

ORIGINAL ARTICLE

## Survival after Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders

Gregory M. Enns, M.B., Ch.B., Susan A. Berry, M.D., Gerard T. Berry, M.D., William J. Rhead, M.D., Ph.D., Saul W. Brusilow, M.D., and Ada Hamosh, M.D., M.P.H.

ABSTRACT

### BACKGROUND

From the Department of Pediatrics, Stanford University, Stanford, CA (G.M.E.); the Department of Pediatrics, University of Minnesota, Minneapolis (S.A.B.); the Department of Pediatrics, Thomas Jefferson University, Philadelphia (G.T.B.); the Department of Pediatrics, Medical College of Wisconsin, Milwaukee (W.J.R.); and the Department of Pediatrics and Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore (S.W.B., A.H.). Address reprint requests to Dr. Enns at the Department of Pediatrics, Division of Medical Genetics, Stanford University School of Medicine, Lucile Packard Children's Hospital, 300 Pasteur Dr., H-315, Stanford, CA 94305-5208, or at [greg.enns@stanford.edu](mailto:greg.enns@stanford.edu).

N Engl J Med 2007;356:2282-92.

Copyright © 2007 Massachusetts Medical Society.

The combination of intravenous sodium phenylacetate and sodium benzoate has been shown to lower plasma ammonium levels and improve survival in small cohorts of patients with historically lethal urea-cycle enzyme defects.

### METHODS

We report the results of a 25-year, open-label, uncontrolled study of sodium phenylacetate and sodium benzoate therapy (Ammonul, Ucyclid Pharma) in 299 patients with urea-cycle disorders in whom there were 1181 episodes of acute hyperammonemia.

### RESULTS

Overall survival was 84% (250 of 299 patients). Ninety-six percent of the patients survived episodes of hyperammonemia (1132 of 1181 episodes). Patients over 30 days of age were more likely than neonates to survive an episode (98% vs. 73%,  $P<0.001$ ). Patients 12 or more years of age (93 patients), who had 437 episodes, were more likely than all younger patients to survive (99%,  $P<0.001$ ). Eighty-one percent of patients who were comatose at admission survived. Patients less than 30 days of age with a peak ammonium level above 1000  $\mu\text{mol}$  per liter (1804  $\mu\text{g}$  per deciliter) were least likely to survive a hyperammonemic episode (38%,  $P<0.001$ ). Dialysis was also used in 56 neonates during 60% of episodes and in 80 patients 30 days of age or older during 7% of episodes.

### CONCLUSIONS

Prompt recognition of a urea-cycle disorder and treatment with both sodium phenylacetate and sodium benzoate, in conjunction with other therapies, such as intravenous arginine hydrochloride and the provision of adequate calories to prevent catabolism, effectively lower plasma ammonium levels and result in survival in the majority of patients. Hemodialysis may also be needed to control hyperammonemia, especially in neonates and older patients who do not have a response to intravenous sodium phenylacetate and sodium benzoate.

**U**REA-CYCLE DISORDERS ARE INBORN ERRORS of metabolism that are characterized by episodic, life-threatening hyperammonemia resulting from partial or complete inactivity of enzymes responsible for eliminating nitrogenous waste. Historically, mortality and morbidity have been very high, and survivors commonly have had devastating neurologic sequelae.<sup>1</sup> Initial efforts to remove accumulated ammonium in patients with hyperammonemic encephalopathy included lactulose therapy,<sup>2</sup> exchange transfusion,<sup>3,4</sup> peritoneal dialysis,<sup>4</sup> hemodialysis,<sup>5</sup> and supplementation with nitrogen-free analogues of essential amino acids.<sup>6</sup> These treatments prolonged survival in some patients, but the overall efficacy was disappointing — and mortality and morbidity remained high.

