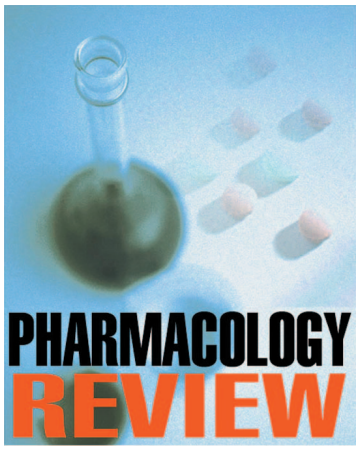

Sodium Phenylacetate and Sodium Benzoate in the Treatment of Neonatal Hyperammonemia

Anna-Kaisa Niemi, MD, PhD,* Gregory M. Enns, MB, ChB*

Author Disclosure

Dr Niemi did not disclose any financial relationships relevant to this article. Dr Enns disclosed that he has received honoraria for lectures and consultant work from Ucyclyd Pharma, Inc.

Abbreviations

AL:	argininosuccinic acid lyase
ASA:	argininosuccinic acid
ATP:	adenosine triphosphate
BZ:	benzoate
CoA:	coenzyme A
HIP:	hippurate
NABZ:	sodium benzoate
NAPA:	sodium phenylacetate
OTC:	ornithine transcarbamylase
PA:	phenylacetic acid
PAGN:	phenylacetylglutamine
PD:	peritoneal dialysis
UCD:	urea cycle disorder

Introduction

Ammonia is present in all body fluids and exists primarily as ammonium ion at physiologic pH. Hyperammonemia is defined as a blood ammonia concentration greater than about 100 mcmol/L in neonates or 50 mcmol/L in children and adults (precise cut-offs vary, depending on individual laboratory normative ranges). The concentration of ammonia is 10 times higher in tissue than in blood. A 5- to 10-fold increase in blood ammonia concentration usually is toxic to the nervous system.

Hyperammonemia in the neonatal period, especially when due to inborn errors of metabolism, can progress rapidly and cause severe neurologic damage or early death. Hyperammonemia can be caused by inborn errors of metabolism as well as by a variety of acquired conditions (Tables 1 and 2). Urgent treatment is required because of the potential for irreversible neurologic sequelae that can, in many cases, be prevented by prompt diagnosis and institution of therapy.

The combination of sodium phenylacetate (NAPA) and sodium benzoate (NABZ) in a 10%/10% solution is an intravenously administered United States Food and Drug Administration (FDA)-approved drug used as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients who have urea cycle disorders (UCDs). Its concomitant use with protein restriction, provision of adequate calories to prevent catabolism, arginine hydrochloride, and hemodialysis in treating neonatal hyperammonemia helps prevent the reaccumulation of ammonia by increasing waste nitrogen excretion. The purpose of this article is to review the pharmacology and use of NAPA/NABZ in the treatment of neonatal hyperammonemia.

*Department of Pediatrics, Division of Medical Genetics, Stanford University School of Medicine, Stanford, Calif.

Neonatal Hyperammonemia

Because the inheritance of most inborn errors of metabolism that cause neonatal hyperammonemia is autosomal recessive (exceptions include ornithine transcarbamylase [OTC] deficiency, which is X-linked, and hyperinsulinism/hyperammonemia syndrome, which is autosomal dominant), family history may offer no information of note or may reveal unexplained neonatal deaths.

UCDs are the most common cause of neonatal hyperammonemia and typically present with symptoms of poor feeding, lethargy, hypotonia, irritability, seizures, respiratory distress, grunting, and hyperventilation. Patients may have a bulging fontanelle if intracranial pressure is increased. Because the clinical presentation of hyperammonemia is nonspecific, other disorders common in neonates, such as sepsis, cardiac failure, and intracranial hemorrhage, are included in the differential diagnosis. Therefore, blood ammonia concentrations should be measured

Table 1. Inborn Errors of Metabolism Associated With Hyperammonemia

Urea cycle defects
- *N*-acetylglutamate synthetase deficiency
- Carbamyl phosphate synthetase deficiency
- Ornithine transcarbamylase deficiency
- Argininosuccinate synthetase deficiency (citrullinemia)
- Argininosuccinate lyase deficiency
- Arginase deficiency

Amino acid transporter deficiencies
- Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
- Lysinuric protein intolerance
- Citrin deficiency (citrullinemia type II)

Organic acidemias
- Methylmalonic acidemia
- Propionic acidemia
- Isovaleric acidemia
- Multiple carboxylase deficiency
- Multiple acyl-CoA dehydrogenase deficiency
- 3-Hydroxymethylglutaryl-CoA dehydrogenase deficiency
- 3-Methylcrotonyl-CoA carboxylase deficiency
- 3-Oxothiolase deficiency
- L-2-Hydroxyglutaric acidemia
- 3-Methylglutaconyl-CoA hydratase deficiency

Fatty acid oxidation defects
- Carnitine transporter deficiency
- Carnitine palmitoyl transferase 2 deficiency
- Carnitine-acylcarnitine translocase deficiency
- Medium-chain acyl-CoA dehydrogenase deficiency
- Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- Very-long-chain acyl-CoA dehydrogenase deficiency

Pyruvate carboxylase deficiency

Mitochondrial disorders

Hyperinsulinism/hyperammonemia syndrome (glutamate dehydrogenase mutations)

Delta^1-pyrroline-5-carboxylate synthase deficiency

in all neonates presenting with nonspecific symptoms of distress. If the concentration is elevated, diagnostic evaluations and treatment should be started immediately (Tables 3 and 4).

