Joint population pharmacokinetic model for clopidogrel and its inactive carboxylic acid metabolite

Zorica Pejčić[1,2], Valentina Topić Vučenović [3], Branislava Miljković[2], Katarina Vučićević[2]

[1]*Medicines and Medical Devices Agency of Serbia, Belgrade, Republic of Serbia*

[2]*University of Belgrade – Faculty of Pharmacy, Department of Pharmacokinetics and Clinical Pharmacy, Belgrade, Republic of Serbia*

[3]*University of Banja Luka Faculty of Medicine, Department of Pharmacy, Banja Luka, Bosnia and Herzegovina*

Introduction

Clopidogrel (CLO) is an antiplatelet agent with complex pharmacokinetics (PK). It is a prodrug, rapidly absorbed after *p.o.* administration and extensively metabolized in the liver, with ~15% of the oral dose oxidized by CYP450 isoenzymes to its active metabolite clopidogrel thiol (CLO-TH), and ~85% of the dose hydrolyzed to the inactive metabolite clopidogrel carboxylic acid (CLO-CA). CLO-CA plasma levels are much higher than those of CLO and CLO-TH [1].

Although the CLO-CA is inactive, it is important to characterize its formation and PK profile, in order to fully understand the complete PK profile of CLO. The PK data obtained in bioequivalence studies are rich, enabling developement of the PopPK model. There are only a few published PopPK models for CLO and its metabolites [2-7], focusing mostly on the CLO-TH in combination with CLO, however, a joint model for CLO and CLO-CA that takes into account first-pass effect (FPE) in the liver has not yet been comprehensively investigated.

Objectives

To synthesize data from two bioequivalence (BE) studies in order to characterize the process of CLO absorption and its conversion to CLO-CA through a semi-physiological joint PopPK model.

Methods

- **2 BE studies: Study 1 and Study 2**
- **2-way cross-over design (CLO generic 75 mg tablets *vs.* reference Plavix 75 mg tablets)**
- **50 healthy subjects (a total of 841 non-zero concentrations of CLO and 1149 of CLO-CA)**
- **CLO absorption → tested as a 1-order model, (lag time or transit compartments), also 2-, 3- or 4- compartment models tested**
- **CLO and CLO-CA elimination → tested as 1- and 2-compartment models with linear elimination**
- **FPE of CLO > 90% → liver compartment included in the model**
- **The fraction metabolized to CLO-TH → fixed, the fractions of CLO-CA and CLO → estimated (study-specific)**
- **Clearance of CLO → fixed**
- **Relative bioavailability → estimated for generic medicines from each study (BA of reference medicine fixed at 100%)**
- **Inter-individual random effects → exponential model,**
- **Intra-individual variability → proportional error model (study-specific)**
- **Inter-occasional variability → in the absorption parameters**
- **Homogenous healthy population → no classical covariate model-building (body-weight → allometric scaling)**
- **Model evaluation → successful minimization, number of significant digits, gradients in the last iteration, OFV, AIC, BIC, precision of parameter estimates, GoF plots**
- **Model validation → sample importance resampling (SIR) and VPCs (1000 replicates)**
- **PopPK analysis → NLME approach in NONMEM® (v7.5).**

Results

Figure 1: The final structural model for CLO and CLO-CA

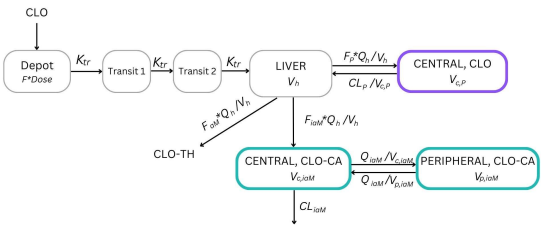

Figure 1. *$CL_{ia,M}$, clearance of inactive metabolite; CL_p, clearance of parent drug; F, bioavailability; $F_{a,M}$, fraction metabolized to active metabolite; $F_{ia,M}$, fraction metabolized to inactive metabolite; F_p, remaining fraction of the parent drug; K_{tr}, transit rate constant; Q_h, liver plasma flow; $Q_{ia,M}$, intercompartmental clearance of inactive metabolite; $V_{c,ia,M}$, volume of central compartment of inactive metabolite; $V_{p,ia,M}$, volume of peripheral compartment of inactive metabolite; $V_{c,p}$, volume of distribution of parent drug; V_h, volume of the hepatic compartment.*