Current therapeutic strategies include reducing the production of nitrogenous waste with the use of a low-protein diet and preventing endogenous catabolism through the provision of adequate nutrition. In addition, exploitation of alternative pathways for excretion of waste nitrogen has played a critical role in the management of urea-cycle disorders since Brusilow and colleagues first suggested using endogenous biosynthetic pathways to eliminate non-urea-waste nitrogen as a substitute for defective urea synthesis.<sup>7</sup> In theory, the total body load of nitrogen can be decreased, despite abnormal urea-cycle functioning, by promoting the synthesis of non-urea nitrogen-containing metabolites that have high excretion rates or rates that may be augmented.<sup>7-11</sup> The first successful demonstration of this concept was the use of arginine supplementation for the treatment of argininosuccinate lyase deficiency.<sup>9</sup>

An open-label, uncontrolled, multicenter study of intravenous sodium phenylacetate and sodium benzoate combined (Ammonul, Ucyclid Pharma) as an emergency treatment for hyperammonemia in patients with urea-cycle disorders was conducted in the United States and Canada from 1980 to 2005. The primary purpose of the study was to determine whether treatment with sodium phenylacetate and sodium benzoate reduced mortality due to acute hyperammonemia, as compared with historical data.

## METHODS

### STUDY DESIGN

We conducted an open-label, uncontrolled, nonrandomized study at 118 hospitals in the United States

and Canada between August 1980 and March 2005. The patients included in the study were hospitalized because of hyperammonemia resulting from a urea-cycle defect. A total of 299 patients with urea-cycle disorders and 1181 episodes of hyperammonemia were included. Four patients for whom demographic data were incomplete were excluded. To enroll a patient, the investigator contacted one of the authors (S.W.B.) at Johns Hopkins School of Medicine (from 1982 through 1996), or Ucyclid Pharma (from 1997 through 2005), which supplied the study drug and case-report forms. The institutional review board at each participating institution approved the study. Written informed consent was obtained from the parents or legal guardians of children enrolled and from adult patients.

### TREATMENT

Infants and children (weighing up to 20 kg [44 lb]) who had carbamyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, or argininosuccinate synthetase deficiency were treated with an initial (loading) dose of sodium phenylacetate (250 mg per kilogram of body weight) and sodium benzoate (250 mg per kilogram) administered intravenously over a period of 90 to 120 minutes. Older children (weighing more than 20 kg) and adults were treated with sodium phenylacetate and sodium benzoate, 5.5 g per square meter of body-surface area, as an intravenous loading dose over a period of 90 to 120 minutes. After the loading dose, maintenance infusions of the same dose were continued over 24 hours until the patient no longer had hyperammonemia and oral therapy could be tolerated. Among the factors limiting tolerance were vomiting, decreased intestinal motility, and the presence of umbilical catheters. Intravenous ondansetron (Zofran, GlaxoSmithKline) (0.15 mg per kilogram) was used in some patients to prevent or treat hyperemesis. Guidelines for administering sodium phenylacetate and sodium benzoate were not available for the treatment of argininosuccinate lyase deficiency or arginase deficiency. Loading and maintenance infusions also contained arginine hydrochloride (210 mg per kilogram for patients with ornithine transcarbamylase deficiency or carbamyl phosphate synthetase deficiency, and 630 mg per kilogram for patients with argininosuccinate synthetase deficiency or argininosuccinate lyase deficiency). Although a dialysis protocol was not used, dialysis, as noted below, was recommended for any neonate with hyperammonemic encephalopathy or any oth-

er patient in whom the ammonium level did not decrease substantially within 8 hours after administration of the loading infusion. Not all investigators followed these treatment guidelines precisely.

#### ASSESSMENT

The primary end point was survival of the episode of hyperammonemia. When a patient died, the investigator was asked to identify the primary and secondary causes of the death and to assess the relationship of the death to the primary disease and to the study drug. Plasma ammonium data were collected and analyzed according to a schedule determined by each investigator.

#### STATISTICAL ANALYSIS

Data were summarized with the use of descriptive statistics. An episode was defined as a single hospitalization for hyperammonemia. For comparisons according to age and diagnosis, P values for survival were calculated with the use of Fisher's exact test for each category, as compared with all other categories. For the comparison according to peak ammonium level, P values for survival were calculated with the use of Fisher's exact test for each category of ammonium level, as compared with all categories of lower ammonium levels.