Early Efforts in Hyperammonemia Therapy

A number of different therapies aimed at removing accumulated ammonia in cases of hyperammonemic encephalopathy have been attempted, including administration of lactulose (reduces the production or absorption of the end products of bacterial nitrogen metabolism in the colon), (1) exchange transfusion, (2)(3)(4) peritoneal dialysis, (3)(4) hemodialysis, (3)(4)(5) and supplementation with nitrogen-free analogues of essential amino acids. (6)(7)(8) Although children treated with alpha-keto amino acid analogues showed some clinical improvement, such as improved seizure control, attention span, and weight gain, death in infancy remained common. (6)(7)(8) Exchange transfusions are ineffective in managing hyperammonemia. In 15 patients treated by exchange transfusion, the decrease in ammonia values immediately following the procedure was not statistically significant. (9) Peritoneal dialysis (PD) has shown variable efficacy in treating hyperammonemia. Seven neonates who had UCDs showed a significant decrease in plasma ammonia values (85%±6%, $P<0.001$) following PD for a mean duration of 60 hours, but PD was ineffective in 13 older children. (9) The early use of these treatments prolonged survival in some cases, but overall efficacy was disappointing, and the mortality and morbidity associated with UCDs continued to be high.

Table 2. Causes of Acquired Hyperammonemia

Sampling artifact

Cardiovascular
- Patent ductus venosus
- Portocaval shunt
- Hypovolemia
- Congestive heart failure

Perinatal asphyxia

Liver failure
- Infectious hepatitis (eg, herpes simplex virus)

Bacterial colonization (urease-positive organisms)
- Neurogenic bladder
- Prune belly syndrome
- Blind loop syndrome
- Ureterosigmoidostomy

Iatrogenic
- Valproate
- Arginine deficiency
- Total parenteral nutrition

Table 3. Differential Diagnosis of Neonatal Hyperammonemia

Onset	Cause	Clues to Diagnosis
<24 h after birth	1. THAN	• Preterm infant • No acidosis/ketosis
<24 h or >24 h after birth	2. Organic acidemias (eg, MMA, PA, IVA), defects of fatty acid oxidation, congenital lactic acidosis	• Term infant • Acidosis (+/− ↑ lactate) • +/− ketosis
>24 h after birth	3. Urea cycle defects:	No acidosis, sometimes alkalosis
	a) CPS deficiency	• Low/absent citrulline • Urine orotic acid low
	b) OTC deficiency	• Low/absent citrulline • Urine orotic acid markedly elevated
	c) AS deficiency	• Citrulline markedly elevated (>1,000 mcmol) • No ASA in urine • Urine orotic acid elevated
	d) AL deficiency	• Citrulline moderately elevated (100 to 300 mcmol) • ASA present in urine • Urine orotic acid elevated

Fatty acid oxidation disorders, especially carnitine-acylcarnitine translocase deficiency, and organic acidemias may be difficult to distinguish from urea cycle defects in some instances. Metabolic acidosis, relatively high blood urea nitrogen (BUN) (urea cycle defects tend to be associated with a low BUN), and ketosis are more typical of organic acidemias. Hypoketotic hypoglycemia is suggestive of a fatty acid oxidation defect, but the level of ketosis is not always a reliable indicator in neonates. Prominent lactic acidosis may suggest pyruvate carboxylase deficiency or mitochondrial disorders. AL=argininosuccinate lysase, AS=argininosuccinate synthetase, ASA=argininosuccinic acid, CPS=carbamyl phosphate synthetase, IVA=isovaleric acidemia, MMA=methylmalonic acidemia, OTC=ornithine transcarbamylase; PA=propionic acidemia, THAN=transient hyperammonemia of the newborn

Alternative Pathway Therapy

In 1914, Lewis demonstrated that NABZ could divert urea nitrogen to hippurate (HIP) nitrogen in two healthy subjects. (10) After ingestion of single 6- or 10-g aliquots of NABZ, blood urea nitrogen and ammonia levels fell, and urine HIP excretion showed a prominent rise, with little change in total urine nitrogen excretion. Shiple and Sherwin (11) later showed that oral administration of phenylacetic acid (PA) results in substitution of phenylacetylglutamine (PAGN) nitrogen for urea nitrogen in urine. Furthermore, coadministration of benzoate (BZ) and PA resulted in as much as 60% of urine nitrogen being excreted as HIP and PAGN. (11) Subsequently, the enzymes responsible for these reactions (acyl-CoA:glycine and acyl-CoA:glutamine *N*-acyltransferases) were identified and localized to both the kidney and liver in humans and primates. (12)(13)(14)(15) Synthesis of HIP (from conjugation of glycine with BZ) and PAGN (from conjugation of glutamine with PA) requires adenosine triphosphate (ATP) and coenzyme A (CoA). (16)

In 1979, Brusilow and associates (17) suggested that the use of endogenous biosynthetic pathways of non-urea waste nitrogen excretion could substitute for defective urea synthesis in patients who have UCDs. By promoting the synthesis of non-urea nitrogen-containing metabolites whose excretion rates are high or may be augmented, theoretically total body nitrogen load could be decreased despite the absence of normal urea cycle function. Two classes of such metabolites are: 1) urea cycle intermediates (citrulline and argininosuccinic acid) and 2) amino acid acylation products (HIP and PAGN). (18)

Urea Cycle Intermediates

In argininosuccinic acid lyase (AL) deficiency, argininosuccinic acid (ASA) accumulates and is excreted in the urine. Because ASA contains two waste nitrogen atoms, production of this metabolite can be exploited to excrete waste nitrogen in AL deficiency, provided that an adequate amount of ornithine is present to supply the necessary carbon skeletons for ASA biosynthesis. (19) By administering pharmacologic doses of arginine, ornithine is synthesized by the action of arginase. Citrulline and ASA subsequently are produced by the sequential action of OTC and argininosuccinic acid synthetase. In AL deficiency, ASA cannot be metabolized further and is excreted in the urine, along with waste nitrogen (Fig. 1). (17)(18)(19)

