Simulations to Estimate Effects of Reduced Phenylalanine Intake on Blood Phenylalanine in Phenylketonuria

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BACKGROUND

Dietary control of phenylalanine (Phe) intake is a primary method of management of phenylketonuria (PKU). The Phe intake and blood Phe level relationship has not been mathematically modeled to date, and the objective of this study was to extend a healthy subject and PKU patient Phe kinetics literature model to incorporate meal-related effects.

METHODS

METHODS: A Phe metabolism model (Kaufman 1999) was extended adding meal-related effects. The model was implemented in the R programming language mrgsolve library. The Kaufman model includes Phe metabolism as a result of phenylalanine hydroxylase (PAH) activity from 0 to 100% of normal including non-PAH transamination and endogenous catabolism. The model was extended to include Phe absorption from the gut assuming 100% Phe bioavailability and rapid absorption after the meal (rate = 0.25 hr^{-1}).

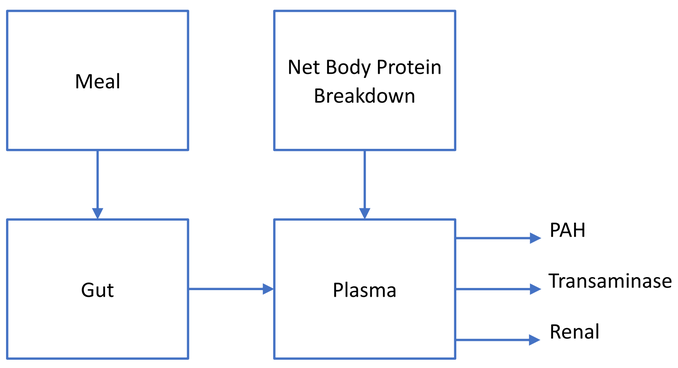


Figure 1: Modeling Phe flow from meal to plasma to elimination. Kaufman's model (PNAS 1999) was modified to include an absorption component and then used for simulation of steady-state Phe (initially assumed to be 0.25 hr^{-1}). The model was further refined to include renal elimination of Phe. The Phe renal elimination rate was estimated to be 2.85×10^{-4} hr^{-1} using a weighted mean of serum and 24-hour urinary Phe data extracted from Lines and Waisman (1971) and Kitigawa (1974). In patients with classical PKU (0% PAH activity and serum Phe = 1000 µmol/L), PAH, transaminase, and renal elimination mechanisms contribute 0%, 99%, and 1%, respectively

The equations are as follows:

$$\frac{dPhe}{dt} = K_{a,gut} \times Gut \times F_{Gut,Plasma} + V_{npd} - V_{PAH} - V_{trans} - V_{renal}$$

$$V_{npd} = const$$

$$V_{PAH} = \frac{V_{max,PAH} \times F_{PAH}}{1 + \frac{K_{m,PAH}}{Phe} + \frac{K_{m,PAH} \times K_{a,PAH}}{Phe^2}}$$

$$V_{trans} = \frac{V_{max,trans}}{1 + \frac{K_{m,trans}}{Phe}}$$

$$V_{renal} = Phe \times CL_{renal} \times V_d$$

$$\frac{dGut}{dt} = -K_{a,gut} \times Gut$$

$$F_{Gut,Plasma} = \frac{1}{MW_{Phe}} \times V_d \times W$$

- Phe is plasma Phe concentration (mmol/L),
- t is time (hr),
- $K_{a,gut}$ is the absorption rate from the gut to plasma (0.25 hr^{-1}),
- V_{npd} is the rate of net protein breakdown (0.012 (mmol/L)/hr),
- V_{PAH} is the rate of Phe breakdown due to PAH ((mmol/L)/hr),
- V_{trans} is the rate of Phe breakdown due to transamination ((mmol/L)/hr),
- V_{renal} is the rate of renal Phe elimination ((mmol/L)/hr),
- $V_{max,PAH}$ is the maximum rate of Phe breakdown due to PAH with a normal subject (0.9 (mmol/L)/hr),
- F_{PAH} is the fraction of normal PAH activity (healthy = 1 and classical PKU = 0; unitless fraction),
- $K_{m,PAH}$ is the Michaelis-Menten constant for Phe with PAH (0.51 mmol/L),
- $K_{a,PAH}$ is the Phe activation constant for PAH (0.54 mmol/L),
- $V_{max,trans}$ is the maximum rate of Phe breakdown due to transamination which is assumed identical between healthy and PKU (0.063 (mmol/L)/hr),
- $K_{m,trans}$ is the Michaelis-Menten constant for Phe with transamination (1.37 mmol/L),
- CL_{renal} is the renal clearance of Phe per body weight (5.696×10^{-4} L/kg/hr),
- $F_{Gut,Plasma}$ is an adjustment for unit conversion and distribution from mass units in the gut to concentration in plasma ((mmol/L)/mg),
- MW_{Phe} is the molecular weight of Phe (165.19 g/mol),
- V_d is the volume of distribution of Phe per body weight (0.5 L/kg), and
- W is body weight (kg; varies by person).

RESULTS

Simulations of varying PAH activity levels match expectations from healthy subjects, heterozygous PKU carriers, and classical PKU (0 to 2% PAH activity). Simulations examined Phe concentrations with nonadherent diets of 50 g/day protein (assuming Phe is 5% of protein by weight and split between three main meals). Simulation results align with expectations that patients with classical PKU (0, 1, and 2% of normal PAH activity) have 1180, 850, and 660 µmol/L blood Phe while heterozygote and healthy subjects have 96 and 65 µmol/L, respectively. With 0% PAH activity, reducing Phe intake by 20, 30 and 50% were estimated to result in decreased blood Phe levels by 21, 30 and 45% respectively.