Outcome at discharge (survival vs. death) was also compared according to coma status at admission. Separate analyses according to coma status at admission were performed for all episodes and for different age groups and enzyme deficiency. P values were calculated with the use of the McNemar test for the comparison between outcome at discharge (alert vs. comatose vs. deceased) and coma status at admission (coma vs. no coma).

## RESULTS

#### SURVIVAL

Over the 25 years of the study, 299 patients with urea-cycle disorders were treated with sodium phenylacetate and sodium benzoate for a total of 1181 episodes of hyperammonemia. The patients included 93 neonates (94 episodes) and 237 patients older than 30 days of age (1087 episodes) (Table 1 and Fig. 1). Thirty-one patients were treated both as neonates and as older patients and thus were included in the totals for both groups. The mean ( $\pm$ SD) number of episodes per patient was  $3.3\pm 6.3$  (range, 1 to 79). Dialysis (including standard hemo-

dialysis, various combinations of arteriovenous and venovenous hemofiltration, and peritoneal dialysis) was used during 136 of the 1181 episodes (12%) and in 105 of 299 patients (35%). Dialysis was used more commonly in neonates (56 neonates, 60% of episodes) than in older patients (80 patients, 7% of episodes). Peritoneal dialysis with no other form of dialysis was used in six neonates and was used in combination with hemodialysis, a form of hemofiltration, or both in four neonates and two older patients. Overall the rate of survival (defined as survival of all known episodes for each patient) was 84% (250 of 299 patients) (Table 1). The survival rate for hyperammonemic episodes was 96% (1132 of 1181 episodes). Patients more than 30 days of age were more likely to survive an episode of hyperammonemia than were neonates (survival rates, 98% and 73%, respectively;  $P<0.001$ ). Patients more than 12 years of age (93 patients, 437 episodes) were most likely to survive an episode of hyperammonemia (survival rate, 99%;  $P<0.001$ , as compared with all other age groups) (Table 2).

The survival rate for episodes of hyperammonemia was significantly lower among male patients with ornithine transcarbamylase deficiency (91%) than among female patients with the same deficiency (98%) and among patients with a deficiency of carbamyl phosphate synthetase, argininosuccinate synthetase, or argininosuccinate lyase ( $P<0.001$ ) (Table 2). The survival rate appeared to be lower among patients with arginase deficiency (80%) than among those with a deficiency of ornithine transcarbamylase, carbamyl phosphate synthetase, argininosuccinate synthetase, or argininosuccinate lyase but the difference did not reach statistical significance (Table 2); there were only five episodes reported in patients with arginase deficiency. Indeed, the single patient with arginase deficiency who died had neonatal sepsis and relatively mild hyperammonemia ( $<200\ \mu\text{mol}$  per liter [ $361\ \mu\text{g}$  per deciliter]).

Thirteen of the 49 patients who died received sodium phenylacetate and sodium benzoate in amounts that were greater than the recommended doses. Of these 13 patients, 7 received a bolus dose of sodium phenylacetate and sodium benzoate ranging from 370 to 620 mg per kilogram. One patient was given a bolus dose of sodium phenylacetate and sodium benzoate approximately 9 times higher than that recommended (2310 mg of each medication per kilogram). In addition, seven patients were given multiple (range, one to

**Table 1. Survival According to Diagnosis and Age at Presentation.**

Variable	Carbamyl Phosphate Synthetase Deficiency	Ornithine Transcarbamylase Deficiency		Argininosuccinate Synthetase Deficiency	Argininosuccinate Lyase Deficiency	Overall Survival*
	All Patients (N=41)	Male Patients (N=86)	Female Patients (N=78)	All Patients (N=80)	All Patients (N=11)	All Patients (N=299)
	<i>number/total number (percent)</i>					
Survived first known episode	37/41 (90)	66/86 (77)	70/78 (90)	75/80 (94)	10/11 (91)	260/299 (87)
Age ≤30 days	9/12 (75)	24/40 (60)	2/3 (67)	28/32 (88)	5/5 (100)	68/93 (73)
Age >30 days	28/29 (97)	42/46 (91)	69/75 (92)	47/48 (98)	5/6 (83)	193/206 (94)
Survived all known episodes	34/41 (83)	61/86 (71)	69/78 (88)	73/80 (91)	10/11 (91)	250/299 (84)
Neonatal onset (age ≤30 days)	8/12 (67)	21/40 (53)	2/3 (67)	27/32 (84)	5/5 (100)	63/93 (68)
Presumed late onset (age >30 days)	27/29 (93)	40/46 (87)	68/75 (91)	46/48 (96)	5/6 (83)	188/206 (91)

