Influence of Age and Sex on the Kinetics of Intravenously Administered L-Phenylalanine

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We studied the kinetics of intravenously administered L-phenylalanine with respect to the effect of age and sex, using a two-compartment model. We found that the volume of the peripheral compartment and total body clearance decrease with age. The sex-related influence was less obvious when distribution volumes and total body clearance were corrected for differences in body size. We emphasize the necessity of having age-matched control subjects in kinetic studies.

Additional Keyphrases: variation, source of changes in kinetic constants with age, exemplified by phenylalanine, proper controls in kinetic studies

In previous studies we have shown that the elimination of intravenously administered L-phenylalanine follows a curve that accords with the two-compartment model (1, 2). These studies also indicated that some of the kinetic constants associated with this model might be related to age. In this report we have more thoroughly examined the possible effect of age and sex on the elimination of L-phenylalanine after intravenous administration to apparently healthy subjects.

Materials and Methods

Subjects. The study was carried out on 50 apparently healthy volunteers (25 men, 25 women) between 22 and 68 years of age. The weight of the men varied between 56 and 94 kg (mean 74 kg), that of the women between 42 and 74 kg (mean 59 kg). None of the subjects had any signs or history of liver, kidney, or endocrine disorders or was being treated with any drugs. None of the women were using oral contraceptives. All subjects had normal concentrations of creatinine and bilirubin in their serum and normal activities of serum alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase.

Intravenous L-phenylalanine loading. The loading was performed in the morning at 0800 hours, after an overnight fast. L-Phenylalanine, 300 μmol/kg body weight, was given intravenously during 3-4 min. Venous blood was sampled before the injection and thereafter at 5-min intervals during the first hour and every 10 min during the next 2 h. The blood was collected in heparinized tubes and the plasma from it was stored at -20 °C until analysis.

Analysis. Plasma phenylalanine and tyrosine were determined by ion-exchange chromatography as earlier described (7). A Beckman Model 120 C amino acid analyzer was used.

Calculations. The plasma phenylalanine concentration after intravenous administration declined bi-exponentially in the plasma in accord with the equation of the two-compartment model:

\[ C = A \cdot e^{-at} + B \cdot e^{-bt} \]

In this equation, C is the plasma concentration minus the
Fig. 1. Effect of age on the apparent distribution volumes of phenylalanine.

The regression line for the total material and the 95% probability lines are indicated. For $V_d$, the regression lines for men and women are also illustrated. $\Theta$, men; $O$, women.

Fig. 2. Effect of age on the elimination rate constant ($k_{el}$) and the transfer rate constants ($k_{12}$ and $k_{21}$).

The regression line for the total material and the 95% probability lines are indicated. For $k_{el}$, the regression lines for men and women are also illustrated. Symbols as in Fig. 1.

The different constants of this model were calculated as described earlier (1). Total body clearance of phenylalanine was determined by $V_d \cdot k_{el}$.

Statistics. We used multiple linear regression analysis to study the effect of age and sex on total body clearance and the various kinetic constants associated with the two-compartment model (4).

Results

The concentration (C) of phenylalanine in plasma declined bi-exponentially in all subjects studied, and its elimination was calculated according to the two-compartment model.

Figure 1 shows the individual values of the distribution volumes ($V_{d,\alpha}$, $V_p$, and $V_c$). The apparent volume of distribution at pseudo-equilibrium ($V_{d,\beta}$) and the volume of the slowly equilibrating tissues $V_p(V_p = V_{d,\beta} - V_c)$ decreased significantly ($p < 0.001$) with age (Figure 1). The correlation coefficients were between 0.3 and 0.4. These distribution volumes of phenylalanine decreased by about 50% from the
age of 20 to the age of 70. The volume of the central compartment \( (V_c) \) did not change with age. A statistically significant sex-related difference \( (p < 0.05) \) was observed in \( V_p \) but not in \( V_{dL} \) and \( V_c \) (Figure 1).

Figure 2 shows the individual values of the elimination rate constant \( (k_{el}) \) and the transfer rate constants \( (k_{21} \) and \( k_{12} \). There was a significant increase in \( k_{21} \) with age, but not in the other rate constants. On statistical treatment of the results, a sex-related difference was found \( (p < 0.05) \) in \( k_{12} \) (Figure 2).

The total body clearance of phenylalanine \( (V_c \cdot k_{el}) \) decreased significantly with age \( (p < 0.001; r = 0.3, \) Figure 3), and there was no sex-related difference when the clearance was corrected to constant body-surface area. The decrease was about 25% over the 50-year period studied in both men and women.

The concentrations of phenylalanine and tyrosine in plasma of fasting subjects were not related to age or sex. The mean phenylalanine concentration was 57 (SD 8) \( \mu \text{mol} \cdot \text{L}^{-1} \) and the mean plasma tyrosine concentration was 63 (SD 10) \( \mu \text{mol} \cdot \text{L}^{-1} \).

**Discussion**

These results show that some of the kinetic constants for phenylalanine associated with the two-compartment model change with age. The sex-related differences were less pronounced and less significant than the changes with age. It must be emphasized that the results are influenced by the unit used. If the difference in body size between men and women is not taken into consideration, sex-related differences will appear in volume constants and in total body clearance. We have chosen to express clearance in liter per square meter of body surface area and volumes in liter per kilogram of body weight, because this mode of expression gave the least variation around the means.

The volume of the peripheral compartment \( (V_p) \) of phenylalanine, which decreased by age, appeared to have a more pronounced decrease and higher values at younger ages in the men than in the women. The volume of the central compartment, on the other hand, was similar in men and women and was not changed at greater age. These differences probably reflect changes in body composition. Both total body water and lean body mass are age- and sex-related (5, 6).

The total body clearance of phenylalanine, which is equal to \( V_c \cdot k_{el} \), decreases by about 5% per 10 years, showing that the elimination capacity of phenylalanine is age-dependent. Earlier, we reported two different conditions with a decreased total body clearance of phenylalanine: cirrhosis of the liver (1) and heterozygosity for phenylketonuria (2). The decrease, which was between 35 and 40% in both conditions, was explained by a reduction of the volume of the central compartment \( (V_c) \) in patients with liver cirrhosis and by a diminished fractional turnover rate \( (k_{el}) \) from the central compartment in heterozygotes for phenylketonuria. The decrease in the total body clearance of phenylalanine with age seems mainly to be due to a reduction in \( k_{el} \). This might imply that the amount of active enzyme per liver cell decreases with age, a similar finding as in heterozygotes for phenylketonuria.

The decreased capacity for eliminating phenylalanine in patients with cirrhosis of the liver and in heterozygotes for phenylketonuria gives rise to an increase of about 40% in the plasma phenylalanine concentration in these fasted groups of subjects. No similar change in plasma phenylalanine concentration with age was observed.

Our results show that some of the kinetic constants of phenylalanine associated with the two-compartment model change with age. Similar changes ought to be observed for other compounds—both natural compounds and drugs—because the changes seem to reflect alterations in body composition and liver function. This emphasizes the necessity of having age-matched reference subjects in kinetic studies.

**References**


