Pharmacokinetic-Pharmacodynamic model for Acute Intermittent Porphyria in porphyric mice treated with a new recombinant PBGD protein

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INTRODUCTION AND OBJECTIVES

Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder caused by a decreased hepatic activity of the porphobilinogen deaminase enzyme (PBGD), the third enzyme in the heme biosynthesis pathway (Figure 1) [1]. In a previous work [2] we developed a data-driven disease model capable of describing the time course of excreted amounts of heme precursors in urine of porphyric (AIP) mice during induced acute attacks. In this project, we aimed to refine the existing disease model to account mechanistically for known autoregulation aspects of the heme pathway, and to develop a pharmacokinetic-pharmacodynamic (PKPD) model for a new recombinant human (rh) PBGD protein.

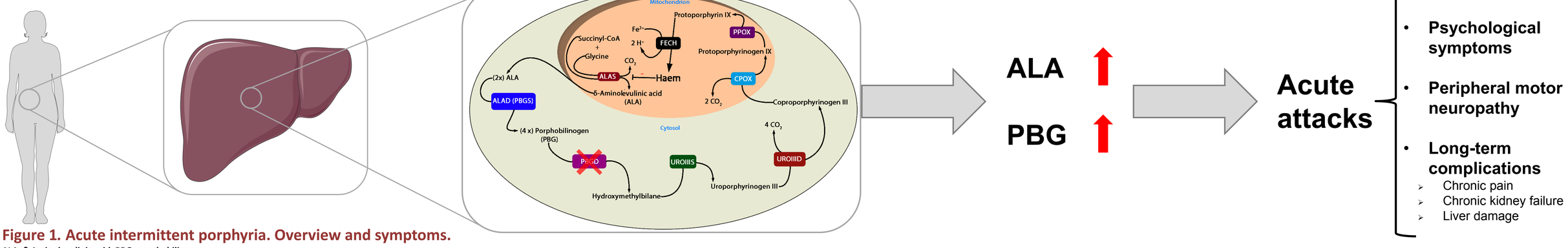


Figure 1. Acute intermittent porphyria. Overview and symptoms.
ALA, δ-Aminolevulinic acid. PBG, porphobilinogen

METHODS

I. Urinary biomarkers

- N = 27 AIP mice.
- rhPBGD variant administration: day 2 (60 or 300 nmol/kg).
- Quantification of 24-hour urine for challenges D1, D9 and D30
- 334 δ-Aminolevulinic acid (ALA), 338 porphobilinogen (PBG) and 307 total porphyrins (tPOR) measurements (Figure 2).

II. Phenobarbital pharmacokinetic model

- Lack of concentration data for phenobarbital in AIP mice.
- An existing one-compartment pharmacokinetic model for oral and intravenous administrations was adapted from the literature [3].
- It was assumed the drug was absorbed instantaneously and completely after an intraperitoneal administration (Figure 3).

III. PBGD activity data

- rhPBGD enzymatic activity data in serum (*in vitro* test).
- N = 16 wild-type C57BL/6 mice.
- rhPBGD enzymatic activity in serum was used as a surrogate marker of rhPBGD systemic exposure (Figure 4).

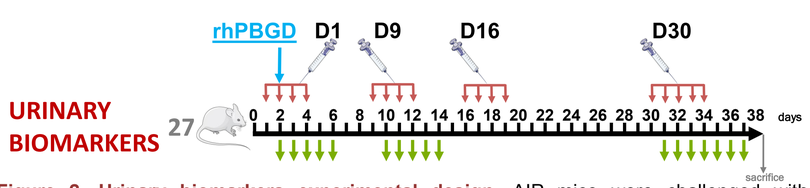


Figure 2. Urinary biomarkers experimental design. AIP mice were challenged with phenobarbital 4 times (Challenges D1, D9, D16 and D30). 4-5 increasing phenobarbital doses (75, 80, 85 and 90 mg/kg) were administered daily in each challenge. The new rhPBGD variant was administered at day 2, either 60 or 300 nmol/kg. 24-hour urine samples were collected from challenges D1, D9 and D30.

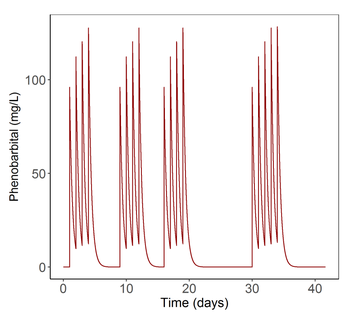


Figure 3. Phenobarbital pharmacokinetic model: simulation results.
Systemic phenobarbital concentrations (mg/L) versus time. Drug accumulation was not predicted, the increase on the concentration levels was caused by the increase in the drug dose during each challenge.

