Non-Linear Population Pharmacokinetic Model for Otamixaban in Healthy Male Subjects

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ABSTRACT

OBJECTIVES

Otamixaban (OTAM) is a direct Factor Xa inhibitor for the intravenous treatment of arterial thrombosis. Healthy subjects (Phase I) showed a more than dose-proportional plasma exposure with increasing doses over a 100-fold dosing range. This phenomenon could be possibly related to a partial saturation of the biliary elimination and/or metabolism of OTAM, while renal excretion is maintained. This work describes the elaboration of a population pharmacokinetic model with Michaelis-Menten elimination that accounts for the non-linear pharmacokinetics of otamixaban in healthy subjects.

METHODS

OTAM was administered intravenously to healthy male subjects (6 per dose group, 14 dose groups) as 6h- or 24h-infusions (1.7 to 183 µg/kg/h) with or without a bolus dose (60 or 140 µg/kg). OTAM plasma concentrations were measured at 13 to 23 pre-defined sampling times by LC/MS/MS. Nonlinear mixed effects model analysis was performed using NONMEM/S-PLUS programs in a Linux Cluster environment. FO and FOCE-1 estimation methods were subsequently used throughout the model building process. Two- and three-compartment models with proportional error, using ADVAN3 and ADVAN11 subroutines, respectively, were built and converted into differential equations (ADVAN6). A $DES block was added that accounted for a dual elimination process with a saturable (Michaelis-Menten) (CLS) and a non-saturable (CLR) component. Final model selection was based on the minimal value of objective function (MVOF) and on the goodness of fit derived from the model parameter values and diagnostic plots.

RESULTS

A three-compartment model with proportional error and dual elimination was retained. This model proved to be superior to a two-compartment model as indicated by the difference in objective function ΔOF=1140. The dual elimination process with a Michaelis-Menten component improved the three-compartment model fit (ΔOF=233). The mean (CV%) values for the main parameters were V=13.3 L (6.1%), CL=18.6 L/h (24.7%), CLS=22.9 L/h (19.9%), CLR=8.99 (5.7%) L/h, C50=372 (29.0%) ng/mL, and KM=1.72 h^{-1}.

CONCLUSIONS

This approach illustrates the integration of a plausible physiologic mechanism into the population pharmacokinetic model of otamixaban, namely a partial saturation of the biliary elimination and/or metabolism, as an attempt to better understand and describe the time course of the plasma concentrations with increasing doses in healthy subjects. A three compartment non-linear PK model with dual elimination showed the lowest VOF. A less complex model might however be suitable and is preferred for future drug development.

INTRODUCTION

- Otamixaban (OTAM) is a direct Factor Xa inhibitor for the intravenous treatment of arterial thrombosis.
- Healthy subjects showed a non-dose-proportional plasma exposure over a 100-fold dosing range of IV infusions given with or without a bolus dose (*Fig.4*).
- This non-dose proportional plasma exposure had been successfully taken into account by expressing V (2 CP model, WINNONLIN) or Cl and K_{13} (3CP POPPKPD model, NONMEM) as a function of the infusion rate [1,2].

Fig.1: Concentration-time Profiles after 6h-Infusions of OTAM (Mean, n=6)

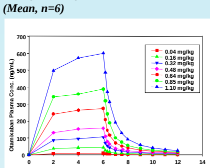


Fig.2: Concentration-time Profiles after Bolus + 6h-Infusions of OTAM (Mean, n=6)

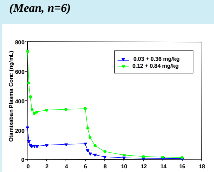


Fig.3: Concentration-time Profiles after 24h-Infusions of OTAM (Mean, n=6)

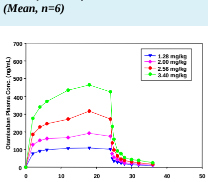
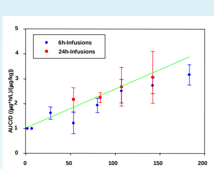
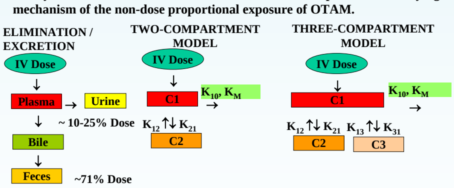


Fig.4: AUC/D vs. Infusion Rate (Mean ± SD, n=6)



The non-dose proportional plasma exposure of OTAM was manifested by an increase in AUC/D, and a 30% decrease in Cl and V, while t1/2 remained unchanged. OTAM is excreted unchanged in urine (~ 10-25% of the dose) and as metabolites in feces (up to 75% of the dose). Partial saturation of the biliary elimination and/or metabolism could be a possible underlying mechanism of the non-dose proportional exposure of OTAM.



