Evaluation of an EHC model: predicting the influence of cholestyramine on the pharmacokinetics of meloxicam

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Background

Concentration-time profiles of drugs undergoing enterohepatic circulation (EHC) are often associated with multiple peak phenomena and a prolonged apparent half-life. Basic models describing EHC were reported in the literature [1]. Lehr et al. developed an EHC model considering the clock time as a control variable for the gall bladder emptying [2].

Objectives

The objective of this study was to apply and evaluate the model by using data of meloxicam, a drug undergoing EHC [3]. Evaluation was to be performed by a) fitting the model to observed meloxicam plasma concentrations and b) by predicting the effect on pharmacokinetics when interrupting the EHC by co-administration of cholestyramine.

Patients and Methods

Study characteristics

Twelve healthy male subjects, aged between 27 and 50 years, were treated in a randomized cross-over study with 30 mg meloxicam single dose given intravenously (bolus) either alone or concomitantly with cholestyramine (4 g Quantalan® 50 suspended in 200 mL water) given three times a day for four days. Consecutive meloxicam doses were separated by at least a 14-days wash-out period. Plasma samples were taken 0.05, 0.08, 0.16, 0.25, 0.5, 0.75, 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 9.5, 10, 12, 24, 32, 48, 72 and 96 h after administration of meloxicam. Further details of the study can be found in literature [3].

Table 1. Dataset and study characteristics

	number of subjects	number of samples above LLQ*	number of samples below LLQ*	Time of dosing
meloxicam	12	227	13	7:45 – 8:00 A.M.
meloxicam and cholestyramine	12	217	23	7:45 – 8:00 A.M.

* lower limit of quantification

Pharmacokinetic data analysis

Overall, 444 plasma concentrations were available for model development [Table 1]. Both study arms were modeled simultaneously. Analyses were performed using NONMEM, version V, level 1.1; ADVAN 6 subroutine; centering Laplace estimation method was applied. A three compartment model (central, peripheral and bile) with first order elimination was used to describe the data [Figure 1]. The mass transfer from gall bladder to the central compartment (bile flow) was controlled by a sine function (FX), switching the rate constant K_{21} periodically on and off. For the cholestyramine treatment arm an additional elimination rate constant out of the gall bladder compartment (K_{20}) was implemented. Total interruption of EHC for simulation was mimicked by setting the rate transfer constant from bile to central compartment (K_{21}) to zero.

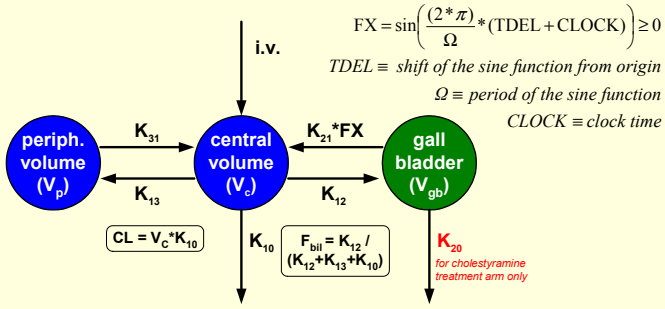

Figure 1. Schematic EHC model of meloxicam

Results

The model successfully described the plasma concentration-time profiles of all subjects [Figure 2] including the multiple peak phenomena [Figure 4]. Clearance and half-life of meloxicam after intravenous administration were determined to be 0.396 L/h and 18.9 h respectively. Simulating the interruption of the EHC resulted in a predicted increased clearance of 0.75 L/h and a shortened half-life of 10.0 h. These model-predicted values are in close agreement with the observed results from the individual compartmental analysis [Table 3]. Parameters Ω and TDEL revealed a three times daily release of the gall bladder at physiological reasonable time points [Figure 3].

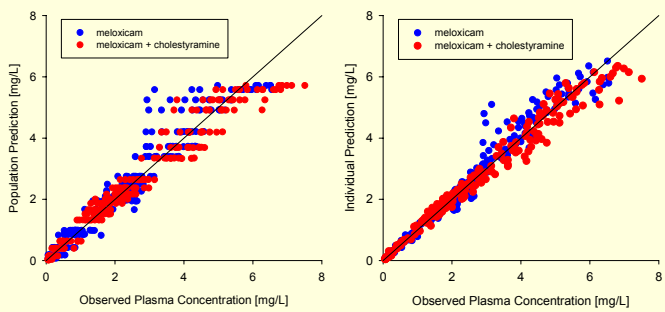

Figure 2. Goodness of fit plots; population (left panel) and individual predictions (right panel), respectively, versus observed plasma concentrations, separated by treatment arms