Similarly, citrulline can serve as a

Table 4. Management of Neonatal Hyperammonemia Caused by Urea Cycle Defects

Laboratory studies
- Blood ammonia
- Anion gap
- Liver transaminases, alkaline phosphatase, bilirubin, prothrombin time
- Blood lactate and pyruvate
- Arterial blood gas
- Serum and urine amino acids
- Urine organic acids
- Urine quantitative orotic acid
- Plasma carnitine (total, free, and esterified)
- Plasma acylcarnitine profile

Treatment: Prevention of catabolism and ammonia accumulation
- Intravenous dextrose (20% or 25%)
- No exogenous protein for 24 to 48 h
- Use continuous insulin drip if hyperglycemic
- Intravenous lipid (once fatty acid oxidation disorders excluded)
- Provide total calories of approximately 100 to 120 kcal/kg per day

Treatment: Medications
- Sodium benzoate and sodium phenylacetate
- Arginine hydrochloride 10%*
- Lactulose 2.5 mL NG/PO tid prn
- Neomycin 50 mg/kg per day PR q 6 h†

Treatment: Other measures
- Central vascular access
- Correction of hypovolemia, anemia, and possible acidosis
- Treatment of underlying infection
- Intubation and ventilation (target $Paco_2$ of 30 to 35 mm Hg)
- Urinary catheter (for monitoring of urine output)
- Hemodialysis

*Acidosis may occur; arterial blood gases should be examined after loading dose.
†Only in neonates >2 days old.

vehicle for waste nitrogen excretion in AS deficiency (citrullinemia), as long as sufficient arginine is supplied (Fig. 1). (17)(18) However, citrulline contains only one waste nitrogen atom, and a high percentage of filtered citrulline is reabsorbed, so urine excretion is relatively poor. (18)

Amino Acylation Products

HIP is an excellent metabolite for renal excretion because its renal clearance is five times the glomerular filtration rate. (17) HIP biosynthesis, by conjugation of BZ with glycine, is accomplished by the action of mitochondrial matrix enzymes (benzoyl thiokinase and a glycine-specific *N*-acyltransferase) (Figs. 1 and 2). (13)(16) Similarly, PAGN is formed by sequential action of phenylacetyl thiokinase and a glutamine-specific *N*-acyltransferase. (12)(13) Because PA has the ability to conjugate glutamine, forming PAGN (a compound that contains two nitrogen atoms), its nitrogen-scavenging ability was hypothesized to be twice as effective as BZ (which contains one nitrogen atom). (18) In 1979, Brusilow and colleagues (17) suggested using combined therapy with NAPA and NABZ for treating hyperammonemic coma.

Initial Clinical Trials of NAPA and NABZ

The potential of alternative pathway therapy was demonstrated initially in 1980. A clinically stable 17-year-old girl who had carbamyl phosphate synthetase deficiency excreted significant amounts of HIP and PAGN in the urine after NABZ (6.25 g/d) or PA (6.4 g/d) was administered orally. Subsequent administration of NABZ (250 to 350 mg/kg, either orally or intravenously) in four patients who had UCD and were in hyperammonemic comas resulted in a prompt decrease in plasma ammonia concentrations and clinical improvement in each case. (20) In a further study, a single oral or intravenous dose of NABZ (250 to 500 mg/kg) lowered plasma ammonia concentrations in five of seven patients who had hyperammonemia (two of three neonates and four of five older children). (9) In another study, (21) 26 patients were treated with intravenous NABZ (250 mg/kg loading dose, followed by 250 to 500 mg/kg per day continuous infusion) and arginine hydrochloride (800 mg/kg loading dose, followed by 200 to 800 mg/kg per day) during acute neonatal hyperammonemia. PD was required during neonatal hyperammonemic coma episodes in 20 of 23 patients. There were three neonatal deaths. It was concluded that alternative pathway therapy (NABZ and arginine supplementation), combined with dietary restriction of protein and provision of supplemental calories in an amount no less than 100 kcal/kg per day, can prolong survival and improve clinical outcome in children who have UCDs.

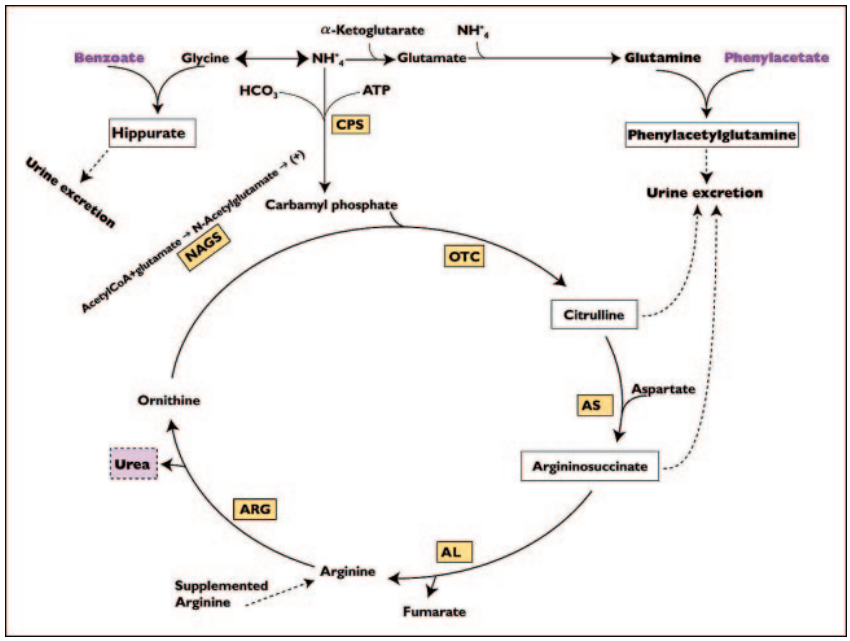

Figure 1. The urea cycle and alternative pathway therapy. AL=argininosuccinic acid lyase, ARG=arginase, AS=argininosuccinic acid synthetase, CPS=carbamyl phosphate synthetase, NAGS=*N*-acetylglutamate synthetase, OTC=ornithine transcarbamylase, ATP=adenosine triphosphate

