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# (54) METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

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(57) **ABSTRACT**

The invention provides a method for determining a dose and schedule and making dose adjustments of PBA prodrugs used to treat nitrogen retention states, or ammonia accumulation disorders, by measuring urinary excretion of phenylacetylglutamine and/or total urinary nitrogen. The invention provides methods to select an appropriate dosage of a PBA prodrug based on the patient's dietary protein intake, or based on previous treatments administered to the patient. The methods are applicable to selecting or modifying a dosing regimen for a subject receiving an orally administered ammonia scavenging drug.

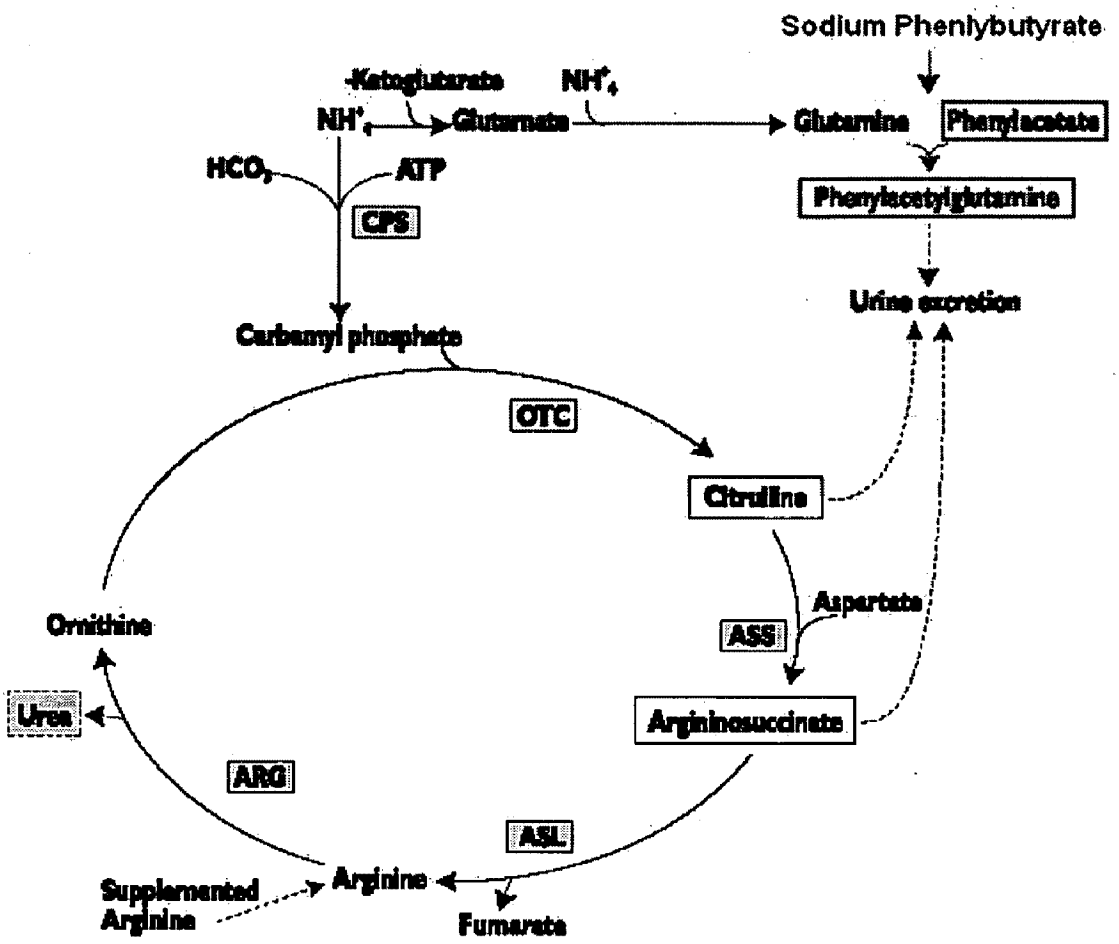


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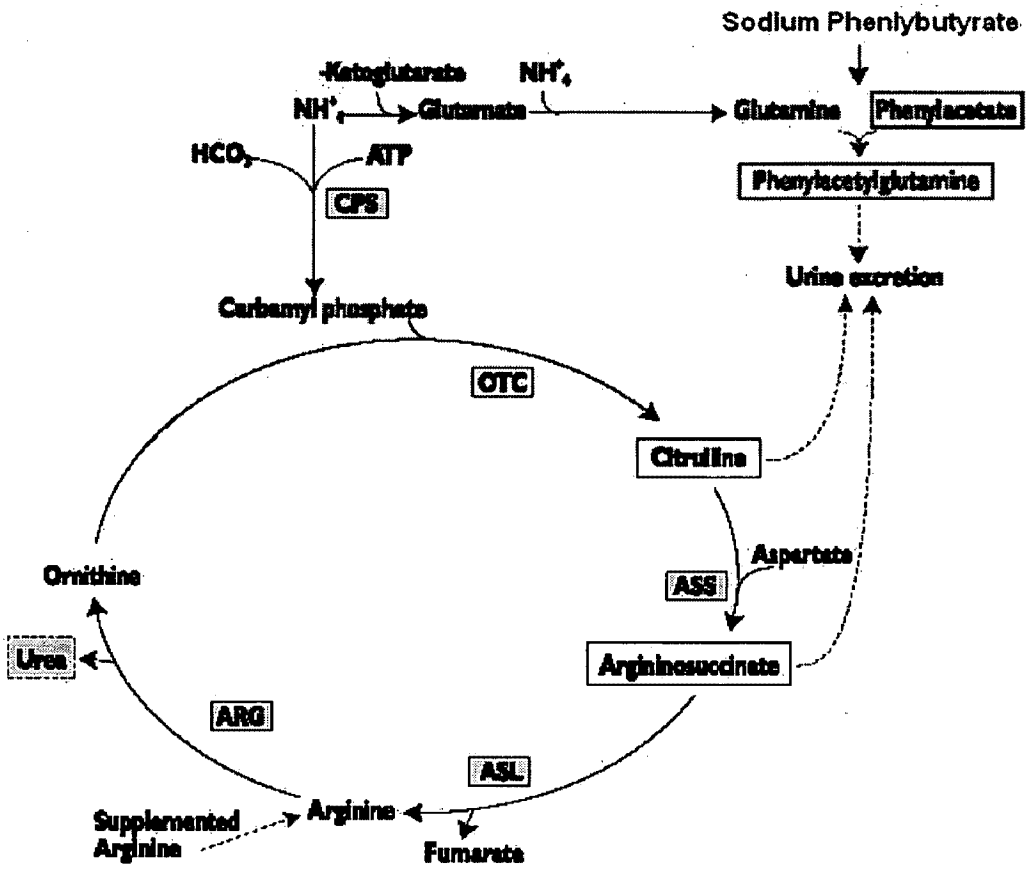
**Figure 1**

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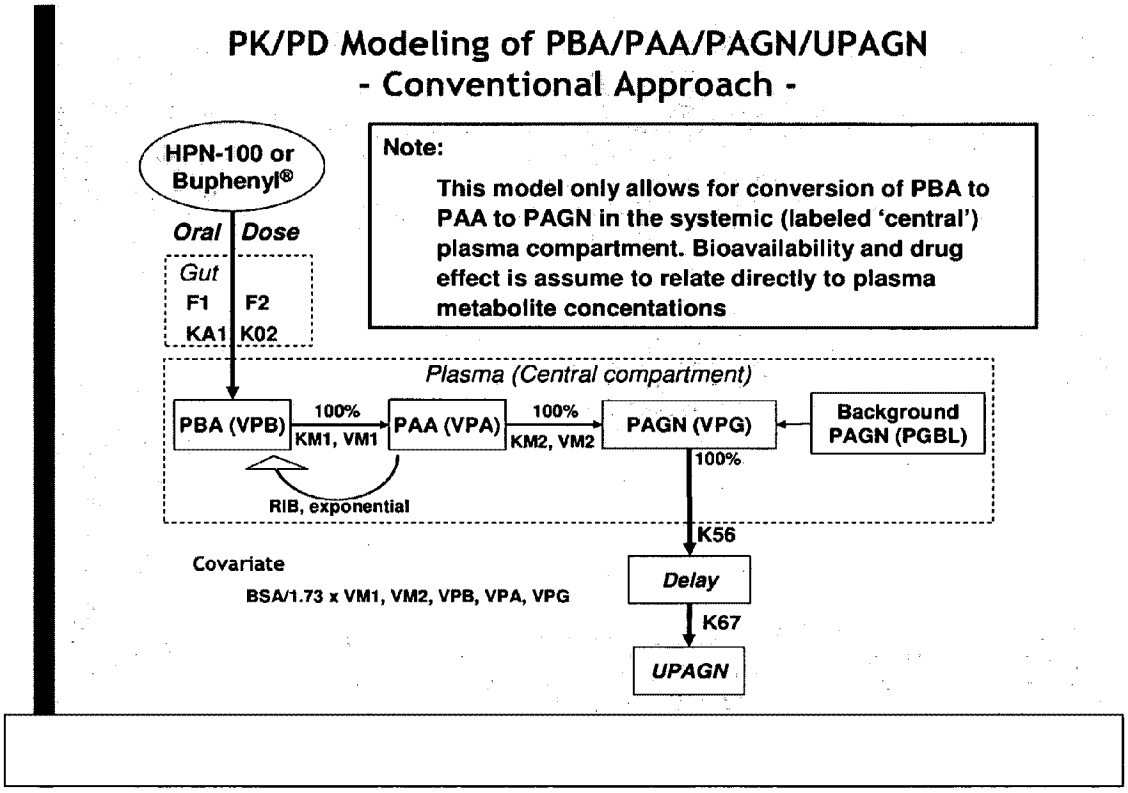
## Figure 2

