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).

The equations are as follows:

\[
\frac{dPhe}{dt} = K_{Phe} \times \text{Gut} \times F_{\text{Gut,Plasma}} + V_{\text{renal}} - V_{\text{PAH}} - V_{\text{EVEMAX}}
\]

\[
V_{\text{PAH}} = \frac{V_{\text{MAX,PAH}} \times F_{\text{PAH}}}{1 + K_{\text{PAH}} \times Phe}
\]

\[
V_{\text{EVEMAX}} = V_{\text{MAX,Ev}}
\]

\[
V_{\text{renal}} = Phe \times C_{\text{renal}} \times V_d
\]

\[
\frac{d\text{Gut}}{dt} = -K_{\text{Gut}} \times \text{Gut} \times F_{\text{Gut,Plasma}} = \frac{1}{MW_{Phe}} \times V_d \times W
\]

- Phe is plasma Phe concentration (mmol/L),
- t is time (hr),
- \(K_{\text{Gut}}\) is the absorption rate from the gut to plasma (0.25 hr⁻¹),
- \(V_{\text{PAH}}\) is the rate of net protein breakdown (0.012 (mmol/L)/hr),
- \(V_{\text{renal}}\) is the rate of Phe breakdown due to PAH (mmol/L)/hr,
- \(V_{\text{EvEMAX}}\) is the rate of Phe breakdown due to transamination (mmol/L)/hr,
- \(V_{\text{renal}}\) is the rate of renal Phe elimination (mmol/L)/hr,
- \(V_{\text{MAX,PAH}}\) is the maximum rate of Phe breakdown due to PAH with a normal subject (0.9 (mmol/L)/hr),
- \(F_{\text{PAH}}\) is the fraction of normal PAH activity (healthy = 1 and classical PKU = 0; unitless fraction),
- \(K_{\text{PAH}}\) is the Michaelis-Menten constant for Phe with PAH (0.51 mmol/L),
- \(K_{\text{EvEMAX}}\) is the Phe activation constant for PAH (0.54 mmol/L),
- \(V_{\text{MAX,Ev}}\) is the maximum rate of Phe breakdown due to transamination which is assumed identical between healthy and PKU (0.063 (mmol/L)/hr),
- \(C_{\text{renal}}\) is the Michaelis-Menten constant for Phe with transamination (1.37 mmol/L),
- \(C_{\text{EvEMAX}}\) is the renal cleavage of Phe per body weight (5.69×10⁻² L/kg/hr),
- \(F_{\text{Gut,Plasma}}\) 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 heterozygous 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.

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.

REFERENCES