Table 1: A summary of CLO and CLO-CA parameter estimates

Parameters (Units)	Dataset		Sampling Importance Resampling (SIR)	
	Estimate	95% CI	Median	2.5–97.5 Percentile
CL_p (L/h/70 kg)	89.5 FIX	-	-	-
$V_{c,p}$ (L/70 kg)	218	188–248	217	189–243
MTT_st1 (h)	0.470	0.425–0.515	0.471	0.429–0.516
F_{gen_st1}	1.08	0.993–1.17	1.08	0.995–1.16
FR_{1_st1}	119	84.3–154	118	88.2–155
CL_{iaM} (L/h/70 kg)	8.70	7.38–10.0	8.60	7.59–9.73
$V_{c,iaM}$ (L/70 kg)	23.7	19.7–27.7	23.4	20.0–26.9
Q_{iaM} (L/h/70 kg)	10.8	8.02–13.6	10.8	8.94–13.0
$V_{p,iaM}$ (L/70 kg)	61.3	50.3–72.3	60.9	52.4–70.2
Q_h (L/h)	50 FIX	-	-	-
V_h (L/70 kg)	1.5 FIX	-	-	-
MTT_st2 (h)	0.410	0.381–0.439	0.411	0.385–0.438
F_{gen_st2}	0.960	0.818–1.10	0.952	0.840–1.07
FR_{1_st2}	76.8	64.8–88.8	76.0	66.3–85.9
Inter-Individual (IIV)/Inter-Occasional Variability (IOV)	**Estimate CV (%)**	**RSE (%)**	**Median CV (%)**	**2.5–97.5 Percentile**
IIV ($V_{c,p}$)	45.82	10.4	45.69	37.38–53.99
IIV ($V_{c,iaM}$)	25.06	13.2	25.30	18.54–30.38
IIV (F_st1)	42.66	13.8	42.40	29.99–51.26
IIV (F_st2)	25.88	24.1	26.31	14.16–35.57
IOV (F_st1)	8.83	32.9	9.29	3.03–13.33
IOV (F_st2)	23.24	13.6	23.76	18.21–28.27
IOV (MTT_st1)	25.44	16.8	25.58	16.22–32.97
IOV (MTT_st2)	27.48	9.9	27.46	21.86–32.39
IIV (FR_{1_st1})	72.80	10.5	73.59	57.52–89.97
IIV (FR_{1_st2})	27.86	13.0	28.36	20.25–34.18
Residual Error	**Estimate (%)**	**RSE (%)**	**Median CV (%)**	**2.5–97.5 Percentile**
$Wp\ (st1)$	41.95	3.4	41.98	39.37–44.50
$Wp\ (st2)$	29.39	5.7	29.51	27.57–31.62

Table 1. *$CL_{ia,M}$, clearance of inactive metabolite; CL_p clearance of parent drug; CV, coefficient of variation; $FR_{1\_}st1$, and $FR_{1\_}st2$, fraction parameter for inactive metabolite for study 1 and study 2, respectively; IIV, inter-individual variability for the corresponding parameter; IOV, inter-occasional variability for the corresponding parameter; MTT_st1, and MTT_st2, mean transit time for study 1 and study 2, respectively; Q_h, liver plasma flow; $Q_{ia,M}$, intercompartmental clearance of inactive metabolite; $F_{gen\_}st1$ and $F_{gen\_}st2$, relative bioavailability of generic compared to reference medicine for study 1 and study 2, respectively; RSE, relative standard error; $V_{c,ia,M}$, volume of central compartment of inactive metabolite; V_h, volume of hepatic compartment; $V_{p,ia,M}$, volume of peripheral compartment of inactive metabolite; $V_{c,p}$, volume of distribution of parent drug; F_st1 and F_st2, bioavailability in study 1 and 2, respectively; Wp, proportional residual error for the corresponding study.*

