Sodium Benzoate for Treatment of Hepatic Encephalopathy

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Abstract: Hepatic encephalopathy (HE) is a serious but usually reversible neuropsychiatric complication of cirrhosis, inborn errors of metabolism involving disorders of the urea cycle, and noncirrhotic portosystemic shunting that most commonly arises from a transjugular intrahepatic portosystemic shunting procedure. Symptoms can include alterations in cognitive function, neuromuscular activity, and consciousness, as well as sleep disorders and mood changes. HE is associated with significant morbidity and mortality and, if not properly treated, will lead to increased hospital admissions and healthcare costs. Although the standard therapies of lactulose and rifaximin (Xifaxan, Salix) are effective for most patients, these drugs may be associated with significant adverse effects and expense and, in some patients, inadequate therapeutic response. A need for adjunctive therapies exists. Drugs that target serum and tissue ammonia metabolism and elimination may be important adjuncts to drugs that reduce ammonia production and absorption from the gastrointestinal tract for patients with severe or persistent overt symptoms of HE. Sodium benzoate is an inexpensive adjunctive agent that can be used in addition to lactulose and rifaximin and may provide an option for some select patients with refractory HE who have failed to respond to standard therapies or who cannot afford them. Although sodium benzoate does not share the same adverse effect profiles of standard therapies for HE, its efficacy has not been well established. Given the significant dose-dependent sodium content of this therapy, it may not be appropriate for patients with significant fluid retention or kidney dysfunction.

Hepatic encephalopathy (HE) is broadly defined as a disturbance in central nervous system function due to acute and chronic hepatic insufficiency. It is characterized by a spectrum of neuropsychiatric manifestations related to a range of pathophysiologic mechanisms.[1] The pathophysiology and treatment of HE associated with acute liver failure greatly differ from those of encephalopathy associated with cirrhosis or intra- and extrahepatic portal systemic shunting and, thus, are not covered in this review. Overt HE affects an estimated 30–45% of patients with cirrhosis

and 10–50% of patients with transjugular intrahepatic portosystemic shunts.[2,3] Covert or minimal HE (West Haven Criteria, Stage 0; Table 1) affects approximately 20–70% of patients with liver disease.[4] HE may manifest as a wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function and modest psychological or behavioral changes to much more severe changes in intellectual capacity and behavior as well as neuromuscular symptoms. In some patients, HE may progress to delirium, coma, and death (Table 1).[5] Over the years, multiple treatment options directed at a variety of possible causes have been used to manage HE, but the efficacy of many agents remains uncertain due to limitations in well-designed clinical trials. Although the pathogenesis of HE is complex and not yet perfectly defined, the mainstay of current management involves the use of agents that target ammonia and enhance its metabolism and elimination from the body. Among other agents, sodium benzoate is often mentioned in HE review articles as an alternative therapy option.[6]

Table 1. West Haven Criteria[1,54,55]

Grade	Symptoms
0	Minimal changes in memory, concentration, intellectual function, and coordination; behavior and personality changes may only be detected with specialized neuropsychiatric testing
1	Sleep disorder Shortened attention span Impaired complex computations Euphoria and/or depression Tremor Impaired construction ability
2	Lethargy or apathy Disorientation to time Mental control=1–4 Amnesia of recent events Impaired simple computations Inappropriate behavior Anxiety Slurred speech Hyperactive reflexes
3	Somnolence Confusion Disorientation to place Mental control=0 Bizarre behavior/anger/rage Clonus/rigidity/nystagmus/Babinski sign
4	Coma (no eyes opening, verbal response, or reaction to simple commands)