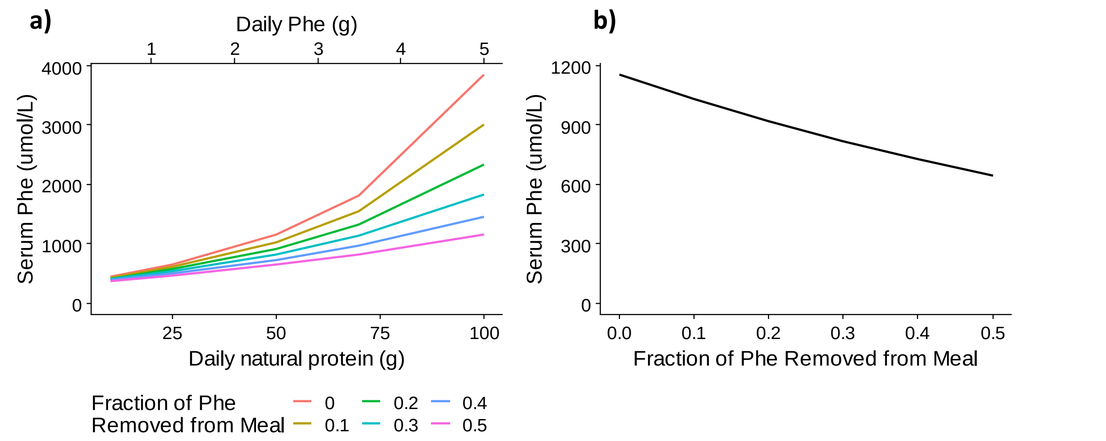
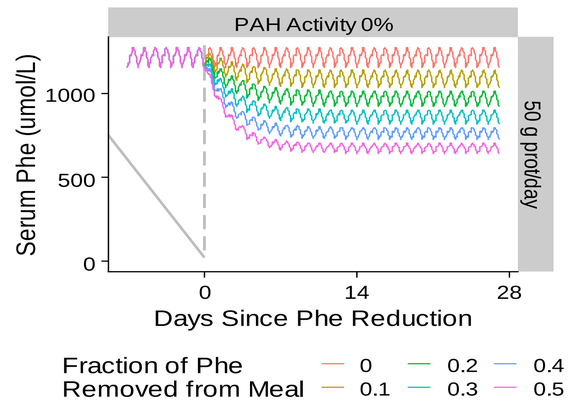


Figure 2: a) Simulated fasting serum Phe for patients with classical PKU (0% PAH activity) by varying protein intake (lines) and reduction from that protein intake (color). b) Simulated example of impact of dietary Phe removal on serum Phe levels in a classic PKU patient with 0 % PAH activity on 50g protein per day diet

Figure 3: Simulated effects of reducing Phe intake on serum Phe. For a classical PKU population (70 kg; serum; daily Phe intake of 2500 mg divided equally between three meals at approximately 8am, noon, and 6pm), simulations were performed to estimate the effect of reducing Phe in meals by up to half



Model validation

Data from placebo subjects in the study SYNB1618-CP-001 were used for external model validation. Subjects with classic PKU (N=4) were in the clinic for 9 days with daily measurements of dietary Phe intake and fasting blood Phe level. In general, the model predicted reasonably well blood Phe levels in PKU patients. (Figure 4)

In order to further refine the model, parameter sensitivity was performed, and the following potential areas of model improvement were identified:

- The maximum activity for transaminases (*Vmax,trans*); observed individual level variability using clinical data +/-35%
- Amount of net protein breakdown (*Vnpd*)
- The Michaelis-Menten constant for transaminases (*Km,trans*)

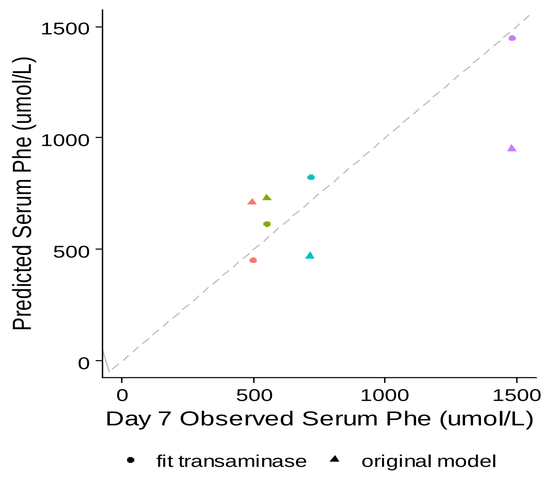


Figure 4: Simulated vs observed blood Phe from placebo subjects (triangles) with PKU in Study SYNB1618-CP-001 on Day 7

CONCLUSIONS

- An extension of a literature model for Phe metabolism was developed.
- The model is reasonable for predicting Phe metabolism based on serum Phe predictions with meals and external validation with clinical data.
- The model can help predict the effect of changes to dietary Phe intake on blood Phe in patients with PKU.
- The model could potentially be extended to improve the efficiency of determining Phe tolerance (mg Phe/day) in patients with PKU.
- Validation and model refinement using clinical data may help to further improve predictions for patients with classical PKU.

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