Table 2. Results of estimated parameters

Model Parameter		Estimate	Relative Standard Error %
V_c	[L]	5.04	1.04
V_p	[L]	5.18$	/
V_{gb}	[L]	0.29$	/
CL	[L/h]	0.396	1.1
F_{bil}	[%]	8.42	9.35
K_{21}	[h^{-1}]	3.85	28.8
K_{13}	[h^{-1}]	0.683	4.71
K_{31}	[h^{-1}]	0.664	3.93
K_{20}	[h^{-1}]	1.63	51.2
TDEL	[h]	-0.285	44.9
Ω	[h]	7.46	1.37
Interindividual variability			
IIV CL	[%CV]	29.6	29.7*
IIV V_c	[%CV]	9	24.4*
Residual variability			
proportional	[%CV]	9.9	14.9*
additive	[mg/L, SD]	0.03	43.9*

$ derived parameter
*given on the variance scale

Table 3. Comparison of half-life and clearance of meloxicam

PK parameters		meloxicam		meloxicam + cholestyramine	
		*reported by Busch et al.**	*estimated by Pop PK model*	*reported by Busch et al.**	*predicted by POP PK model$*
half-life	[h]	19.5	18.9	12.7	10.0
clearance	[L/h]	0.426	0.396	0.636	0.75

* Busch et al. [3] by individual compartmental analysis
$ mimicked by setting K21of EHC population PK model to zero

Discussions

EHC of meloxicam could be successfully described by the model proposed by Lehr et al. Implementation of the clock time in the model allows to describe the gall bladder emptying in a circadian rhythm which is physiological plausible.

Interruption of the EHC could reliably be predicted. Slight over prediction of the influence of interrupting EHC on clearance and half-life might be caused by an incomplete interruption of the EHC with cholestyramine. Small multiple peaks were even present in subjects treated with cholestyramine supporting this interpretation.

The model might serve as a tool to describe the pharmacokinetics of drugs undergoing EHC and to assess the impact of interrupting the EHC e.g. by co-medication with cholestyramine or charcoal.

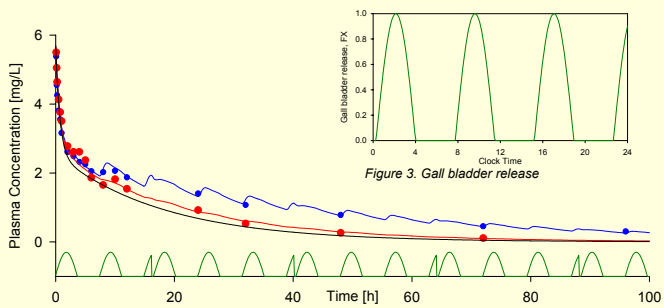

Figure 3. Gall bladder release

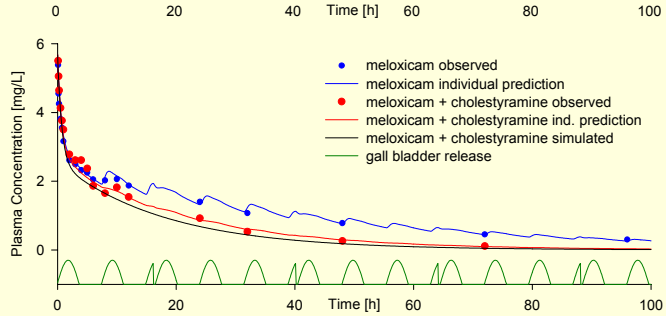

Figure 4. Individual plasma concentration time profiles of selected subjects

Conclusions

- EHC of meloxicam could be successfully described.
- Interruption of the EHC could reliably be predicted.
- Slight over prediction of the influence of interrupting EHC on clearance and half-life might be caused by an incomplete interruption of the EHC with cholestyramine.
- The model might serve as a tool to describe the pharmacokinetics of drugs undergoing EHC and to assess the impact of interrupting the EHC e.g. by co-medication with cholestyramine or charcoal.

References: [1] Roberts M. et al., Clin. Pharmacokinet., 41, 751-790, 2001; [2] Lehr. et al., PAGE Meeting 2004, www.page-meeting.org; [3] Busch U. et al., Eur. J. Clin. Pharmacol., 48, 269-272, 1995