A conventional clinical pharmacology model in which only drug reaching the central (systemic) circulation is assumed to be active.

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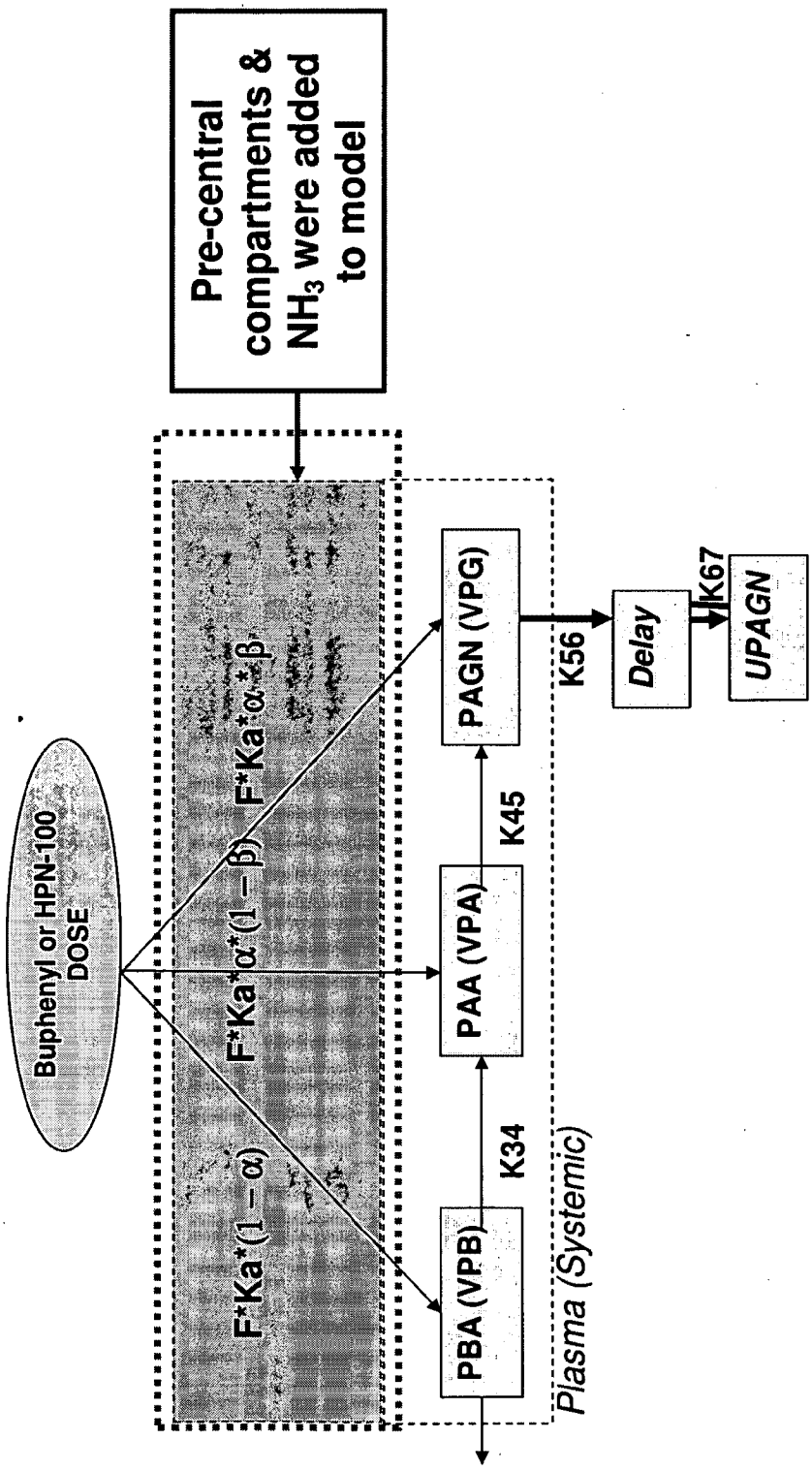