\* Three patients with arginase deficiency were treated with sodium phenylacetate and sodium benzoate; one had neonatal onset of the disease and died during the first episode, and two had a total of four episodes and survived. Because ornithine transcarbamylase deficiency is an X-linked disorder, male patients typically have a more severe clinical phenotype than do female patients, so for this disorder a distinction on the basis of sex was made.

seven) additional bolus infusions of sodium phenylacetate and sodium benzoate after administration of the initial bolus. Two other male patients with ornithine transcarbamylase deficiency were given high maintenance doses of each medication (an 18-year-old was given 6.25 g per square meter of body-surface area over a 23-hour period and a neonate 4380 mg per kilogram over a 25-hour period).

The majority of patients had adverse events during treatment for hyperammonemia; disorders of the metabolic system, the nervous system, and the respiratory system were most commonly reported (Table 3). In the 49 patients who died, coexisting conditions were common and included seizures (19 patients), infection (18), cerebral edema or increased intracranial pressure (16), disseminated intravascular coagulation (9), kidney failure (6), multiorgan system failure (5), and cerebral hemorrhage (5).

#### SURVIVAL AND COMA AT ADMISSION

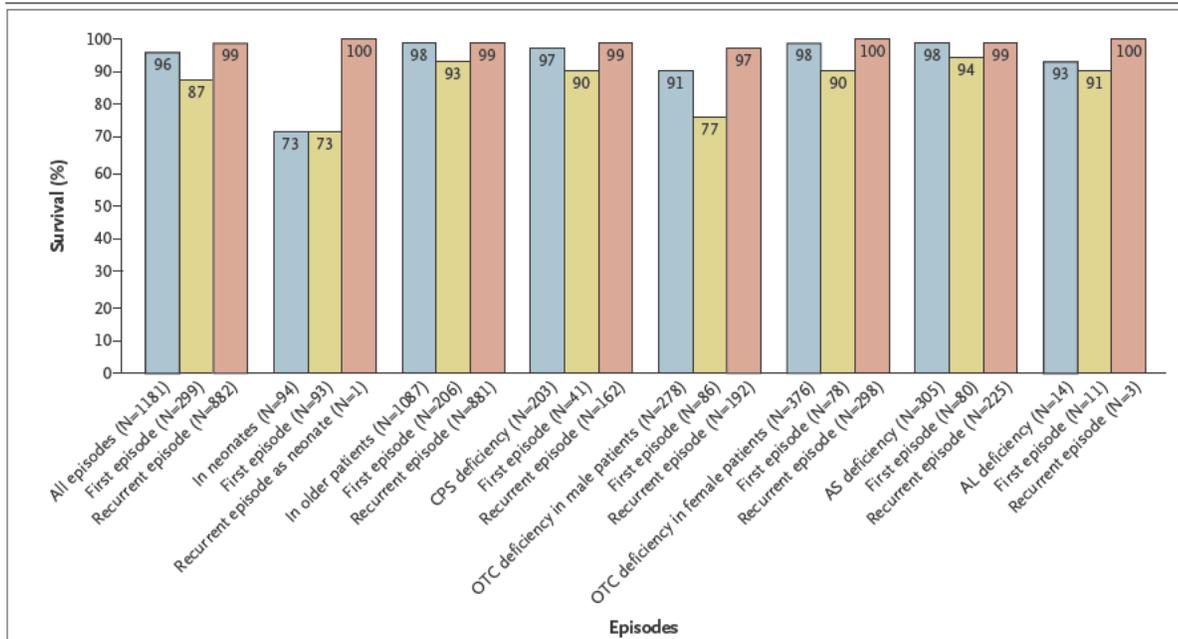
Among 209 patients, there were 1020 episodes of hyperammonemia without coma at the time of admission. When coma was not present on admission, in the overwhelming majority (992) of these episodes (97%), coma was also absent at the time of discharge. However, 22 episodes in which coma was absent on admission resulted in death (2%), and in 6 episodes (<1%) coma persisted at the time

of discharge (five patients with coma at discharge were transferred to other hospitals for treatment with dialysis, and one was transferred to another center for liver transplantation). Among 82 patients, there were 120 episodes in which the patients were comatose on admission. Overall, when patients were comatose on admission, no coma was present at the time of discharge (97 episodes, 81%); 23 episodes in which the patients were comatose at admission resulted in death (19%) (Table 2).