Ammonia Hypothesis

The etiology of HE is multifactorial, but elevated blood ammonia levels are a key component of the pathogenesis of the disorder.[7] Ammonia is generated in the intestine as a result of bacterial breakdown of dietary protein and urea in the colon by urease-containing bacteria and metabolism of glutamine in the wall of the small intestine.[8] Ammonia absorption occurs in the colon via nonionic diffusion and is transported through the portal vein to the liver.[9] In healthy individuals, ammonia is largely removed by the liver and, to a lesser extent, by muscle. In the healthy liver, periportal hepatocytes metabolize ammonia to urea through the urea cycle—1 mole of urea removes 2 moles of waste nitrogen—while a smaller number of perivenous hepatocytes convert ammonia to glutamine.[10]

For patients with cirrhosis, multiple factors, including increased ammonia production and absorption and reduced ammonia elimination, contribute to arterial hyperammonemia. Ammonia metabolism is further impaired in patients who also have muscle wasting and/or kidney dysfunction.[11] Intestinal absorption of ammonia is enhanced as a result of the increased splanchnic blood flow associated with portal hypertension. The elimination of ammonia is impaired in patients with cirrhosis due to intra- and extrahepatic portal systemic shunting of blood and the reduced ability of hepatocytes to metabolize ammonia via the urea cycle. In addition, patients with cirrhosis often have less muscle mass available to synthesize glutamine and reduce circulating ammonia, an important alternative pathway for ammonia detoxification. Lastly, production of ammonia and ammonium by the kidneys is increased as a result of metabolic alkalosis often resulting from diuresis, hyperventilation, and hypokalemia. Thus, elevated arterial, serum, and venous ammonia levels occur in approximately 90% of patients with HE, although the absolute levels correlate poorly with scores of HE.[12,13]

There are several reasons that elevated ammonia levels do not correlate well with cognitive function or grade of HE. Although arterial ammonia can be used to assess for the presence of HE, the cost, pain, intermediate accuracy, and difficulty of undertaking arterial punctures in patients whose clotting is significantly impaired limit use of this test. The usefulness of all types of ammonia level tests (venous, arterial, and capillary) is impacted by the difficulty of proper processing, including the need to keep samples on ice to prevent metabolism and evaporation. Some studies have shown that the arterial partial pressure of ammonia correlates better with clinical grade of HE than the arterial ammonia level in acute episodes of HE.[14] In addition, the presence of systemic inflammatory responses affects the level of HE and probably influences the impact of ammonia and glutamine metabolism in the brain.[15-18]

For sodium benzoate to be effective, renal clearance of hippurate (uremic protein) is required. For patients with end-stage renal disease, some benzoate and hippurate will be removed by dialysis. Studies evaluating the effect of dialysis on clearance of sodium benzoate are limited. However, a case study involving an infant found that sodium benzoate is removed fairly efficiently by dialysis (convective clearance of 37 mL/min and 12 mL/min for hemodialysis and hemofiltration, respectively).[19] Despite the efficiency of clearance of sodium benzoate by dialysis, sodium benzoate was still effective in lowering serum ammonia levels.

Standard Treatments

Conventional therapy for HE is directed at avoiding precipitating factors (such as renal failure, diuretics, infection, gastrointestinal bleeding, constipation, and drugs known to alter mental status) and reducing plasma ammonia levels and negative sequelae associated with elevated ammonia levels. A variety of treatment strategies have been used, including administration of nonabsorbable disaccharides, selective antibiotics, agents that modulate interorgan ammonia, probiotics, fermentable fibers, and zinc.[10] Unfortunately, current pharmacotherapy is rather limited due to the complexity of the disorder and incomplete and sometimes conflicting data in the literature. Lactulose has been used for years and has been shown to improve cognitive function and reduce ammonia levels in patients with HE.[4,20-23] Lactulose is widely thought to be converted to lactic acid and acetic acid in the gut, creating an acidic environment favorable for the conversion of ammonia (NH_3) to ammonium (NH_4^+), which is not readily absorbed into systemic circulation. Additionally, the cathartic action of lactulose facilitates removal of ammonium from the body, making less ammonia available for absorption. Although a meta-analysis of 22 randomized trials questioned the effectiveness of lactulose for the treatment of HE,[24] sufficient evidence is not available to refute the widely accepted anecdotal evidence that supports the clinical use of lactulose for this purpose.[25]