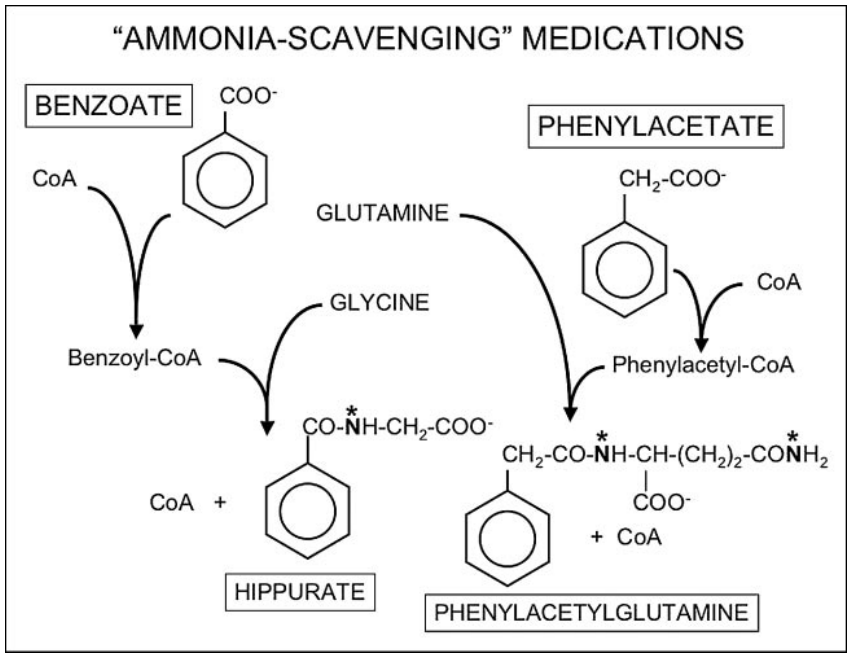

Figure 2. Mechanism of nitrogen scavenging by sodium benzoate and sodium phenylacetate. Hippurate and phenylacetylglutamine are formed by conjugation of benzoate with glycine and phenylacetate with glutamine, respectively. These reactions are performed by specific liver and kidney *N*-acyltransferases (see text). *=nitrogen atoms excreted

NAPA/NABZ

In 1984, Brusilow and colleagues (22) reported the results of a therapeutic protocol for the treatment of hyperammonemia caused by UCDs using a combination of intravenous NAPA plus NABZ. The initial clinical trial of combined therapy involved 12 episodes of hyperammonemia in seven children ages 3 to 26 months who had a variety of UCDs. The plasma ammonia concentrations decreased to normal or nearly normal levels in all patients, except in a 9-month-old boy who had OTC deficiency and the highest pretreatment ammonia value and the longest delay between symptom onset and therapy.

The combination of NAPA (10%) and NABZ (10%) is an intravenously administered drug approved by the FDA as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients who have urea cycle enzyme deficiencies. The concomitant use of NAPA/NABZ with protein restriction, high caloric nutrition, arginine hydrochloride, and hemodialysis in neonatal hyperammonemia helps to increase waste nitrogen excretion through the formation of HIP and PAGN by two different pathways (Figs. 1 and 2). Pharmacogenetic factors partly determine the activity of enzymes responsible for formation of HIP and PAGN and, therefore, play a role in determining the individual rate of nitrogen removal. Hemodialysis is recommended in cases of severe hyperammonemia or if ammonia concentrations are not significantly reduced within 4 to 8 hours after starting NAPA/NABZ therapy.

When a diagnosis of hyperammonemia is established in a neonate, NAPA/NABZ infusion should be started as soon as possible. A loading dose is administered over 90 minutes, followed by a similar mainte-

Table 5. Recommended NAPA/NABZ and Arginine HCl Dosages for Treating Neonatal Urea Cycle Defects

Administration	Components of Infusion Solution			Dosage Provided		
	NAPA/ NABZ	Arginine HCl Injection, 10%	Dextrose Injection, 10%	Sodium Phenylacetate	Sodium Benzoate	Arginine HCl Injection, 10%
Patients weighing 0 to 20 kg						
Argininosuccinate Lyase Deficiency						
Loading Dose: over 90 to 120 min	2.5 mL/kg	6.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose: over 24 h	2.5 mL/kg	6.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Argininosuccinate Synthetase Deficiency						
Loading Dose: over 90 to 120 min	2.5 mL/kg	6.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose: over 24 h	2.5 mL/kg	6.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Carbamyl Phosphate Synthetase Deficiency						
Loading Dose: over 90 to 120 min	2.5 mL/kg	2.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose: over 24 h	2.5 mL/kg	2.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Ornithine Transcarbamylase Deficiency						
Loading Dose: over 90 to 120 min	2.5 mL/kg	2.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose: over 24 h	2.5 mL/kg	2.0 mL/kg	25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
If the diagnosis is unknown, arginine HCl may be administered at the higher (600 mg/kg) dose.						

nance dose administered over 24 hours (Table 5). NAPA/NABZ is diluted in sterile 10% dextrose to a dose of 250 mg/kg in both loading and maintenance infusions. Because of the saturable pharmakokinetics of PA, no more than one loading dose of NAPA/NABZ is recommended regardless of the initial ammonia concentration. The maintenance infusion can be continued until ammonia values are within normal limits. Arginine hydrochloride 10% can be mixed in the same dextrose solution as NAPA/NABZ. NAPA/NABZ should be administered through a central line because extravasation may cause irritation, burns, and necrosis.