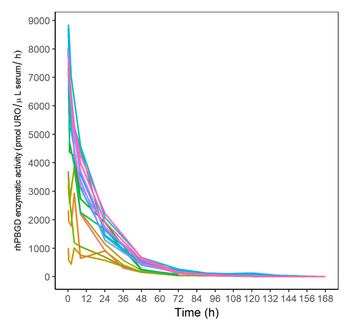
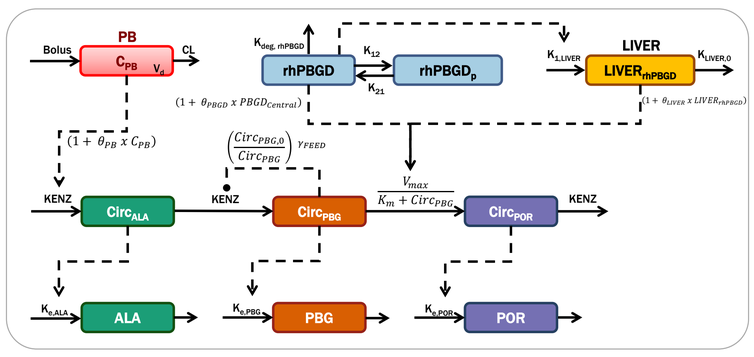


Figure 4, Pharmacokinetic profile of recombinant PBGD in serum.
rhPBGD enzymatic activity in serum [pmol uroporphyrins (URO) / µL serum / h]. This enzymatic activity was obtained from an *in vitro* test in which the wild-type mice serum was incubated with PBG (substrate of rhPBGD enzyme).

RESULTS

The final model assumed that excreted biomarkers were dependent on the amounts of their respective biomarkers in liver and blood, represented by virtual circulating compartments. Phenobarbital increases circulating ALA synthesis in a linear way. The transit between circulating PBG and tPOR was modelled using a Michaelis-Menten process. A negative feedback of circulating PBG amounts was implemented. rhPBGD pharmacokinetics was well described using a two-compartment model with linear elimination. Drug effect was estimated using data for the rhPBGD dose of 60 nmol/kg by using a linear model. An additional delayed drug effect was added for the dose of 300 nmol/kg, representing the rhPBGD activity in the liver.

I. Model building



$$\frac{dC_{PB}}{dt} = -\frac{CL}{V_d}\ x\ C_{PB}$$

$$\frac{dPBGD}{dt} = -K_{deg,rhPBGD}\ x\ rhPBGD\ - K_{12}\ x\ rhPBGD + K_{21}\ x\ rhPBGDp$$

$$\frac{dPBGDp}{dt} = K_{12}\ x\ rhPBGDp - K_{21}\ x\ rhPBGD$$

$$\frac{dLIVER_{rhPBGD}}{dt} = K_{1,LIVER}\ x\ rhPBGD - K_{LIVER,0}\ x\ LIVER_{rhPBGD}$$

$$\frac{dCirc_{ALA}}{dt} = KENZ\ x\ (1 + \theta_{Pheno}\ x\ C_{PB}) - KENZ\ x \left(\frac{Circ_{PBG_0}}{Circ_{PBG}}\right)^{\gamma_{FEED}}\ x\ Circ_{ALA}$$

$$\frac{dCirc_{PBG}}{dt} = KENZ\ x \left(\frac{Circ_{PBG_0}}{Circ_{PBG}}\right)^{\gamma_{FEED}}\ x\ Circ_{ALA} - \frac{V_{max}}{K_m + Circ_{PBG}}\ x\ E_{rhPBGD}\ x\ Circ_{PBG}$$

$$\frac{dCirc_{tPOR}}{dt} = \frac{V_{max}}{K_m + Circ_{PBG}}\ x\ E_{rhPBGD}\ x\ Circ_{PBG} - KENZ\ x\ Circ_{tPOR}$$

$$\frac{dALA}{dt} = K_{e,ALA}\ x\ (Circ_{ALA}{}^{\gamma_{ALA}})$$

$$\frac{dPBG}{dt} = K_{e,PBG}\ x\ (Circ_{PBG}{}^{\gamma_{PBG}})$$

$$\frac{dtPOR}{dt} = K_{e,tPOR}\ x\ (Circ_{URO}{}^{\gamma_{URO}})$$

$$E_{rhPBGD} = 1 + \theta_{rhPBGD}\ x\ rhPBGD + \theta_{LIVER}\ x\ LIVER_{rhPBGD}$$