Antimicrobials are used to suppress intestinal flora, thereby reducing the bacterial production of ammonia and other bacteria-derived toxins. Rifaximin (Xifaxan, Salix), an antibiotic with very limited systemic absorption, has been shown to be at least as effective as lactulose in improving neurologic symptoms in HE and is well tolerated.[26-32] A large placebo-controlled study investigating rifaximin in patients who were already using lactulose (91% of both arms) showed a highly statistically significant benefit with rifaximin, both for preventing recurrences of HE and for decreasing hospitalizations related to HE over a 6-month period.[32] Thus, it appears that rifaximin has established an important foothold in the management paradigm of HE. However, it is important to note that, because of eligibility criteria, none of the patients in this study had Model for End-Stage Liver Disease scores greater than 25, and the effectiveness of rifaximin remains undocumented in patients with more advanced liver dysfunction.

Other drawbacks of current standard therapy include the expense of rifaximin and, although likely cost-effective,[33] the frequently intolerable dose-dependent adverse effects of lactulose, which limit its clinical use. Adverse effects from lactulose can influence compliance, safety, and quality of life.[10] Lactulose is unpleasantly sweet and is associated with significant diarrhea, flatulence, abdominal distention and discomfort, dehydration, and hypernatremia in many patients. Given these limitations, it becomes clear that additional alternative therapeutic agents that promote the excretion of ammonia could be advantageous when used in conjunction with lactulose and/or rifaximin to manage refractory HE. Sodium benzoate provides an alternative pathway to the urea cycle for the removal of nitrogen waste by interacting with glycine to form hippurate that is excreted by the kidneys.

Sodium Benzoate

Sodium benzoate is a widely used food and beverage preservative.[34] As a sole agent, it is not US Food and Drug Administration (FDA)-approved for medicinal use, but, since 1979, it has been used off-label to treat HE in patients with hyperammonemia, initially in those with urea cycle enzyme deficiencies and later in patients with cirrhosis. Sodium benzoate is thought to activate a non–urea cycle pathway for ammonia removal. A medication that contains sodium benzoate and sodium phenylacetate 10%/10% (Ammonul, Ucyclyd Pharma) is FDA-approved for use in patients with urea cycle disorders and hyperammonemia, as is the similar drug sodium phenylbutyrate (Buphenyl, Ucyclyd Pharma), a prodrug of phenylacetate. Sodium benzoate/sodium phenylacetate must be injected intravenously through a central venous catheter after dilution with sterile 10% dextrose injection (D10W), whereas sodium phenylbutyrate is available as a tablet (500 mg) or powder (for oral, nasogastric, or gastrostomy tube administration).

A prodrug of sodium phenylbutyrate, glycerol phenylbutyrate (Ravicti, Hyperion Therapeutics), a liquid taken 3 times daily with meals, was recently approved for use as adjunctive therapy for the chronic management of urea cycle disorders. In a study that included 44 adults who had been using sodium phenylbutyrate in which patients were randomly assigned to take sodium phenylbutyrate or glycerol phenylbutyrate for 2 weeks before being switched to the other drug for an additional

