Clock time as a control variable for gall bladder emptying in an enterohepatic circulation model

T. Lehr[1], C. Tillmann[2], A. Staab[2], D. Trommeshauser[2], H.G. Schaefer[2] and C. Kloft[1]

[1]Dept. Clinical Pharmacy, Institute of Pharmacy, Freie Universitaet Berlin, Kelchstr. 31, 12169 Berlin, Germany (ckloft@zedat.fu-berlin.de)

[2]Dept. Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma, Germany

Background

Plasma concentration-time profiles (PCTP) of an investigational drug X in clinical development showed multiple peaks and a long half-life of about 200 h. Enterohepatic circulation (EHC) has often been associated with multiple peak phenomena in PCTP and a prolonged half-life [1]. In the literature, models have been presented by Ezzet et al. [2] and Funaki [3] to describe the pharmacokinetics (PK) of drugs undergoing EHC. However, these models are limited in the number of gall bladder (GB) emptyings, resulting in a limited number of peaks that can be described in the PCTP by the model. Wajima et al. [4] proposed an improved model using a periodic sine function [Fig. 2] to control gall bladder release, which does not result in a limited number of GB emptyings.

Objectives

The goal of this investigation was to apply and optimize the sine function model to explore whether EHC might be a possible explanation for the specific properties of the compound investigated.

Patients and Methods

Study characteristics

PK profiles of 47 healthy male subjects from three studies [Table 1] (single and multiple oral dosing as well as iv infusion) with 997 plasma concentrations were analyzed. Sampling times ranged up to 1008 h after the last dose administration.

Table 1. Study characteristics

	Study A	Study B	Study C
Subjects	21	14	12
Observations	451	231	315
Dose route	iv infusion	oral	oral
Dosing	single dosing	single dosing	multiple dosing
Start of dosing	8:30 – 9:00 A.M.	10:00 – 11:00 A.M.	10:00 – 10:30 A.M.

Pharmacokinetic data analysis

Analyses were performed using NONMEM, version V, level 1.1; ADVAN 6 subroutine; FO (study C; combined studies A and C) and FOCE INTERACTION (studies A and B) estimation methods were applied. The data were best described by a two compartment model (central and gall bladder) with first order absorption and first order elimination [Fig. 1]. The mass transfer from gall bladder to the central compartment (bile flow) was controlled by a sine function (FX) [Fig. 2], switching the rate constant periodically on and off.

Several trigonometric functions (e.g. sine, tangent) were tested and applied to each study separately as well as to combined studies.

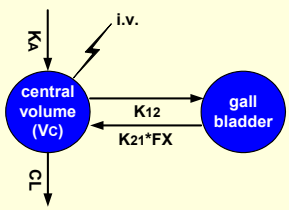

Figure 1. Schematic EHC model

$$FX = \sin\left(\frac{(2*\pi)}{\Omega} * (TDEL + TIME)\right) \geq 0 \qquad \textit{Wajima et al.}$$

$$FX = \sin\left(\frac{(2*\pi)}{\Omega} * (TDEL + CLOCK)\right) \geq 0 \qquad \textit{Lehr et al.}$$

TIME	*time elapsed from first dose*
CLOCK	*clock time*
Ω	*period of the sine function*
TDEL	*start time difference of the sine function period for a particular study*

Figure 2. Original (Wajima et al.) and modified (Lehr et al.) sine functions

Results

Implementation of "clock time" rather than "time elapsed from first dose" in the sine function was found to be a prerequisite for successful application of the EHC model. The model described the plasma concentration-time profiles of all studies adequately [Fig. 3; Fig. 4]. Results of estimated parameters are listed in Table 2. The frequency of the gall bladder emptying was found to be similar across the three studies (2.1 – 2.7 times per day). Modeling of combined studies required implementation of a study specific time parameter (TDEL), to account for different administration times of the studies.

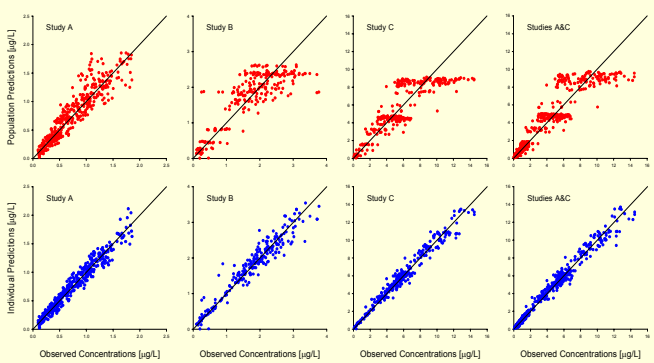

Figure 3. Goodness of fit plots; population and individual predictions respectively versus observed plasma concentrations