$$K_m = \frac{V_{max}}{K_{ENZ}} - 1$$

$$rhPBGD\ (t=0) = \frac{Dose_{rhPBGD}}{Scaling\ factor\ (Dose \rightarrow Activity)}$$

$$C_{PB}\ (t=0) = \frac{Dose_{PB}}{V_d}$$

$$Circ_i(t=0) = 1$$

Figure 5. Graphical and mathematical representation of the final PK/PD model. PB, Phenobarbital compartment. C_{PB}, PB concentrations. V_d, PB apparent volume of distribution. CL, PB total clearance. Θ_{PB}, PB lineal effect. $Circ_{ALA, PBG, tPOR}$, unobserved circulating levels of ALA, PBG, and tPOR, respectively. KENZ, rate constant governing the turn-over process of the circulating biomarkers. $K_{e, ALA}$, $K_{e, PBG}$ and $K_{e, URO}$, urinary ALA, PBG and tPOR synthesis rate constants, respectively. ALA, urinary ALA compartment. PBG, urinary PBG compartment. tPOR, urinary tPOR compartment. γ_{ALA}, γ_{PBG} and γURO, shape parameters of the circulating compartments. rhPBGD, central rhPBGD compartment. rhPBGDp, peripheral rhPBGD compartment. K_{12} and K_{21}, transfer rate constants between rhPBGD central and peripheral compartment. $K_{deg, rhPBGD}$, rhPBGD elimination rate constant. LIVER, delayed drug effect compartment. $LIVER_{rhPBGD}$, rhPBGD activity in the liver. $K_{1,LIVER}$ and $K_{LIVER,0}$, rate constants governing the LIVER compartment. θ_{rhPBGD} and θ_{LIVER}, linear drug effect slopes. E_{rhPBGD}, rhPBGD effect. V_{max} and K_m, parameters governing the Michaelis-Menten transfer between $Circ_{PBG}$ and $Circ_{tPOR}$. γ_{FEED}, shape parameter of the PBG→ALA feedback.

Table 1. Model typical parameter estimates

Parameters	Typical estimate (RSE %)	IAV (RSE %)	Shrinkage (%)
Θ_{PB} (L/mg)	$7.2x10^{-3}$ (40.1)	-	-
KENZ (h^{-1})	0.338 (37.9)	-	-
$K_{e, ALA}$ (pmol x mg creatinine^{-1} x h^{-1})	$1.52x10^{4}$ (5.4)	76 (27.2)	6.7
$K_{e, PBG}$ (pmol x mg creatinine^{-1} x h^{-1})	$2.32x10^{3}$ (14.3)	78.4(17.2)	11.3
$K_{e, tPOR}$ (pmol x mg creatinine^{-1} x h^{-1})	0.172 (15.3)	-	-
γ_{ALA}	3.09 (26.4)	-	-
γ_{PBG}	5.63 (65.2)	-	-
γ_{tPOR}	6.32 (31)	-	-
V_{MAX} (arbitrary units x h^{-1})	0.628 (15.8)	-	-
γ_{FEED}	0.7 (41.3)	-	-
Θ_{rhPBGD} (pmol URO^{-1} x µL serum x h)	$1.06x10^{-4}$ (31.8)	-	-
$K_{LIVER, 0}$ (h^{-1})	$2.07x10^{-3}$ (21.2)	-	-
Θ_{LIVER} (pmol URO^{-1} x µL serum x h)	1.48 (24.7)	-	-
Residual error ALA	0.828 (15.1)	-	
Residual error PBG	0.914 (8)	-	2.3
Residual error URO	0.771 (6)	-	

RSE, relative standard error. IAV, inter-animal variability. Ƞ-shrinkage is shown for the IAV parameters. Ɛ-shrinkage is shown for the residual error Ɛ parameter, shared by the three biomarkers.