**Figure 3**

A modified clinical pharmacology model as described in this application in which an ammonia scavenging agent converted into PAGN prior to reaching the systemic circulation is fully active with respect to excretion of waste nitrogen. As a corollary, concentrations of metabolites in the systemic circulation do not correlate consistently with drug effect.

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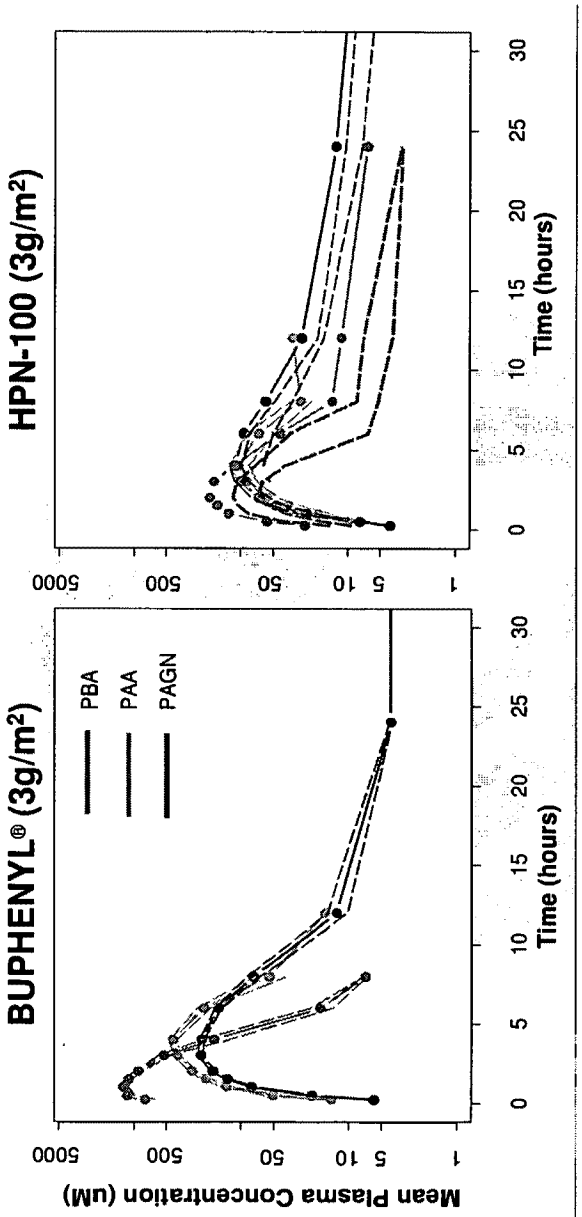
FIGURE 4




In each panel, the curves represent measured levels of PBA, PAA or PAGN in subjects receiving BUPHENYL® (sodium phenylbutyrate) (sodium PBA) at 3g/m$^2$ dosage, or HPN-100 in an amount calculated to provide an equimolar amount of PBA to that provided by the sodium PBA dosage. Three curves for each material are for three subjects who received the specified dosages of sodium PBA or HPN-100. In the left panel, the upper curve represents PBA levels; the intermediate one represents PAA levels; and the lowest of the three sets of lines represents PAGN levels. In the right panel, the three lowest curves at the 10-15 hour time span are all for PBA; and the highest three curves at 15-25 hours represent PAGN levels. PAA levels were not determined after approximately12 hours, and fall generally close to the PAGN curves up to that time.

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