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*[Continued on next page]*

(54) Title: DOSING AND MONITORING PATIENTS ON NITROGEN-SCAVENGING DRUGS

(57) Abstract: The invention provides a method for determining a dose and dosing schedule, and making dose adjustments of patients taking PBA prodrugs as nitrogen scavengers to treat nitrogen retention states, including ammonia accumulation disorders as well as chronic renal failure, 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 waste nitrogen scavenging drug, and to monitoring patients receiving such drugs.

**Figure 1a**
Nitrogen Retention States

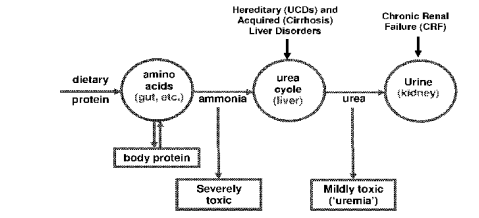
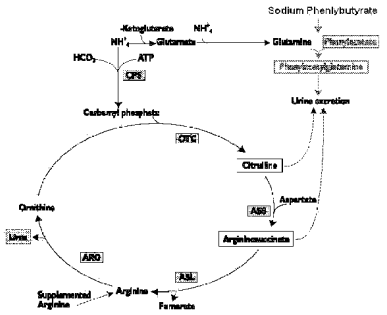



**Figure 1b**
The Urea Cycle



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# DOSING AND MONITORING PATIENTS ON NITROGEN-SCAVENGING DRUGS

## Cross-Reference to Related Applications

**[0001]** This application is a continuation in part of U.S. Nonprovisional Patent Application Serial No. 12/350,111, filed January 7, 2009 which is pending, and a continuation in part of International Application No. PCT/US08/30362, filed January 9, 2009, each of which claims benefit of priority to U.S. Provisional Application Serial Number 61/093,234, filed August 29, 2008, each of which is incorporated herein by reference in its entirety. This application is also related to the U.S. provisional patent application entitled "Treating special populations having liver disease with nitrogen-scavenging compounds," naming Sharron Gargosky as inventor, serial number 61/048,830, filed on April 29, 2008.

## Technical Field

**[0002]** This invention relates to treatment of patients with nitrogen retention states, including urea cycle disorders (UCDs), cirrhosis complicated by hepatic encephalopathy (HE) and chronic renal failure (CRF), using administered compounds that assist in elimination of waste nitrogen from the body. The compounds can be orally administered small-molecule drugs, and the invention provides methods for delivering such compounds and selecting suitable dosages for a patient as well as adjusting dosages and monitoring effectiveness of a treatment. As depicted in Figure 1a, inherited disorders (e.g., UCDs) and acquired disorders (e.g. cirrhosis, typically with portal systemic shunting, complicated by HE) involving the liver which impair the normally efficient clearance of ammonia from the portal circulation and conversion to urea via the urea cycle, depicted in Figure 1b, result in elevated levels in the blood of ammonia, a potent neurotoxin. CRF, while associated in some instances with mildly elevated levels of ammonia, (Deferrari, Kid Int. 1980; 20:505), results in retention of other nitrogenous waste products normally excreted in the urine, in particular urea, the blood levels of which are commonly used to assess renal function.

**[0003]** Restriction of dietary protein (i.e. intake of dietary nitrogen) is commonly used in the management of each of these nitrogen retention states, to avoid accumulation of ammonia or metabolic products containing ammonia, e.g., urea. References herein to ammonia and ammonia

scavenging refer primarily to treating UCDs and HE and conditions that emulate UCDs, although the terms ammonia scavenging and waste nitrogen scavenging are used interchangeably.

