Modeling concentration-time relationships of benzylpenicillin in milk after intramuscular injection of penethamate in dairy cows

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ABSTRACT
A pharmacokinetic simulation model was constructed to predict the concentration of benzylpenicillin (BP) in milk after i.m injection of penethamate (PNT, a prodrug of BP) formulations in cows. The values of C_{max}, t_{max} and AUC_{0-24} from model simulation were comparable to that with literature data of a marketed PNT formulation (Mamyzin) and suggested a close agreement. The model was used to investigate the effect of milk volumes on the concentration of BP in milk. Such a simulation model could be useful in designing new and innovative formulations.

INTRODUCTION
Bovine mastitis is mainly caused by bacteria infecting the tissue and milk containing compartments of the udder of dairy cows. Antibiotics are used intramuscularly to treat bovine mastitis but since the cure rate of this disease is too low for certain mastitis causing organisms (Staphylococcus aureus), there is a need for new innovative products with improved efficacy. Since treatment failures can be related to the pharmacokinetics of antibiotic in milk, it is important to understand the effects of dose, delivery rate, milking frequency and milk volumes on antibiotic milk concentrations. Amongst the intramuscular treatments of mastitis available, PNT is widely used because its physicochemical properties favour penetration from blood to milk where it is rapidly hydrolysed to BP. Given the limited data on PNT in animal studies, and given the difficulties of analysing such an unstable drug, a model was developed in order to gain some insight into the pharmacokinetics of PNT and BP in milk after intramuscular administration, and to guide formulation development and the design of animal studies.

EXPERIMENTAL METHODS
Simulations were conducted using STELLA software (ISEE Systems, Inc. NH, USA) version 8.1.

The model comprises the injection site compartment, the body compartment, and the udder (two compartments: alveolar and cisternal). It was constructed in segments and then linked in a stepwise manner: Step (1) absorption (zero or first order) of PNT from i.m. injection site into the body (2) elimination of PNT and BP from the body and hydrolysis of PNT to BP in the body (3) transfer of PNT and BP from the body to alveolar milk, transfer to cisternal milk and elimination by hydrolysis of PNT and BP from milk (alveolar and cisternal) and milking of PNT and BP from milk (alveolar and cisternal) and milk production, flow of milk from alveolar to cisternal compartments and milking out of milk from the cisternal compartment.

Parameters used in the model were: pK_{a}, chemical half-life, clearance and volume of distribution (Vd), of PNT and BP. The parameter values used were based on the kinetic studies described in Jain et al., 2012. Where values were not available, estimates were made based on values for similar molecules (e.g. clearance for weakly basic drugs) or on physiological calculations (e.g. permeability (P) of PNT and BP and area (A) of the blood/milk interface).

The simulations were carried out for an i.m. aqueous PNT suspension formulation (Mamyzin®) for a cow weight of 600 kg (Friton et al., 2003). The absorption rate constants, k_{a} (first or zero order) were adjusted to best match simulated concentrations of BP in the total milk with those from literature data (Friton et al., 2003).
Simulations were also performed on milk volumes to understand how milk production might influence antibiotic concentrations in milk.

RESULTS AND DISCUSSION

The simulations for milk concentration time profile of BP based on mean square error values suggested that first-order absorption (Figure 1) may be occurring for the Mamyzin formulation.

Table 1 shows the values of $C_{\text{max}}$, $t_{\text{max}}$ and $\text{AUC}_{0-24}$ from model simulation compared to that with Mamyzin® data and suggests a close agreement between STELLA model predictions and Mamyzin® data.

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ (µg mL$^{-1}$)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>$\text{AUC}_{0-24}$ (µg.h mL$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamyzin®</td>
<td>0.4 ± 0.1</td>
<td>4.7 ± 2.6</td>
<td>4.6 ± 1.1</td>
<td>5.1 ± 1.0</td>
</tr>
<tr>
<td>STELLA model</td>
<td>0.4</td>
<td>4.0</td>
<td>3.8</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Figure 2 shows that increasing milk production from 8 L day$^{-1}$ to 36 L day$^{-1}$ resulted in 1.75 times decrease in concentration of BP in total milk at $t_{\text{max}}$ suggesting the influence of milk volumes on the concentrations of BP in total milk. This means that alteration in dose may be required for cows producing different milk volumes in different stages of lactation to maintain BP concentrations above MIC$_{90}$ in the milk.

CONCLUSION

A pharmacokinetic simulation model was constructed for i.m. PNT formulations. The simulations for first-order absorption rate model showed that the milk concentration time profile of BP was comparable with the literature data for Mamyzin®. Importance should be given to reporting milk yield and milking frequency as the model suggests that they influence the antibiotic levels in milk. This model may be useful in providing insights into design of formulations and animal studies, before proceeding to expensive animal trials. Although the model has been written for PNT, with minimal modification in the pharmacokinetic parameters such as $pK_a$, chemical half-life as a function of pH, clearance, Vd and PA, it could be utilised for predicting concentration of other drugs in milk.

REFERENCES