II. Model selection

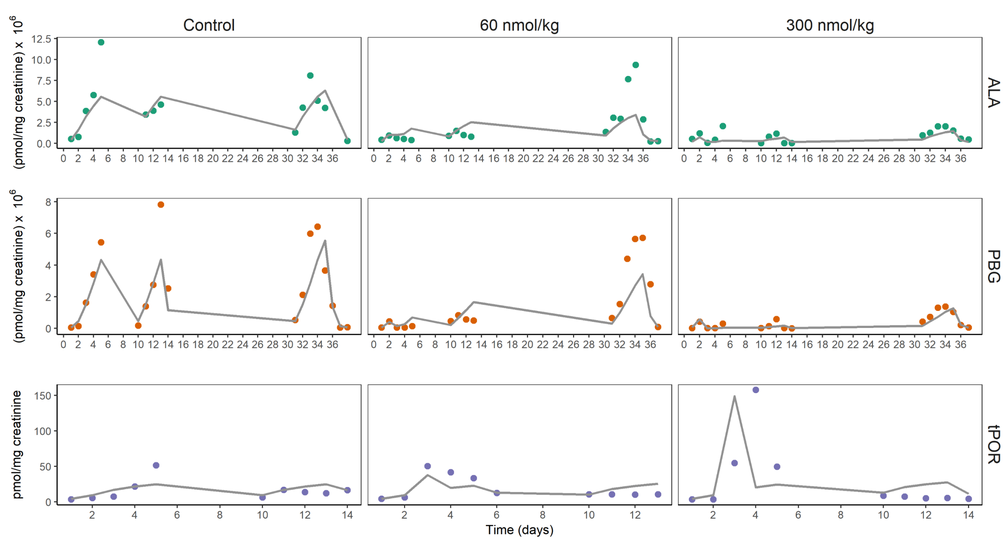


Figure 6. Individual predictions vs time. Heme precursor predictions for the best mice model fittings for control and treated groups. Lines show individual model predictions, points are observed measurements.

III. Model evaluation

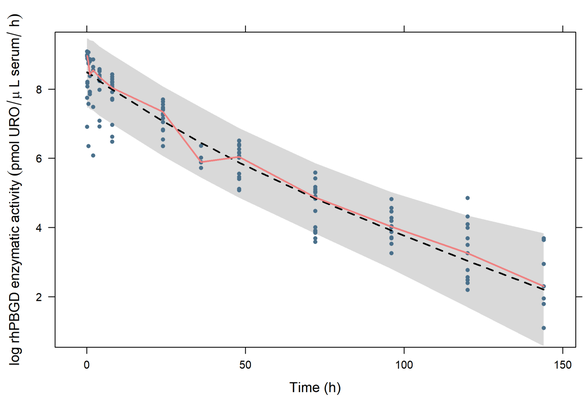


Figure 7. rhPBGD kinetics: Visual Predictive Check. 1000 studies were simulated. Red line, median for for observed data. Dashed black line, median for predicted data. Shaded area, 90% prediction interval. Blue points: observations.

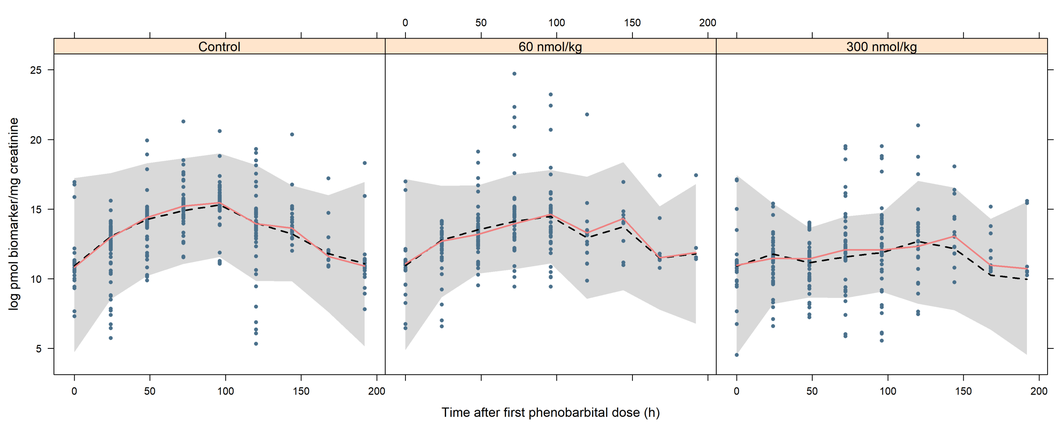


Figure 8. Prediction-corrected Visual Predictive Checks for excreted biomarkers data: control and treated groups.
1000 studies were simulated. Red line, median for observed data. Dashed black line, median for predicted data. Shaded area, 90% prediction interval. Blue points: observations.

CONCLUSIONS & FUTURE PERSPECTIVES

This mechanistic pharmacokinetic-pharmacodynamic model successfully described the time course of urinary data from control and treated porphyric mice with a new recombinant human protein for both dose values tested. This model provides a mechanistic framework to explore the impact of new therapies and to support the design of experimental settings to project results to humans.

References

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[3] Iven H, Feldbusch E. Naunyn Schmiedebergs Arch Pharmacol. 1983;324(2):153–9.