A mechanistic Pharmacokinetic-Pharmacodynamic model describing AIP mice treated with a new PBGD protein

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Objectives: Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder caused by a genetic mutation that reduces the hepatic activity of the porphobilinogen deaminase enzyme (PBGD). Precipitating factors lead to acute attacks associated to the accumulation of the neurotoxins 5-Aminolevulinic Acid (ALA) and Porphobilinogen (PBG). As the current standard-of-care drug, hemin, causes several side effects to chronical patients, new therapies are needed. We aimed to develop a more mechanistic pharmacokinetic-pharmacodynamic (PKPD) model using a new PBGD protein.

Methods: Acute attacks were induced at day 1, 9 and 30 in AIP mice by intraperitoneal injection of four daily increasing doses of phenobarbital. The PBGD variant was administered at day 2 as a single dose intravenously (two dose levels: 60 and 300 nmol/kg). 24-h urine was collected from mice (n=27) and ALA, PBG and total porphyrins (tPOR) were quantified in control and treated animals. A PK model was adapted from the literature to simulate phenobarbital concentrations. Enzymatic PBGD activity data in serum (n=16) was used as a surrogate marker of the drug concentrations to build the model. Data was analyzed using the population approach with NONMEM 7.3, and Berkeley-Madonna was used to test different feedback mechanisms.

Results: A Michaelis-Menten process and a feedback mechanism were implemented into the model. PBGD pharmacokinetics was well described using a two-compartment model with linear elimination. Drug effect was estimated using data for the low PBGD dose of 60 nmol/kg, assuming that recombinant PBGD linearly increases the endogenous enzyme maximum capacity, in agreement with its known biological action.

This model under-predicted the observed PBGD effect for the dose of 300 nmol/kg. This issue was solved by the incorporation of an additional delayed linear drug effect. The final disease PKPD model was able to describe the median values and the dispersion of the data.

Conclusions: A more mechanistic pharmacokinetic-pharmacodynamic model for acute intermittent porphyria in porphyric control and treated mice has been developed. This model allows us to build a mechanistic framework to study the impact of new therapies for acute intermittent porphyria and to extrapolate preclinical results to help taking informed decisions about potential dosing schemes in early clinical trials.

Max. 350 palabras