Background Art

**[0004]** Drug dosing is usually based upon measurement of blood levels of the active drug species in conjunction with clinical assessment of treatment response. However, the present invention is based on evidence that for certain prodrugs of phenylacetic acid (PAA), measuring the blood level of the prodrug (e.g. PBA) or of PAA formed from it is unreliable in assessing drug effect: drug levels in the blood do not correlate with efficacy in this case. In addition, assessment of treatment effect by measuring levels of ammonia in the blood in UCD patients is also potentially unreliable. Individual ammonia level measurements vary several-fold over the course of a day for a given patient, and withdrawing multiple blood samples under carefully controlled conditions over an extended period of time is clinically impractical as a way to monitor a treated patient. The variability in blood ammonia levels reflects the fact that ammonia levels in UCD patients are affected by various factors including dietary protein and timing in relation to meals, such that any individual value fails to provide a reliable measure of how much ammonia the drug is mobilizing for elimination; i.e. drug effect. The invention demonstrates that prodrugs of phenylbutyric acid (PBA) behave similarly to sodium PBA, in that measuring PBA levels is unreliable for assessing their effectiveness. This invention provides a novel method for dosing in patients with nitrogen retention states, in particular patients with liver disease and clinical manifestations of hepatic encephalopathy and patients with UCDs. It is particularly applicable to prodrugs that liberate or are metabolized to form phenylacetic acid, i.e., prodrugs of PAA, and those prodrugs that are metabolized to form PBA.

**[0005]** Hepatic encephalopathy (HE) refers to a reversible spectrum of neurologic signs and symptoms which frequently occur in patients with cirrhosis or certain other types of liver disease.

**[0006]** Urea cycle disorders (UCDs) comprise several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. The urea cycle is depicted in Figure 1b, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination of excessive ammonia. UCDs include inherited conditions associated with insufficient function of any one of several ammonia-processing enzymes. Individuals born with no meaningful residual urea synthetic capacity typically present in the first few days of life (neonatal presentation). Individuals with residual function typically present later in childhood or even in adulthood, and

symptoms may be precipitated by increased dietary protein or physiological stress (e.g. intercurrent illness.) Some enzymes whose deficient functioning causes UCDs include the following:

- Carbamyl phosphate synthetase (CPS),
- ornithine transcarbamylase (OTC),
- argininosuccinate synthetase (ASS),
- argininosuccinate lyase (ASL),
- arginase (ARG; EC Number 3.5.3.1; autosomal recessive), (ARG) and
- N-acetyl glutamine synthetase (NAGS)

**[0007]** Mitochondrial transporter deficiency states which mimic many features of urea cycle enzyme deficiencies, and thus emulate UCDs and are treatable by the methods described herein for treating UCDs, include the following:

- Ornithine translocase deficiency (hyperornithinemia, hyperammonemia, homocitrullinuria or HHH Syndrome)
- Citrin (aspartate glutamate transporter) deficiency

**[0008]** The common feature of UCDs and similar conditions and hepatic encephalopathy that render them treatable by methods of the invention is an accumulation of excess waste nitrogen in the body, and hyperammonemia. CRF is similarly characterized by build-up of excessive waste nitrogen in the blood in the form urea, and the ammonia scavenging drugs described herein are likewise effective to prevent accumulation of excess levels of urea. In normal individuals, the body's intrinsic capacity for waste nitrogen excretion is greater than the body's waste nitrogen production, so waste nitrogen does not accumulate and ammonia does not build up to harmful levels. For patients with nitrogen retention states such as UCD or HE, the body's intrinsic capacity for waste nitrogen excretion is less than the body's waste nitrogen production based on a normal diet that contains significant amounts of protein. As a result, waste nitrogen builds up in the body of a patient having a nitrogen retention disorder, which usually results in excess ammonia in the blood. This has various toxic effects; drugs that help eliminate the excess ammonia are an important part of an overall management strategy for such disorders.

**[0009]** To avoid build-up of ammonia to toxic levels in patients with nitrogen retention states, dietary intake of protein (a primary source of exogenous waste nitrogen) must be balanced by the patient's ability to eliminate excess ammonia. Dietary protein can be limited, but a healthy diet requires sufficient protein to support normal growth (i.e. in growing children) and repair; thus in

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