POPULATION PHARMACOKINETIC MODELLING OF ENTEROHEPATIC RECIRCULATION OF ROFECOXIB IN RATS

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Introduction
Rofecoxib (VIOXX®) belongs to the family of non-steroidal anti-inflammatory drugs (NSAIDs) and is a potent and highly selective cyclo-oxygenase-2 (COX-2) inhibitor. In rats, rofecoxib displays enterohepatic recirculation (EHC) [1]. Rofecoxib is metabolised by liver P-450 into 5-hydroxyrofecoxib and 5-hydroxyrofecoxib glucuronide, which is then excreted from the bile into the duodenum. After deconjugation and reduction, rofecoxib is regenerated and reabsorbed from the GI tract [2].

Different approaches have been developed to describe EHC data. Thus far, classical compartmental models with recycling loops do not appear sufficient to describe EHC in animals without gallbladder (e.g., rats), as model parameters are not suitable to describe noisy data with irregular patterns.

Methods
Male Sprague-Dawley rats, instrumented with one or two canulas, received an IP (10 mg/kg), an oral (5 mg/kg) or an IV dose of rofecoxib (6, 10 mg/kg in 5 min, 0.5 mg/kg in 60 min).

Data analysis
Constrained longitudinal splines can be used to describe and interpolate pharmacokinetic data in the absence of rhythmic patterns [3]. A longitudinal spline consists of a template spline, common to all subjects, and an individual-specific distortion spline. Data was analysed separately by route of administration.

Conclusions
• In contrast to humans where EHC shows a rhythmic pattern associated with meals, rats do not display such cyclic behaviour. This limits the use in rodents of the few published approaches to describe EHC in humans.
• CLS is a semi-parametric approach that can be used to characterise EHC in rats. However, data extrapolation is limited if the design of subsequent experiments have different sampling schemes or include other routes of administration. In addition, covariates cannot be easily implemented into distortion spline parameters.

Our objective is to investigate the PK/PD relationship of rofecoxib in animal models of analgesia. However, prediction of individual concentrations is very difficult due to large inter- and intra-individual variability in pharmacokinetics. This problem is aggravated by limitations in the sample size per animal.

In this study, we explored the feasibility of a semi-parametric and a parametric approach to estimate the contribution of EHC to the increase in total exposure to rofecoxib, namely: 1) constrained longitudinal splines (CLS) and 2) an adaptation of a compartmental model, which includes first-order rates for recycling. The pop PK model was developed with dense data set containing IV, IP and PO data.

Arterial blood samples were collected via a permanent canula (a. femoralis) at pre-defined sampling times. Plasma concentrations were measured by LC-MSMS analysis.

Results
A 4th-order polynomial with five breakpoints was used for modelling IV and PO data. The CLS model was not able to describe the large inter-individual variability in the data after IP administration.

A parametric approach that incorporates first-order rates seems to capture the pharmacokinetic performance with data from bile-cannulated animals. However, prediction of individual concentrations is very difficult due to large inter- and intra-individual variability in pharmacokinetics. This problem is aggravated by limitations in the sample size per animal.

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Compartmental model
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References