Table 2. Results of estimated parameters

Model parameter		Study A FOCE INT		Study B FOCE INT		Study C FO		Studies A & C FO	
		EST [a]	RSE [b]	EST [a]	RSE [b]	EST [a]	RSE [b]	EST [a]	RSE [b]
K_A	[1/h]	n.a.		0.374	(17)	0.299	(23)	0.281	(21)
V_C	[L]	328	(5)	506	(4)	509	(7)	579	(5)
K_{12}	[1/h]	0.239	(10)	0.1 FIX		0.0134	(20)	0.0273	(24)
K_{21}	[1/h]	0.213	(4)	0.263	(5)	0.0865	(25)	0.117	(17)
CL	[L/h]	2.46	(5)	2.7	(7)	2.19	(11)	2.68	(6)
TDEL	[h]	4.26	(2)	4.73	(6)	1.81	(1)	[A] 5.72 [C] 4.18	(2) (3)
Ω	[h]	9.75	(1)	11.2	(1)	8.92	(1)	10.8	(1)
F1	[%]	n.a.		n.a.		n.a.		130	(7)
Inter-individual variability									
ω K_A	[%CV]	n.d.		54.7	(65)	n.d.		n.d.	
ω V_C	[%CV]	17.3	(62)	17.1	(30)	17.5	(30)	16.3	(25)
ω K_{12}	[%CV]	26.4	(73)	n.d.		n.d.		n.d.	
ω K_{21}	[%CV]	n.d.		n.d.		93.1	(45)	n.d.	
ω CL	[%CV]	20.1	(30)	27.3	(30)	34.6	(41)	28.3	(28)
Residual error									
σ proportional	[%CV]	9.33	(20)	11.2	(38)	9.64	(18)	12.1	(16)
σ additive	[µg/L]	0.059	(23)	0.145	(58)	0.133	(78)	0.07	(22)

[a] Population estimate
[b] Relative standard error in percent (standard error divided by population estimate*100)
n.a.: not applicable; n.d.: not determined

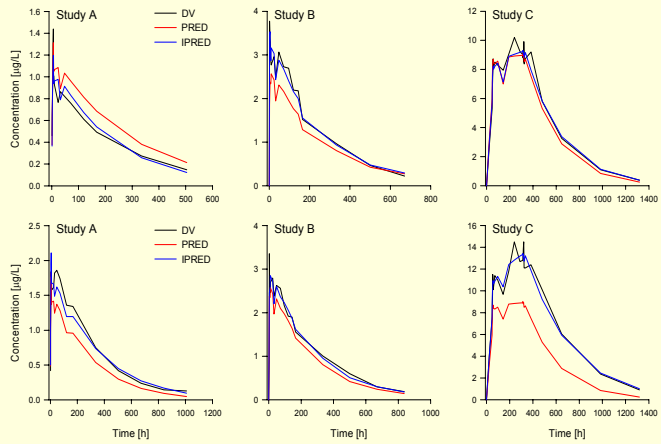

Figure 4. Individual plasma concentration time profiles of selected subjects; DV: observed plasma concentration; PRED: population prediction; IPRED: individual prediction

Conclusions

The model presented by Wajima et al. has the limitation that the on- and offsets of the gall bladder emptyings do not occur at the same time points of a day [Fig. 5], if the estimated Ω is not an integer factor of 24. Thus, a successful application of this model to drugs with a long half-life and a resulting long sampling schedule over weeks is difficult. By implementation of the clock time the sine function is reset every day resulting in a stabilized model. In consequence, this model only allows a similar gall bladder emptying rhythm each day [Fig. 5]. The model presented can explain multiple peak phenomenon in PCTP. Thus, the observed multiple peak phenomenon and the long half-life of the compound investigated might be explained by an enterohepatic circulation.

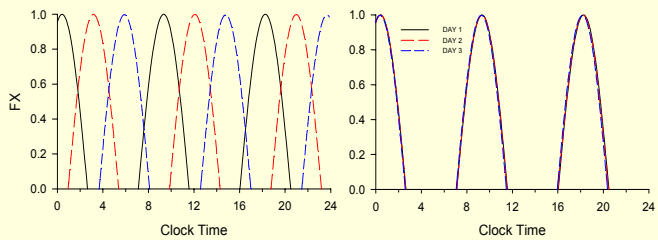

Figure 5. Gall bladder emptying over 3 days without correction for clock time (left panel) and with correction for clock time (right panel); Ω = 8.92 h, TDEL= 1.81 h (study C)

Summary

- A model was successfully developed that describes the multiple peak phenomenon of the compound investigated
- EHC might be a possible explanation for the observed properties of the compound
- Implementation of clock time as a control variable for gall bladder emptying results in a stabilized EHC model that can be applied especially for drugs with long half-life, long sampling period and multiple peak phenomenon
- Modeling of combined studies is also possible, if a study specific time parameter (TDEL) is implemented

References: [1] Roberts M. et al., Clin. Pharmacokinet., 41, 751-790, 2001; [2] Ezzet F. et al., Clin. Ther., 23, 871-885, 2001; [3] Funaki T., J. Pharm. Pharmacol., 51, 1143-1148, 1999; [4] Wajima T. et al., J. Pharm. Pharmacol., 54, 924-934, 2002