OBJECTIVES

Elaboration of a Population Pharmacokinetic (POPPK) model for OTAM using rich sampling data. The following criteria will be evaluated:

- The model (two- *vs.* three-compartment model) should adequately describe therapeutically relevant individual plasma concentration-time profiles.
- The non-dose proportional plasma exposure over the investigated dosing range (7 to 183 µg/kg/h of OTAM) should at least be captured over the intended therapeutic dosing range, i.e. 35 to 175 µg/kg/h of OTAM.

MATERIAL AND METHODS

MATERIALS

Rich OTAM plasma concentration-time data were collected in healthy male subjects from two parallel group rising dose studies (6 subjects per dose group, 13 dose groups) after:

- 6h-infusions of 17 to 183 µg/kg/h of OTAM with or without a bolus dose (*Fig.1 and 2*),
- 24h-infusions of 53 to 142 µg/kg/h of OTAM (*Fig.3*)

OTAM plasma concentrations were measured by LC/MS/MS with a Lower Limit of Quantitation (LLOQ) of 1 ng/mL.

Population characteristics were age (19-40 years), body weight (54.6-92.6 kg), height (156-192 cm), Body Mass Index (BMI) (18.9-26.9), and creatinine clearance (Clcr) (75.1-132.5 mL/min).

NONMEM (GloboMax Corporation) for NONLinear Mixed Effects Model analysis installed on a customized Popkin Linux Cluster environment [3].

METHODS

In parallel development of the two- (2CP) and three-compartment (3CP) base models. The mixed additive/proportional error model was reduced to a proportional error model

Y = IPRED*(1+YREL)

First order (FO) and First Order Conditional Estimation (FOCE) methods were used.

The non-dose proportional plasma exposure is expressed in this model as a partially saturable clearance, where CL_R is the linear (non-saturable) clearance and Cl_S is the saturable clearance that follows the Michaelis-Menten equation [4].

$$V = \frac{Vmax * S}{S + Km}$$

V= velocity reaction (h^{-1})
S = concentration (ng/ml)
Km = conc. at 50% of Vmax (ng/mL)

Stepwise model building:

- 2CP and 3CP NONMEM models were built using the ADV3/TRANS4 and ADV11/TRANS4 commands, respectively, with initial parameter estimates from 2CP and 3CP models (WINNONLIN, Pharsight Corporation).
- Control files commands were converted into differential equations (ADV6) and the model parameters were verified.
- A dual elimination pathway, one with saturable (CL_S) and one with non-saturable (CL_R) elimination, was integrated into the differential equation that described the mass transfer for the central compartment by addition of the terms

-A(1)*K10 - A(1)*KM/ (1+CP/C50),

where CP=A(1)/S1, KM=Cl_S/V1, and C50 is the concentration at 50% of Vmax [4]

Criteria for the final base model selection were:

- Reasonable parameter estimates of THETAs and ETAs and minimal value of objective function (MVOF),
- Goodness of fits (GOF), including IPRE and PRED vs. OBS, IND and POP Weighted RES vs. IPRE and PRED, IND and POP Weighted RES vs. Time, Histograms/Box plots THETAs and ETAs, Spaghetti plots CONC, PRED, IPRE vs. Time.

Stability of the final 2CP and 3CP model parameter estimates (FO) was verified by nonparametric bootstrap analysis (creation of 250 new data samples).

Simulations of plasma concentration-time profiles after high and low doses of OTAM were performed for 50 subjects using the four models.

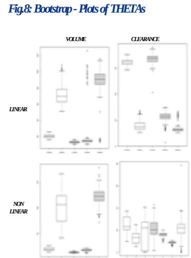
RESULTS

Table 1: Two- (2CP) and three (3CP) Compartment Population PK Model Parameters - THETA (SE) values

MODEL / PARAMETER		2CP LINEAR	2CP NON LINEAR	3CP LINEAR	3CP NON LINEAR
V1	*L*	20.5 (2.13)	18.3 (1.24)	13.1 (1.04)	13.3 (0.81)
V2	*L*	67.7 (12.5)	118 (15.2)	14.2 (1.28)	18.1 (1.48)
V3	*L*	-	-	90.5 (9.58)	124 (11.3)
CL	*L/h*	32.3 (1.10)	22.4 (2.62)	33.5 (1.58)	18.6 (4.60)
CLS	*L/h*	-	15.2 (2.88)	-	22.9 (4.56)
CLR	*L/h*	-	24.5 (5.36)	-	8.99 (0.52)
C50	*ng/mL*	-	75.7 (25.4)	-	372 (108)
MVOF	-	7920	7841	6934	6701

