Implementation of variability in a physiologically-based pharmacokinetic approach for simulating the first-in-animal study

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INTRODUCTION

Specificities of lung disease therapeutic area:
- modeling of the process of drug inhalation
- estimation of drug concentrations in lungs.

Physiology-based pharmacokinetic (PB-PK) modeling approaches are useful tools for exploring these items. A generic, basic PB-PK model was proposed for simulating plasma and tissue concentration-time curves after IV dosing (Germani 2005, Poulin & Theil 2002), based on the fraction bound in plasma and hepatic intrinsic clearance. This approach was used for prioritizing the in vivo pharmacokinetic screen. In this study, the basic model was further modified for accommodating the inhalation process and to evaluate the influence of different sources of variability using stochastic simulations.

METHODS

System of mass balance equations:

\[
\frac{dC_T}{dt} = Q_T \cdot C_{in} - \sum_{i=1}^{n} Q_i \cdot C_i
\]

where:
- \(C_T\): total concentration
- \(Q_T\): blood flow
- \(C_{in}\): input concentration
- \(Q_i\): flow to tissue
- \(C_i\): concentration in tissue

Modeling of tissue partition:

\[
\log\left(\frac{C_T}{C_i}\right) = \log\left(\frac{Q_T}{Q_i}\right) + \log\left(\frac{k_{wi} + k_{wi}^{-1}}{k_{wi} + k_{wi}^{-1}}\right)
\]

where:
- \(k_{wi}\): tissue-to-plasma partition coefficient

Modeling of clearance contributions:

\[
E_T = \frac{Q_{CLT}}{V_{CLT}}
\]

where:
- \(Q_{CLT}\): hepatic clearance
- \(V_{CLT}\): hepatic blood flow

Stochastic simulation of inhalation of cocaine. \(k_{wi}\), \(k_{wi}^{-1}\), \(Q_T\) (cardiac flux) are supposed to be normally distributed with CV=25%.

These results suggest that the variability of \(Q_T\) is less important than the variability of the compound-specific input parameters.

REFERENCES


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