Supplementary Methods & Material

Phenobarbital pharmacokinetic and effect site models

To generate the phenobarbital concentration-time profiles, a one-compartment pharmacokinetic model developed in mice was available from the literature and implemented (Iven and Feldbusch, 1983) assuming phenobarbital pharmacokinetics is not affected by the porphyric disease.

In the current study, phenobarbital was injected intraperitoneally (*i.p.*), whereas the literature model was developed after intravenous (*i.v.*) or oral administration. Thus, it was assumed that phenobarbital was absorbed instantaneously and completely after *i.p.* administration. The latter assumption was supported by the fact that bioavailability after phenobarbital oral administration was almost complete.

$$\frac{\mathrm{d}C_{Pheno}}{\mathrm{dt}} = -\frac{\mathrm{CL}}{\mathrm{V_d}} \times C_{Pheno} \qquad eq.S1$$

Where dC_{Pheno}/dt represents the rate of change of the predicted plasma concentrations of phenobarbital (mg/kg/L) governed by the elimination characterized by CL, the total drug clearance, and the distribution where Vd is the apparent volume of distribution. The reported estimates of 0.074 L (L/h/kg) for CL and of 0.78 L/kg were used.

The effect was assumed to be triggered by the phenobarbital concentrations in a virtual effect compartment ($C_{e,Pheno}$), which increases linearly the appearance of ALA/PBG circulating levels through a θ_{Pheno} parameter (equations S1-2).

$$\mathrm{E_{Pheno}} = \theta_{\mathrm{Pheno}} \mathrm{x}\ \mathrm{C_{e,Pheno}} \qquad eq.S2$$

$$\frac{\mathrm{dC_{e,Pheno}}}{\mathrm{dt}} = \mathrm{K_{e,pheno}} \times \left(\mathrm{C_{Pheno}} - \mathrm{C_{e,Pheno}}\right) \qquad eq.S3$$

$K_{e,Pheno}$ represents the first order rate constant governing the distribution equilibrium of concentrations between plasma and target site (i.e. liver compartment).

AIA/Rifampicin kinetic-pharmacodynamic model

Pharmacokinetic information of AIA and rifampicin in the different species was not available and the kinetic-pharmacodynamic (K-PD) approach (Jacqmin et al., 2007) -where the kinetic information of the combine acute attacks inducers (AIA/rifampicine) is inferred from the pharmacodynamic profiles- was used.

For the K-PD approach, dummy AIA and Rifampicin doses administered to the biophase compartment (BIO) were used. BIO represents the virtual concentrations of AIA/rifampicine in equilibrium with the observed effect (equation 14)

$$\frac{\mathrm{d}BIO}{\mathrm{dt}} = -K_{E,AIA/Rif} \times \mathrm{BIO} \qquad eq.S4$$

Where $K_{E,AIA/Rif}$ stands for the first order elimination rate constant from the virtual compartment. This parameter was estimated using precursor data from control WT animals.

References

Iven, H., and Feldbusch, E. (1983). Pharmacokinetics of phenobarbital and propylhexedrine after administration of barbexaclone in the mouse. Naunyn. Schmiedebergs. Arch. Pharmacol. *324*: 153–159.

Jacqmin, P., Snoeck, E., Schaick, E.A. van, Gieschke, R., Pillai, P., Steimer, J.-L., et al. (2007). Modelling Response Time Profiles in the Absence of Drug Concentrations: Definition and Performance Evaluation of the K–PD Model. J. Pharmacokinet. Pharmacodyn. *34*: 57–85.