BOOTSTRAP

Fig.8: Bootstrap - Plots of THETAs



SIMULATIONS

Table 2: Simulations (50 Subjects, Mean (CV%))

Dose	IV Bolus mcg/kg	Infusion mcg/kg/h	C_{5min} (ng/mL) Obs	2CP	2CPNONLIN	3CP	3CPNONLIN
Low	30	60	216 (12)	104 (44)	111 (32)	153 (43)	143 (38)
	-	53	-	-	-	-	-
High	120	140	735 (21)	406 (38)	433 (33)	560 (39)	600 (37)
	-	142	-	-	-	-	-

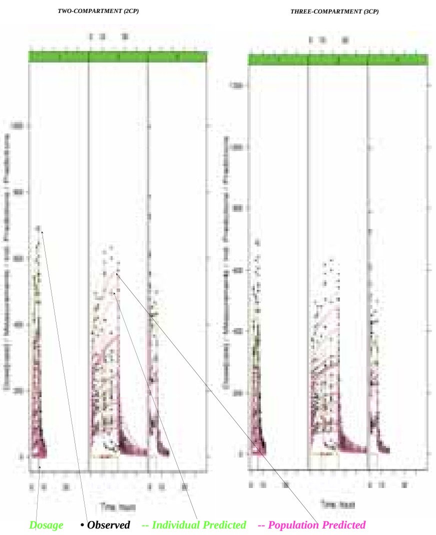
Dose	IV Bolus mcg/kg	Infusion mcg/kg/h	C_{ss} (ng/mL) Obs	2CP	2CPNONLIN	3CP	3CPNONLIN
Low	30	60	106 (9)	127 (34)	109 (32)	110 (43)	104 (36)
	-	53	101 (20)	118 (35)	104 (30)	123 (45)	113 (38)
High	120	140	344 (30)	285 (38)	265 (34)	262 (42)	274 (31)
	-	142	413 (38)	302 (36)	320 (32)	324 (47)	341 (34)

Dose	IV Bolus mcg/kg	Infusion mcg/kg/h	C_{6h} Post-End-of-Infusion (ng/mL) Obs	2CP	2CPNONLIN	3CP	3CPNONLIN
Low	30	60	7.0 (22)	4.3 (101)	4.9 (109)	7.8 (80)	8.5 (86)
	-	53	2.6 (19)	7.8 (120)	7.7 (134)	17 (112)	17 (74)
High	120	140	19 (19)	14 (108)	19 (96)	22 (109)	24 (52)
	-	142	30 (29)	21 (114)	41 (130)	43 (91)	54 (71)

The more complex three-compartment non-linear pharmacokinetic model with partially saturable elimination showed the lowest MVOF, but did not yet fully describe the non-linear plasma exposure of OTAM.

RESULTS Cont'd

Fig.6: OTAM Plasma Concentration-time Profiles with the Nonlinear PK Models – Linear Scale



@ 24h-infusions were stopped after 9 and 12 hours in two subjects

Fig.7: Individual (IPRE) and Population (PRED) Predicted vs. Observed (OBS)

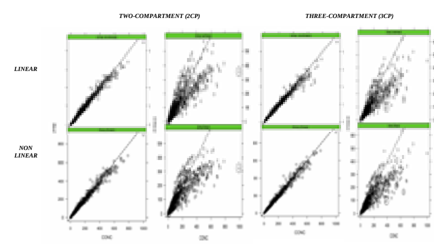
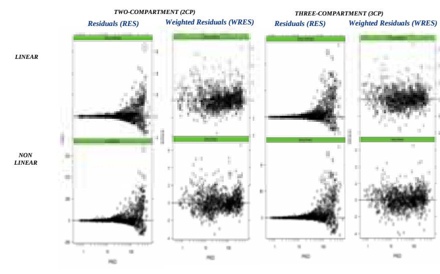


Fig.8: Residuals (RES) and Weighted Residuals (WRES) vs. Predicted (PRED)



Three-Compartment Model

CONCLUSIONS

- Two- and three-compartment population PK base models were developed to describe OTAM plasma concentrations in healthy male subjects.
- The non-dose proportional plasma exposure of OTAM was integrated in these models as a Michaelis-Menten elimination process.
- A three compartment base model with saturable Michaelis-Menten elimination (non-linear model) was retained based on the minimal value of objective function (MVOF). However, this model did not yet fully describe the more dose-proportional plasma exposure of OTAM
- Therefore, less complex two- or three-compartment models might be preferred for future drug development. Further development and improvement of the POPPK models is on going.

REFERENCES

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