Pharmacokinetics

Pharmacokinetics is the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body (ie, what the body does to the drug). Both PA and BZ show saturable, nonlinear elimination, with a decrease in clearance with increased dose. Therefore, following established treatment protocol dosing guidelines is important. Brusilow and associates (22) studied the pharmacokinetics of NAPA and NABZ in two children who had carbamyl phosphate synthetase deficiency, ages 5 months and 1 year. Similar to findings in adults, the levels of PA and BZ peaked at the same time, and the level of BZ decreased faster. PA levels were initially higher than BZ levels and remained so throughout the study. HIP reached a peak earlier than PAGN, but PAGN levels remained high for a longer period compared with HIP in both patients. Urinary HIP nitrogen (18% to 57% of waste nitrogen) and urinary PAGN nitrogen (15% to 53% of waste nitrogen) combined accounted for approximately 60% of the "effective" urinary waste nitrogen.

No pharmacokinetic studies on NAPA/NABZ performed exclusively in neonates have been published. However, Green and associates (23) monitored the disposition of intravenous NABZ alone in newborns who had hyperammonemia (n=4) following administration of 460 mg/kg per day in four divided doses. An eight-fold range in serum BZ concentrations was noted among treated neonates. The elimination half-life of BZ was 2.8±3.1 hours. The total plasma clearance of BZ was 1.00±0.61 mg/kg per minute, with most of the clearance attributed to glycine conjugation in three of four neonates. The excreted total of BZ and HIP was 84±31% of the administered BZ. One neonate who had reduced renal clearance excreted only 12% of BZ as HIP. In this case, PD was the major route of BZ clearance. (23) Intravenous infusions of BZ and PA (given on different days) were administered to five children who had lysinuric protein intolerance and were clinically stable during the period of study. (24) Plasma BZ levels peaked at 6.0 mmol/L (range, 5.2 to 7.0 mmol/L) 2 hours after the start of the infusion (2.0 mmol/kg over 90 min) and decreased linearly, with a mean half-life of 273 minutes. Plasma HIP levels peaked 120 minutes after the start of the infusion at 0.24 mmol/L (range, 0.14 to 0.40 mmol/L) and remained stable for 3 hours. Less than 2% of the

administered dose of BZ appeared unchanged in the urine. Plasma PA levels also peaked at 120 minutes and decreased similarly to BZ (half-life=254 min), although peak levels were lower (4.8 mmol/L; range, 3.7 to 6.1 mmol/L). Plasma PAGN levels peaked at 270 minutes, with a mean concentration of 0.48mmol/L (range, 0.22 to 1.06 mmol/L). Forty percent (range, 15% to 110%) of infused PA was excreted as PAGN in 24 hours. (24)

Pharmacodynamics and Outcome Studies

Pharmacodynamics is the process of biochemical and physiologic effects of a drug, the mechanisms of drug action, and the relationship between drug concentration and effect (ie, what the drug does to the body). Treatment with NAPA/NABZ results in decreased plasma ammonia concentrations and improved neurologic status in most cases, although if severe hyperammonemia is present, alternative pathway therapy may not have any appreciable effect. (14)(22)(23)(24)(25)(26)(27) A study of 26 children found a survival of 85% following treatment with alternative pathway therapy for 7 months to 5 years. (21) A total of 64 postneonatal episodes of hyperammonemia occurred in 19 of 26 patients, with excessive protein intake, interruption of medications, and intercurrent infections being common causes of metabolic decompensation. Of the 23 survivors, 10 had normal development, 7 had mild mental retardation (intelligence quotient [IQ] 52 to 68), and 6 had moderate-to-severe mental retardation (IQ <52). Msall and colleagues (28) reported that rapid treatment with NAPA/NABZ substantially improved survival compared with historic controls. One-year survival was 92% in children who had UCDs treated with protein restriction and alternative pathway therapy. Mental impairment was common, with 79% of children having developmental disabilities at 12 to 74 months of age. Maestri and associates (25) concluded that in infants at risk for hyperammonemia caused by UCDs based on family history, prospective treatment with NAPA/NABZ is effective in avoiding hyperammonemic coma and results in more favorable outcome compared with patients who are rescued from hyperammonemic coma. The brief period of prospective treatment while awaiting results of confirmatory diagnostic studies does not appear to have any adverse effect on the growth and development of infants who do not have the diagnosis.

