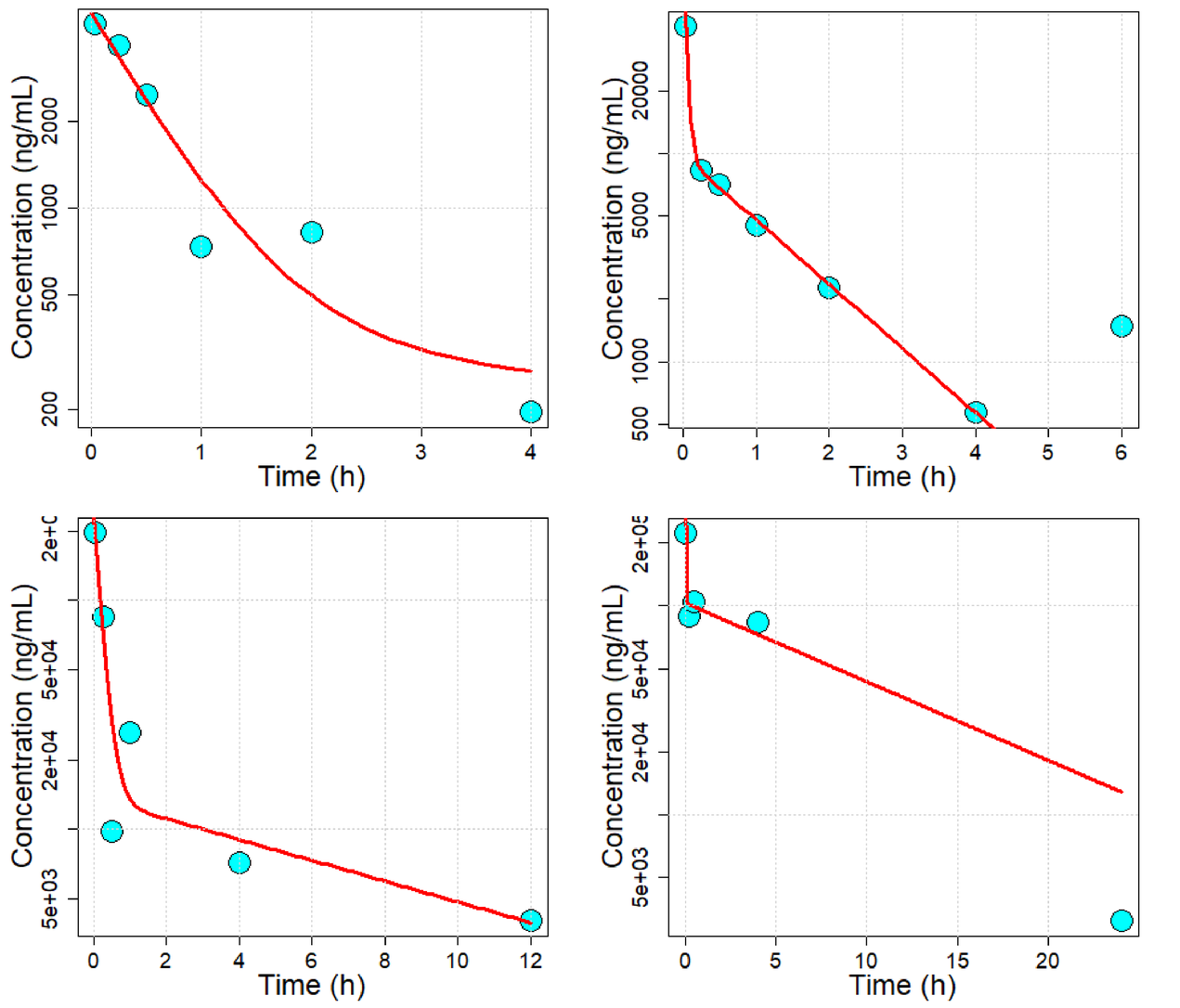


Figure 3: Biexponential fitting of PK data. Top left: 2.5mg/kg. Top right: 10mg/kg. Bottom left: 41.5mg/kg. Bottom right: 60mg/kg.

PK/PD analysis

A mathematical model was developed for each of the hybrid constants to simulate the dosing regimens used in the dose fractionation study. Examples are demonstrated in Figure 4. The PK model was used to calculate the following: (a) percentage of time above the minimum inhibitory concentration (%T>MIC), maximum concentration to MIC ratio (Peak/MIC) and area under the concentration-time curve to MIC ratio (AUC_{24}/MIC), see Figure 5.

