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.

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.

Methods

Male Sprague-Dawley rats, instrumented with one or two cannulas, 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).

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

Data analysis

CLS model

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.

Longitudinal spline:

$$L(t) = \sum_{k=1}^{nb_1} \alpha_k \left[\sum_{i=1}^{nb_2} \beta_{ij} N_{i,\xi_2}(k) \right] N_{k,\xi_1}(t)$$

nb_1 = number of breakpoints, $N_{k,\xi 1}(t)$ are natural cubic basis functions of the template spline, $N_{k\xi 2}(t)$ are linear spline basis functions of the distortion spline; α are coefficients (elements of population parameters) and β are coefficients for subject j (function of a random vector ETAj in NONMEM), ξ_1 and ξ_2 are vectors with elements the breakpoints

Compartmental model

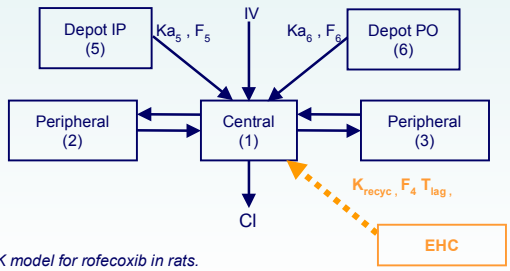

Figure 1: PK model for rofecoxib in rats.

Results

CLS model

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.

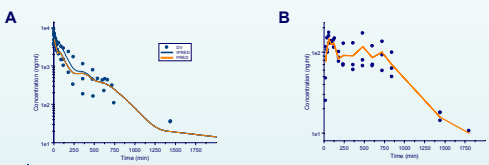

Figure 2:PK of rofecoxib after IV (10 mg/kg in 5 min, panel A) and oral (5 mg/kg, panel B) doses. The CLS model required separate data analysis for each route of administration.

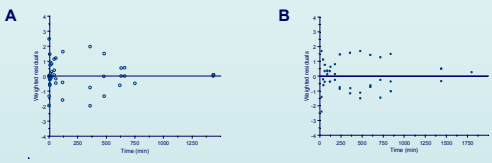

Figure 3: CLS model - Weighed residuals after IV (panel A) and oral administration (panel B).

EHC compartmental model

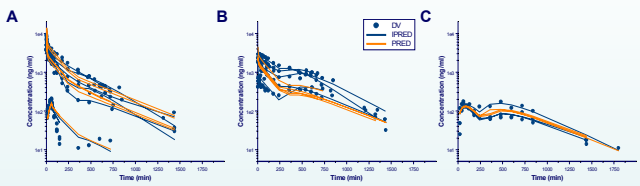

Figure 4: PK of rofecoxib after iv (A), ip (B) and po (C) administration. Predicted profiles were estimated by simultaneous modelling of all three routes and doses (fig 1).

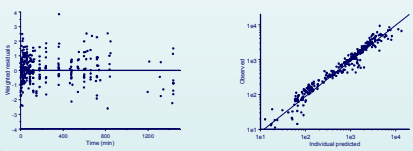

Figure 5: Diagnostic plots of the adapted compartmental model for EHC of rofecoxib

Table 1: Population pharmacokinetic parameter estimates for Cl, V_1, D_4, F_4, $K_{recycling}$, F_5 (ip) and F_6 (po) and their Coefficient of Variation (CV%). Intra-individual residual variability was 32%. Inter-individual variability was 76% for Cl and 65% for F_5 (ip) and 388% for $K_{recycling}$. T_{lag} was fixed on population estimate obtained by separate analysis (260 min).

Cl (ml/min)	V_1 (ml)	D_4 (min)*	F_4 (%)	$K_{recycling}$ (min^{-1})	F_5 (%)	F_6 (%)
4.45 (23%)	130 (62%)	96.5 (31%)	28% (26%)	0.002 (22%)	46.2% (32%)	13.8 (19%)

** D_4 estimation required identification of time patterns (0,1) as covariates.*

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.

•A parametric approach that incorporates first-order rates seems to capture the variable increase in concentrations associated with EHC, without the limitations of the CLS model. Prospective evaluation of this model requires comparison of performance with data from bile-cannulated animals.

•Our preliminary findings suggest that EHC does not only increase total exposure to rofecoxib in rats, but it prolongs the duration of exposure to pharmacologically active concentrations.

References

[1] Halpin et al. Drug Metab Dispos. 28 (10) 2000 [2] Baillie et al. Drug Metab Dispos. 29 (12) 2001 [3] Park et al. J. Pharmacokinet. Biopharm 25 (5) 1997