Adverse Reactions

Experiments in rats and a mouse model of OTC deficiency (sparse-fur mouse) demonstrated that BZ has the potential to inhibit fatty acid oxidation and pyruvate dehydrogenase activity, possibly by depleting stores of hepatic glycine, free CoA, and acetyl-CoA. (29)(30)(31)(32)(33) In the sparse-fur mouse, supplementation with carnitine counteracted the adverse effects of higher doses of BZ. The levels of free CoA, acetyl-CoA, and ATP in both brain and liver increased following carnitine administration. (34) PA is neurotoxic in a rat model, possibly through depletion of acetyl-CoA. (35) PA also inhibits 5-hydroxytryptophan decarboxylase in guinea pig kidneys and dihydroxyphenylalanine decarboxylase in beef adrenal medulla. (36)(37) Despite these findings in animal models, NABZ and NAPA are remarkably nontoxic in humans when used in the treatment of UCDs at the recommended doses. (14)(18)(38)

Because of the difficulty in distinguishing symptoms related to hyperammonemia from symptoms caused by a reaction to medication, adverse effects are similarly difficult to attribute directly to alternative pathway therapy. Oral BZ therapy has been associated with nausea and vomiting, (21)(26) but overall toxicity appears to be low as long as standard dosing guidelines are followed. (38) The use of benzyl alcohol as a bacteriostatic agent in neonatal intensive care units has resulted in severe metabolic acidosis, lethargy progressing to coma, seizures, and death. BZ and HIP, breakdown products of benzyl alcohol, were identified in the urine of affected neonates. (39) A theoretical concern related to BZ use in neonates is its potential ability to displace bilirubin from high-affinity albumin binding sites. (23) However, to our knowledge, no cases have been reported of significant hyperbilirubinemia or kernicterus attributable to BZ use.

No adverse effects, other than an unpleasant odor, were reported in healthy humans and two patients who had UCDs receiving between 1 and 10 g of PA. (38)(40) Intravenous PA was not associated with any clinical toxicity during bolus dosing, but vomiting, confusion, and lethargy occurred in three of 17 cancer patients who had solid tumors during the course of a 14-day continuous infusion. A strong PA odor also was noticeable on patients' clothes and on examiners' hands following physical examination. (41) A further oncology trial of PA reported somnolence, fatigue, headache, lightheadedness, and dysgeusia associated with PA concentrations between 3.7 and 7.5 mmol/L. (42)

The most common adverse reaction reported with NAPA/NABZ use is vomiting, occurring in about 9% of patients. (21) In a study of healthy adults, nausea, vomiting, and somnolence were reported following

administration of NAPA/NABZ in doses used to treat hyperammonemia. (43) Simell and associates (24) induced hyperammonemia in five patients who had lysinuric protein intolerance and administered alanine with either intravenous PA or BZ. They reported dizziness, nausea, and vomiting in four patients at the end of the infusion. Mean peak plasma levels of 6 mmol/L (BZ) and 4 mmol/L (PA) were documented. (24)

The most significant adverse effects and toxicity related to NAPA/NABZ use have occurred in cases of inadvertent overdosage. Continuous intravenous infusion rates causing plasma PA concentrations that saturate the capacity of conversion of PA to PAGN result in rapid phenylacetate accumulation and subsequent toxicity. (41) Praphanphoj and coworkers (44) reported three patients ages 2 to 6 years who were given inappropriately high doses of intravenous NAPA/NABZ (915 mg/kg over 12 h, 1,750 mg/kg over 18 h, and 750 mg/kg over 10 h). The children had plasma BZ and PA levels of approximately 10 mmol/L 4 hours after infusion and developed altered mental status, Kussmaul breathing, metabolic acidosis, cerebral edema, and hypotension. Two of the three patients died, and one survived after hemodialysis. (44)

Adjunctive Therapeutic Modalities

In addition to NAPA/NABZ, the importance of providing appropriate nutrition, protein restriction, arginine hydrochloride, and hemodialysis or continuous venovenous hemofiltration for treating neonatal hyperammonemia cannot be overemphasized. Central access is critical to provide high-dextrose fluids and intravenous lipid, with the goal being to administer approximately 100 to 120 kcal/kg per day. (27) An insulin drip often is needed to control hyperglycemia and promote anabolism. Protein should be withdrawn immediately and reintroduced slowly after 24 to 48 hours. Alternative pathway therapy with arginine hydrochloride infusion works synergistically with NAPA/NABZ, so the arginine hydrochloride bolus and maintenance infusions typically are administered simultaneously with NAPA/NABZ (Table 5). It is crucial to transfer the neonate who has confirmed hyperammonemia to a center that has experience in all aspects of UCD management, including nutrition and hemodialysis, or other forms of continuous renal replacement therapy (such as continuous venovenous hemofiltration or continuous venovenous hemodiafiltration) as soon as possible. (45)

Use of NAPA/NABZ for Treatment of Other Conditions

The use of NAPA/NABZ to treat other conditions that can cause neonatal hyperammonemia, such as organic acidemias, fatty acid oxidation disorders, and transient hyperammonemia of the newborn, has not been studied in detail. However, these conditions may be difficult to distinguish from UCDs in some instances. (46)(47) Clinicians have used NAPA/NABZ to treat non-UCD conditions with variable efficacy. (48)(49)

Conclusion

NAPA/NABZ is effective, in conjunction with appropriate high-calorie nutrition, protein restriction, intravenous arginine hydrochloride, and hemodialysis, in the treatment of neonatal hyperammonemia caused by UCDs. Survival rates and neurologic outcomes of patients are improved compared with historical outcomes. NAPA/NABZ also can safely be used in prospective treatment of infants at risk for a UCD because of a positive family history who have not undergone prenatal diagnostic testing. Because of nonlinear pharmacokinetics and the potential for accumulation of especially PA with higher doses of NAPA/NABZ, clearly written medical prescriptions and cross-checking of drug dosage are important safeguards. In addition, the immature liver function of neonates merits careful observation and monitoring of infants because of the importance of liver conjugation reactions for both NABZ (with glycine to form HIP) and NAPA (with glutamine to PAGN). Because neonates who have severe hyperammonemia may not improve following NAPA/NABZ administration, the importance of immediate transfer to a center that has experience in caring for such children, including the ability to perform hemodialysis, cannot be overemphasized.

ACKNOWLEDGMENTS. This review was supported by a grant from the Packard Children's Health Fund for AKN.

