

Targeted temperature management reduces CYP2C19 metabolism: a population pharmacokinetic study using pantoprazole



Wisse van Os¹, J.G. Coen van Hasselt⁴, Michael Poppe², Christian Clodi², Christoph Schriefl², Matthias Mueller², Raute Sunder-Plaßmann³, Birgit Reiter³, Maximilian Rechenmacher², Michael Holzer², Harald Herkner², Michael Schwameis², Bernd Jilma¹, Christian Schoergenhofer¹, Christoph Weiser²

¹Department of Clinical Pharmacology; ²Department of Emergency Medicine; ³Clinical Institute of Laboratory Medicine, Medical University of Vienna, Austria; ⁴Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, the Netherlands

Introduction

- Targeted Temperature Management (TTM) is part of standard post-resuscitation care.
- TTM-induced hypothermia and the inflammation that often follows after rewarming may affect the drug-metabolising activity of hepatic enzymes like CYP2C19.

Objective

- Evaluate the effect of TTM on the pharmacokinetics (PK) of pantoprazole as a probe of CYP2C19-dependent metabolism, using population PK modelling.

Methods

- Subjects: 16 patients who underwent successful cardiopulmonary resuscitation and received pantoprazole as part of post-resuscitation care.
- Dose: 40 mg intravenous bolus every 24 hours.
- Pantoprazole PK was evaluated in three study periods:

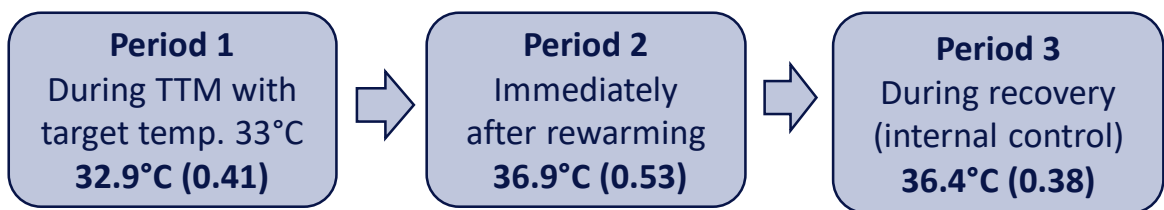


Figure 1. The study periods in which PK was measured. Body temperatures measured during each study period are displayed as median (interquartile range)

- To quantify PK differences between study periods, PK samples were grouped in three occasions based on study period, and inter-occasion variability (IOV) was tested on structural model parameters.
- Tested covariates: body temperature and C-reactive protein levels (CRP, as marker of inflammation)
- In a separate covariate model, we estimated factors by which typical values of PK parameters were altered in each study period relative to the other study periods.
- Structural model parameters were *a priori* allometrically scaled based on body weight.
- M3 method was used for data below quantification limit (14% of post-dose samples).

Results

- PK data was best described by a two-compartment model with IOV on clearance (CL) and the central volume of distribution (Vc), IIV on CL, and a combined error model.
- Using study periods as covariates explained the data better than using body temperature and CRP.
- Final model included factors by which CL was altered both during TTM and immediately after rewarming, indicating 40% and 29% lower CL in these study periods, respectively, compared to the internal control period. This explained 21% of IOV on CL.
- Similarly, a factor indicating a 64% increase in Vc after rewarming compared to the other study periods was included. This explained 15% of IOV on Vc.

Table 3. Parameter estimates of the final model. The estimates of factors by which structural model parameters are altered in specific study periods are highlighted

Description	Parameter	Units	Estimate	RSE (%)
Structural model^a				
Clearance	θ_{CL}	L/h	4.83	15.8
Central distribution volume	θ_{Vc}	L	7.22	11.6
Peripheral distribution volume	θ_{Vp}	L	3.25	12.3
Inter-compartmental clearance	θ_Q	L/h	1.91	22
Inter-individual variability				
Clearance	$\omega_{CL,IIV}$	CV%	46.8	17.3
Inter-occasion variability				
Clearance	$\omega_{CL,IOV}$	CV%	31.5	27.1
Central distribution volume	$\omega_{Vc,IOV}$	CV%	48.2	19.1
Residual variability				
Additive error (SD)	σ_{add}	mg/L	0.0381	20.4
Proportional error	σ_{prop}	CV%	12.3	13
Covariate model				
Factor period 1 on CL	θ_{CL-P1}	-	0.598	17.2
Factor period 2 on CL	θ_{CL-P2}	-	0.709	17.2
Factor period 2 on Vc	θ_{Vc-P2}	-	1.64	11.2
Allometric scaling: CL, Q	$\theta_{allo,CL,Q}$	-	0.75 FIX	-
Allometric scaling: Vc, Vp	$\theta_{allo,Vc,Vp}$	-	1 FIX	-

^a Structural model parameters were allometrically scaled according to: $P = \theta_P \times \left(\frac{WT}{90}\right)^{\theta_{allo}}$, with θ_P being the typical value of model parameter P for an individual with the median body weight in the study population (90 kg), WT being patient body weight, and θ_{allo} being the allometric exponent (0.75 for CL and Q, 1 for Vc and Vp); RSE, relative standard error; CV%, coefficient of variation; SD, standard deviation.