Figure 2: GOFs of the final model: purple color CLO (ng/mL), light blue color CLO-CA (µg/mL)

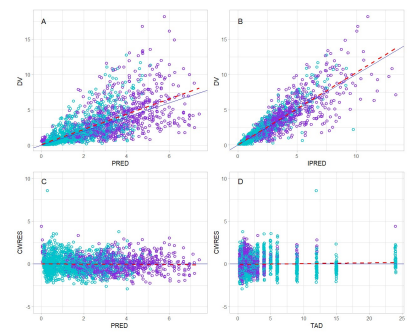

Figure 2. *(DV) observed values; (PRED) population predicted values; (IPRED) individual model predicted values; (CWRES) conditional weighted residuals; (TAD) time after dose (hour). The solid lines: the lines of identity in (A,B) and the zero lines in (C,D). The dashed lines: the regression lines.*

Figure 3: VPCs of the final model

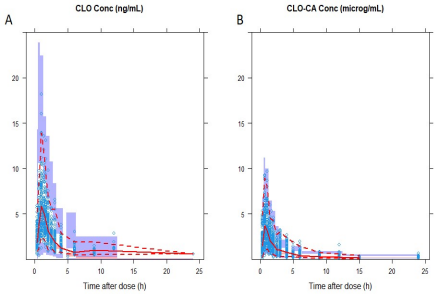

Figure 3. *Blue rectangles: the observed concentrations; solid and dashed red lines: the 50th, 5th and 95th percentiles of the predictions; semi-transparent red shaded area: the simulation-based 95% CI for the median; semi-transparent purple fields: the 95% CI around the 5th and 95th percentiles of the predicted data.*

Discussion

By combining the data from two BE studies we have developed a unified model for CLO and CLO-CA, which effectively captured the PK properties of both compounds.

The parameters' values were estimated with adequate precision, and in agreement with literture data [4-6]. The RSE for the structural parameters ranged up to 14.9%.

The GoF plots indicated good agreement between the data, and the VPCs indicated the good predictive abilities of the model.

The data best fitted the 1-compartment model for CLO, as in [2], but in contrast to the 2-compartment models in [3,4]. For CLO-CA our 2-compartment model was in line with findings of [5,6].

Certain parameters were estimated separately for each study, which stabilized the model. The obtained values for the fractions metabolized to CLO-CA were ~87% for both studies, aligning with the literature values [1,4]. Inclusion of 2 transit compartments improved the model compared to lag time (AIC dropped for 5.416 units). The transit rate constants (K_{tr}) were calculated for each study (6.38 h^{-1} and 7.32 h^{-1}), based on the estimated MTTs.

The inclusion of the liver compartment aligned with the extensive FPE of CLO [1,4].

Since the population was homogenous, and the polymorphism data were not available, the influence of covariates was not tested. Given that CYP2C19 is not critical in CLO-CA formation, it is less likely that this covariate would enhance the model. On the contrary, as CES1 is responsible for the formation of CLO-CA [4,8], the availability of CES1 phenotypes may have resulted in its inclusion in the final model.

The model lays a solid groundwork for potential future enhancements to create a more complex model, incorporating the formation of CLO-TH, genetic variations, and other factors (such as concurrent drug therapies that interact with CLO) gleaned from patient data.

Conclusion

We developed a comprehensive joint semi-physiological PopPK model for CLO and its inactive metabolite, CLO-CA. This model incorporates two transit compartments for absorption and accounts for FPE in a liver compartment. The model is based on bioequivalence data obtained from two studies, providing a robust framework for understanding the pharmacokinetics of these compounds.

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