References

1. Simmons F, Goldstein H, Boyle JD. A controlled clinical trial of lactulose in hepatic encephalopathy. *Gastroenterology*. 1970;59:827–832

2. Francois B, Cornu G, de Meyer R. Peritoneal dialysis and exchange transfusion in a neonate with argininosuccinic aciduria. *Arch Dis Child*. 1976;51:228–231

3. Donn SM, Swartz RD, Thoene JG. Comparison of exchange transfusion, peritoneal dialysis, and hemodialysis for the treatment of hyperammonemia in an anuric newborn infant. *J Pediatr*. 1979;95:67–70

4. Wiegand C, Thompson T, Bock GH, Mathis RK, Kjellstrand CM, Mauer SM. The management of life-threatening hyperammonemia: a comparison of several therapeutic modalities. *J Pediatr*. 1980;96:142–144

5. Kiley JE, Pender JC, Welch HF, Welch

CS. Ammonia intoxication treated by hemodialysis. *N Engl J Med*. 1958;259:1156–1161
6. Batshaw M, Brusilow S, Walser M. Treatment of carbamyl phosphate synthetase deficiency with keto analogues of essential amino acids. *N Engl J Med*. 1975;292:1085–1090
7. Thoene J, Batshaw M, Spector E, et al. Neonatal citrullinemia: treatment with keto-analogues of essential amino acids. *J Pediatr*. 1977;90:218–224
8. McReynolds JW, Mantagos S, Brusilow S, Rosenberg LE. Treatment of complete ornithine transcarbamylase deficiency with nitrogen-free analogues of essential amino acids. *J Pediatr*. 1978;93:421–427
9. Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. *J Pediatr*. 1980;97:893–900
10. Lewis HB. Studies in the synthesis of hippuric acid in the animal organism. *J Biol Chem*. 1914;18:225
11. Shiple GJ, Sherwin CP. Synthesis of amino acids in animal organisms I. Synthesis of glycocoll and glutamine in the human organism. *J Am Chem Soc*. 1922;44:618–624
12. Moldave K, Meister A. Synthesis of phenylacetylglutamine by human tissue. *J Biol Chem*. 1957;229:463–476
13. Webster LT, Siddiqui UA, Lucas SV, Strong JM, Mieyal JJ. Identification of separate acyl- CoA:glycine and acyl-CoA:L-glutamine N-acyltransferase activities in mitochondrial fractions from liver of rhesus monkey and man. *J Biol Chem*. 1976;251:3352–3358
14. Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr*. 2001;138(1 suppl):S46–S54
15. Zimmerman L, Jornvall H, Bergstrom J. Phenylacetylglutamine and hippuric acid in uremic and healthy subjects. *Nephron*. 1990;55:265–271
16. Chantrenne H. The requirement for coenzyme A in the enzymatic synthesis of hippuric acid. *J Biol Chem*. 1951;189:227–233
17. Brusilow SW, Valle DL, Batshaw M. New pathways of nitrogen excretion in inborn errors of urea synthesis. *Lancet*. 1979;2:452–454
18. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. *Adv Pediatr*. 1996;43:127–170
19. Brusilow SW, Batshaw ML. Arginine therapy of argininosuccinase deficiency. *Lancet*. 1979;1:124–127
20. Brusilow S, Tinker J, Batshaw ML. Amino acid acylation: a mechanism of nitrogen excretion in inborn errors of urea synthesis. *Science*. 1980;207:659–661
21. Batshaw ML, Brusilow S, Waber L, et al. Treatment of inborn errors of urea synthesis: activation of alternative pathways of waste nitrogen synthesis and excretion. *N Engl J Med*. 1982;306:1387–1392
22. Brusilow SW, Danney M, Waber LJ, et al. Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med*. 1984;310:1630–1634
23. Green TP, Marchessault RP, Freese DK. Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr*. 1983;102:785–790
24. Simell O, Sipila I, Rajantie J, Valle DL, Brusilow SW. Waste nitrogen excretion via amino acid acylation: benzoate and phenylacetate in lysinuric protein intolerance. *Pediatr Res*. 1986;20:1117–1121
25. Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. *J Pediatr*. 1991;119:923–928
26. Feillet F, Leonard JV. Alternative pathway therapy for urea cycle disorders. *J Inherit Metab Dis*. 1998;21(suppl 1):101–111
27. Singh RH, Rhead WJ, Smith W, Lee B, King LS, Summar M. Nutritional management of urea cycle disorders. *Crit Care Clin*. 2005;21(4 suppl):S27–S35
28. Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. *N Engl J Med*. 1984;310:1500–1505
29. Kalbag SS, Palekar AG. Sodium benzoate inhibits fatty acid oxidation in rat liver: effect on ammonia levels. *Biochem Med Metab Biol*. 1988;40:133–142
30. Griffith AD, Cyr DM, Egan SG, Tremblay GC. Inhibition of pyruvate carboxylase by sequestration of coenzyme A with sodium benzoate. *Arch Biochem Biophys*. 1989;269:201–207
31. Gregus Z, Fekete T, Varga F, Klaassen CD. Availability of glycine and coenzyme A limits glycine conjugation in vivo. *Drug Metab Dispos*. 1992;20:234–240
32. Ratnakumari L, Qureshi IA, Butterworth RF. Effect of sodium benzoate on cerebral and hepatic energy metabolites in SPF mice with congenital hyperammonemia. *Biochem Pharmacol*. 1993;45:137–146
33. Beynen AC, Geelen MJ. Short-term inhibition of fatty acid biosynthesis in isolated hepatocytes by mono-aromatic compounds. *Toxicology*. 1982;24:183–197
34. Ratnakumari L, Qureshi IA, Butterworth RF. Effect of L-carnitine on cerebral and hepatic energy metabolites in congenitally hyperammonemic sparse-fur mice and its role during benzoate therapy. *Metabolism*. 1993;42:1039–1046
35. Potempska A, Loo YH, Wisniewski HM. On the possible mechanism of phenylacetate neurotoxicity: inhibition of choline acetyltransferase by phenylacetyl-CoA. *J Neurochem*. 1984;42:1499–1501
36. Davison AN, Sandler M. Inhibition of 5-hydroxytryptophan decarboxylase by phenylalanine metabolites. *Nature*. 1958;181:186–187
37. Fellman JH. Inhibition of DOPA decarboxylase by aromatic acids associated with phenylpyruvic oligophrenia. *Proc Soc Exp Biol Med*. 1956;93:413–414
38. Batshaw ML, Brusilow SW. Evidence of lack of toxicity of sodium phenylacetate and sodium benzoate in treating urea cycle enzymopathies. *J Inherit Metab Dis*. 1981;4:231
39. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med*. 1982;307:1384–1388
40. Ambrose AM, Power FW, Sherwin CP. Further studies on the detoxification of phenylacetic acid. *J Biol Chem*. 1933;101:669–675
41. Thibault A, Cooper MR, Figg WD, et al. A phase I and pharmacokinetic study of intravenous phenylacetate in patients with cancer. *Cancer Res*. 1994;54:1690–1694
42. Thibault A, Samid D, Cooper MR, et al. Phase I study of phenylacetate administered twice daily to patients with cancer. *Cancer*. 1995;75:2932–2938
43. MacArthur RB, Altincatal A, Tuchman M. Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers. *Mol Genet Metab*. 2004;81(suppl 1):S67–S73
44. Praphanphoj V, Boyadjiev SA, Waber LJ, Brusilow SW, Geraghty MT. Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. *J Inherit Metab Dis*. 2000;23:129–136
45. Lemley KV, Hintz SR, Enns GM. Continuous renal replacement therapy in the initial management of neonatal hyperammonemia due to urea cycle defects. *NeoReviews*. 2000;1:e173–e179. Available at: http://neoreviews.aappublications.org/cgi/content/full/1/9/e173