The survival rate for hyperammonemic episodes was significantly lower among patients who were comatose at admission, both among neonates ( $P=0.002$ ) and among older patients ( $P<0.001$ ). Children 2 to 12 years of age who were comatose at admission had a relatively lower rate of survival of a hyperammonemic episode (79%) than those in other groups over 30 days of age. The survival rate was lowest among male patients with ornithine transcarbamylase deficiency who were comatose at admission (68%) (Table 2).

#### SURVIVAL AND PEAK AMMONIUM LEVEL

Survival was significantly improved for patients who had hyperammonemic episodes with a peak plasma ammonium level of 500  $\mu\text{mol}$  per liter (902  $\mu\text{g}$  per deciliter) or less than among those with higher peak ammonium levels ( $P<0.001$ ). Patients less than 30 days of age with a peak ammonium



**Figure 1. Survival of Episodes of Hyperammonemia, According to Age, Diagnosis, and First Episode versus Recurrent Episodes.**

Because ornithine transcarbamylase (OTC) deficiency is an X-linked disorder, male patients typically have a more severe clinical phenotype than do female patients, and for that reason a distinction on the basis of sex was made. CPS denotes carbamyl phosphate synthetase, and AS argininosuccinate synthetase.

level greater than 1000  $\mu\text{mol}$  per liter (1804  $\mu\text{g}$  per deciliter) were least likely to survive a hyperammonemic episode (survival, 38%;  $P < 0.001$ ) (Table 4 and Fig. 2).

**CHANGES IN AMMONIUM LEVELS**

Plasma ammonium levels decreased substantially in most patients after therapy with the use of the intravenous treatment protocol (alternative-pathway therapy for nitrogen excretion). For all episodes in which both a baseline ammonium level (the last value recorded before treatment with sodium phenylacetate and sodium benzoate plus arginine hydrochloride was begun) and the level measured after treatment was initiated were known (582 patients), the median ammonium level fell from 185  $\mu\text{mol}$  per liter (334  $\mu\text{g}$  per deciliter) to 36  $\mu\text{mol}$  per liter (65  $\mu\text{g}$  per deciliter) at the final assessment (–79% change from baseline). Plasma ammonium levels decreased substantially in both neonates and older patients, although the median ammonium levels were markedly higher in neonates than in older patients at baseline. Among patients who died, median ammonium levels were similar at baseline and at the final assessment

(334 and 364  $\mu\text{mol}$  per liter [603 and 657  $\mu\text{g}$  per deciliter] among neonates and 168 and 116  $\mu\text{mol}$  per liter [303 and 209  $\mu\text{g}$  per deciliter] among older patients, respectively). Median ammonium levels decreased substantially in patients who survived (from 374 to 24  $\mu\text{mol}$  per liter [675 to 43  $\mu\text{g}$  per deciliter] among neonates and 179 to 36  $\mu\text{mol}$  per liter [323 to 65  $\mu\text{g}$  per deciliter] among older patients).

**DISCUSSION**

Historically, survival among patients with urea-cycle disorders was poor after episodes of hyperammonemia; most children with a severe enzyme deficiency died as neonates — and few survived infancy.<sup>1,12,13</sup> In 1979, Brusilow et al. hypothesized that hyperammonemic coma caused by urea-cycle disorders might be treated with a combination of sodium phenylacetate and sodium benzoate.<sup>7</sup> The potential of the use of alternative pathways of nitrogen excretion to treat hyperammonemic coma was demonstrated soon thereafter; the administration of sodium benzoate either orally or intravenously in four patients

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.