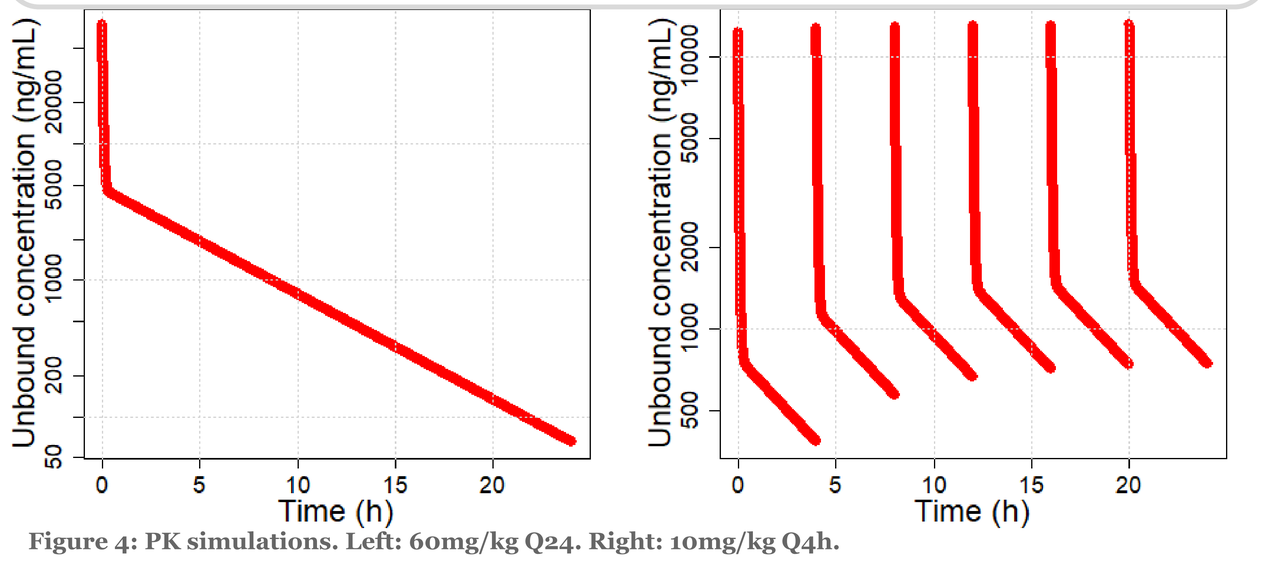
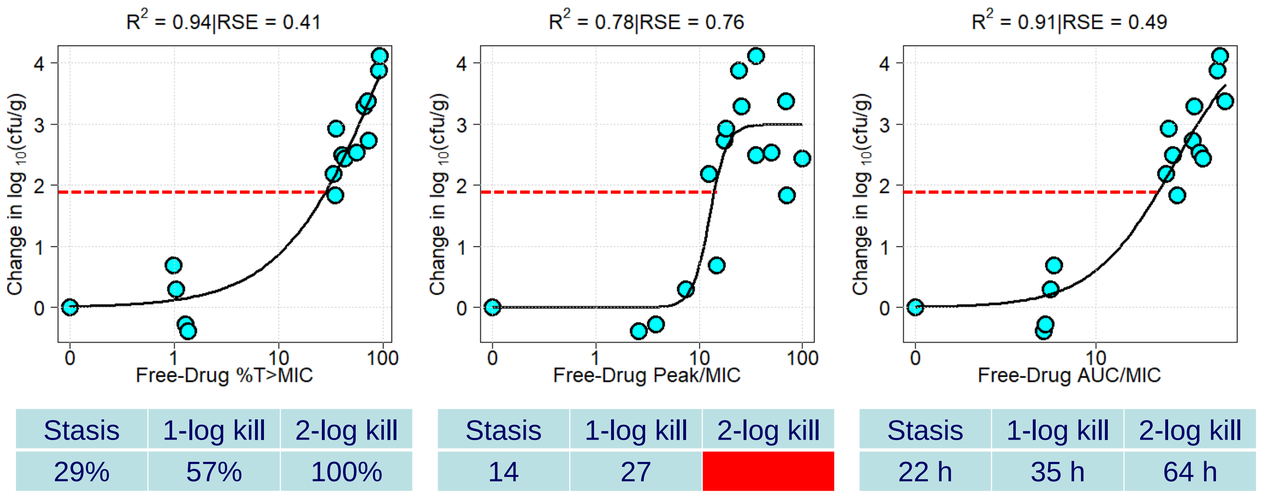


Figure 4: PK simulations. Left: 60mg/kg Q24. Right: 10mg/kg Q4h.



Stasis	1-log kill	2-log kill
29%	57%	100%

Stasis	1-log kill	2-log kill
14	27	

Stasis	1-log kill	2-log kill
22 h	35 h	64 h

Figure 5: PK/PD parameters. Left: %T>MIC. Middle: Peak/MIC. Right: AUC/MIC. The red dotted lines represent stasis.

Impact on the 3Rs

- *In silico* simulation and modelling can be used to improve study designs leading to **fewer animals being required** to achieve the experimental objectives
- *In silico* modelling techniques provide fast and cost-effective replacement of (or supplements) *in vivo* experiments.
- A combination of rational design & *in silico* modelling led to a **reduction of 40% in the number of animals** required to identify the PD driver and magnitude of effect
- Murine infection models can be used to forecast effective regimens in patients.
- Outcomes from animal data can be used to predict patient outcomes particularly in instances where clinical studies are difficult or impossible.
- Data analysis indicates efficacy of the test article is a time- or AUC-driven.