46. Saudubray JM, Coude FX, Ogier H, Cathelineau L, Briand P, Charpentier C. Hyperammonemia secondary to hereditary organic acidurias: a study of 29 cases. *Adv Exp Med Biol*. 1982;153:135–140
47. Ogier de Baulny H, Slama A, Touati G, Turnbull DM, Pourfarzam M, Brivet M. Neonatal hyperammonemia caused by a defect of carnitine-acylcarnitine translocase. *J Pediatr*. 1995;127:723–728
48. Petrowski S, Nyhan WL, Reznik V, et al. Pharmacologic amino acid acylation in the acute hyperammonemia of propionic acidemia. *J Neurogenet*. 1987;4:87–96
49. Chung MY, Chen CC, Huang LT, Ko TY, Lin YJ. Transient hyperammonemia in a neonate. *Acta Paediatr Taiwan*. 2005;46:94–96

NeoReviews Quiz

10. Most inborn errors of metabolism that cause neonatal hyperammonemia are of autosomal recessive inheritance. The family history may be unremarkable or may reveal unexplained neonatal deaths. Of the following, the *only* inborn error of metabolism associated with neonatal hyperammonemia that is X-linked in inheritance is:

    A. Hyperinsulinism/hyperammonemia syndrome.
    B. Isovaleric acidemia.
    C. Medium-chain acyl-CoA dehydrogenase deficiency.
    D. Ornithine transcarbamylase deficiency.
    E. Pyruvate carboxylase deficiency.

11. A 60-hour-old term newborn presents with poor feeding, lethargy, hypotonia, and generalized tonic-clonic seizures. In the diagnostic evaluation for causes that include sepsis/meningitis, liver disease, intracranial hemorrhage, and heart failure, the only positive test is a markedly raised blood ammonia concentration of 600 mcmol/L. Of the following, the *most* common cause of neonatal hyperammonemia is:

    A. Parenteral hyperalimentation.
    B. Perinatal asphyxia.
    C. Urea cycle disorder.
    D. Valproate toxicity.
    E. Viral hepatitis.

12. The drug combination of sodium phenylacetate and sodium benzoate is approved by the United States Food and Drug Administration as adjunctive treatment in the management of acute hyperammonemia resulting from a urea cycle disorder. The drug is used concomitantly with protein restriction, high-calorie nutrition, arginine supplementation, and hemodialysis to increase waste nitrogen excretion. Of the following, the *most* accurate statement regarding sodium phenylacetate/sodium benzoate in the treatment of hyperammonemia is that:

    A. Exceedingly high initial blood ammonia concentrations may warrant two or more loading doses of the drug.
    B. More than 90% of the administered dose of phenylacetate and benzoate is excreted unchanged in the urine.
    C. Nitrogen scavenging is more effective with sodium benzoate than with sodium phenylacetate.
    D. Optimal route of administration of the drug is through a central venous catheter.
    E. Plasma concentrations of phenylacetate and benzoate peak within 20 minutes after the start of the bolus infusion.

Pharmacology Review: Sodium Phenylacetate and Sodium Benzoate in the Treatment of Neonatal Hyperammonemia

Anna-Kaisa Niemi and Gregory M. Enns

NeoReviews 2006;7;e486
DOI: 10.1542/neo.7-9-e486

NeoReviews™
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF THE PEDIATRICS

Pharmacology Review: Sodium Phenylacetate and Sodium Benzoate in the Treatment of Neonatal Hyperammonemia

Anna-Kaisa Niemi and Gregory M. Enns

NeoReviews 2006;7;e486
DOI: 10.1542/neo.7-9-e486