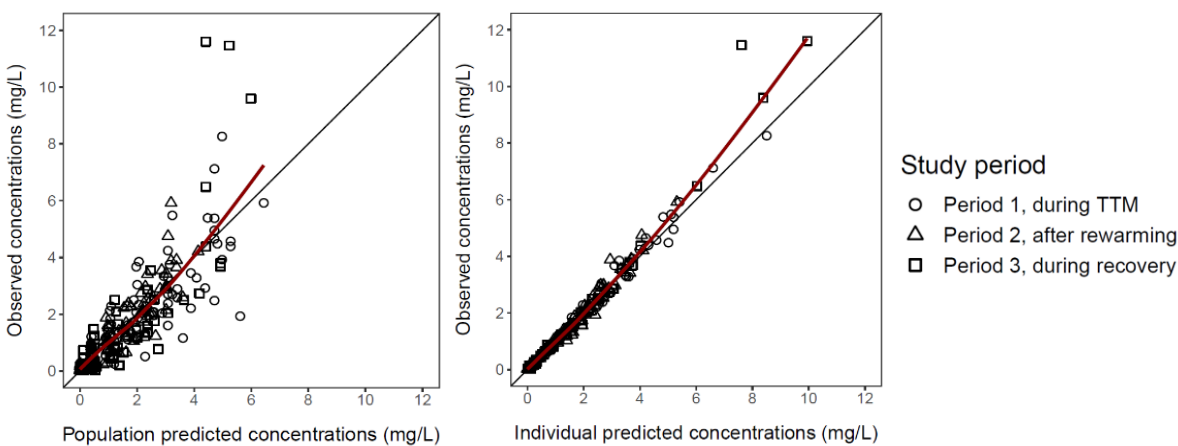


Figure 2. Observed concentrations vs population and individual predicted concentrations of pantoprazole for the final model

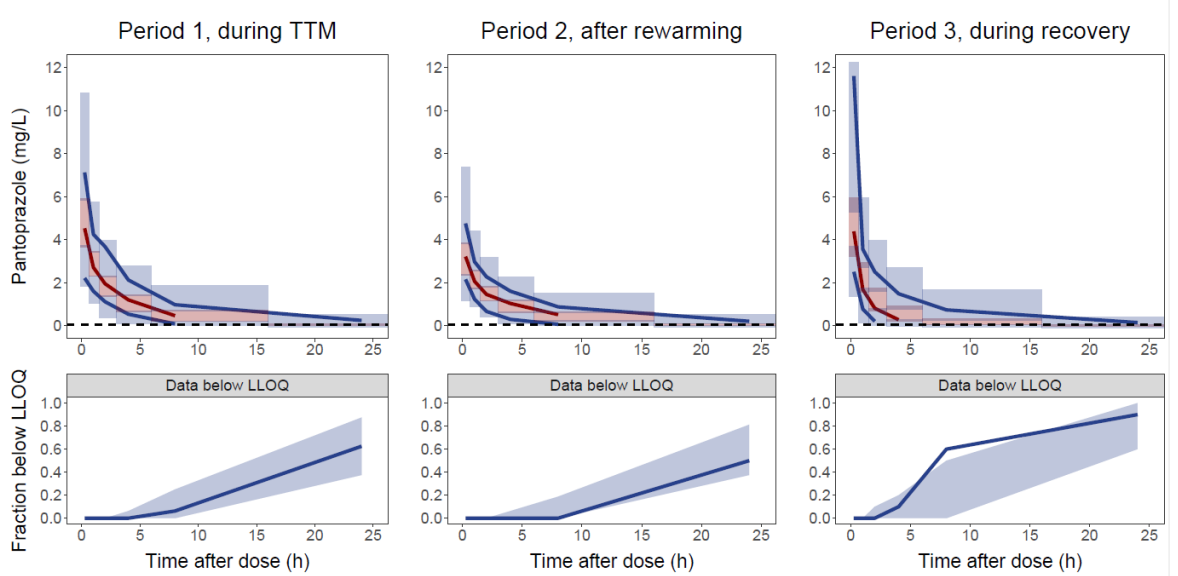


Figure 3. Visual predictive check stratified by study period. In the upper panels, the dashed black line indicates the lower limit of quantification (LLOQ). The lower panels in each plot are the VPCs for data below the LLOQ

Conclusions

- TTM at 33°C reduced pantoprazole metabolism compared to the internal control period, potentially due to CYP2C19 functioning outside its optimum temperature range.
- Reduced CL and increased Vc immediately after rewarming are likely explained by inflammation downregulating enzyme activity and increasing vascular permeability.
- PK of other drugs with CYP2C19-dependent metabolism used in TTM may be subject to similar alterations, potentially resulting in increased toxicity or impaired pro-drug activation.