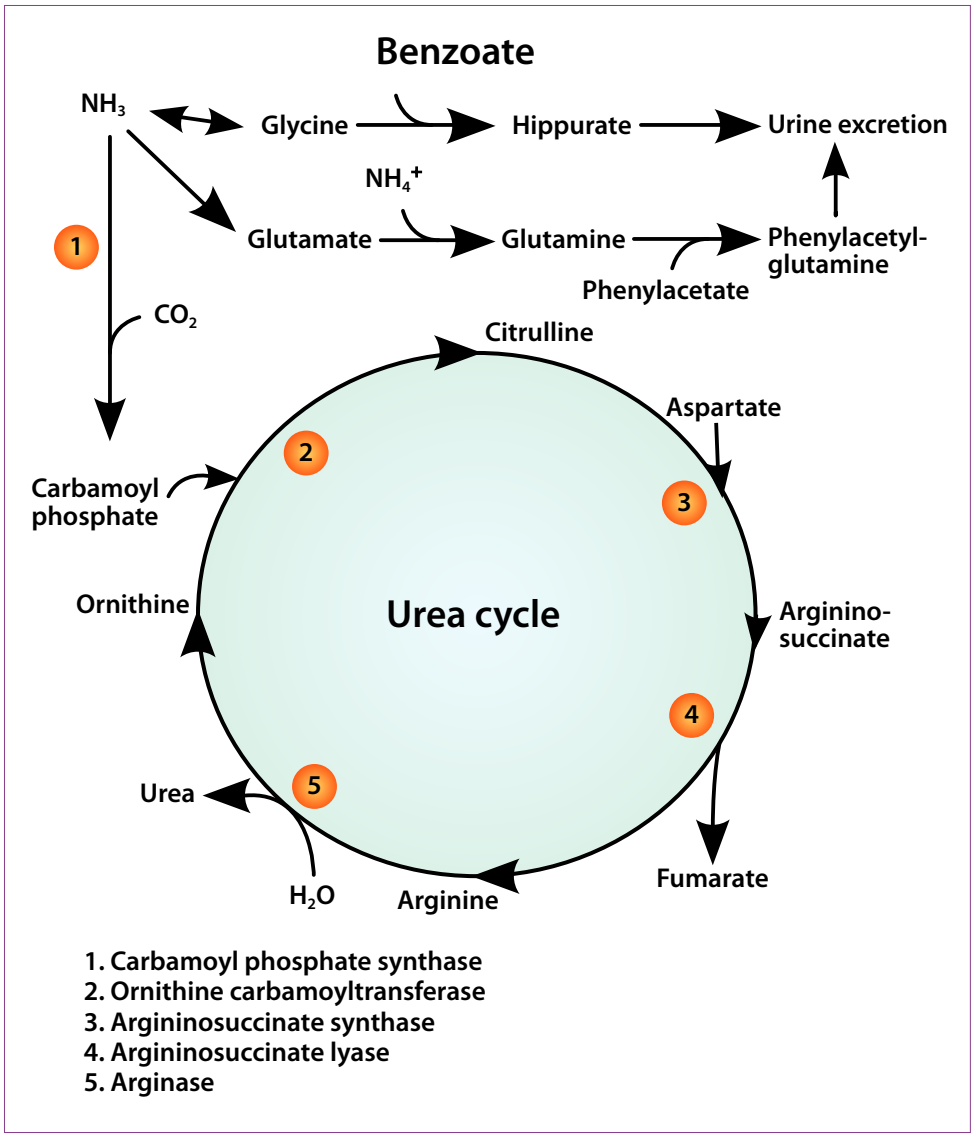

Figure. The diagram illustrates the urea cycle and alternative pathways of ammonia elimination, including the use of sodium benzoate, to form hippurate, which is eliminated by the kidneys.

CO_2=carbon dioxide; H_2O=water; NH_3=ammonia; NH_4^+=ammonium.

2 weeks, blood testing showed that glycerol phenylbutyrate was as effective as sodium phenylbutyrate in controlling ammonia levels.[35]

Another agent in clinical development for treatment of HE is ornithine phenylacetate. This agent has been proposed as being potentially effective for ammonia reduction, wherein L-ornithine acts as a substrate for glutamine synthesis from ammonia in skeletal muscle while phenylacetate facilitates the excretion of the ornithine-related glutamine as phenylacetylglutamine in the kidneys.[36,37]

Mechanism of Action

Sodium benzoate is thought to be a metabolically active agent in which benzoate is first conjugated by coenzyme A to form benzoyl CoA, which then conjugates with glycine in liver and kidney mitochondria to form hippurate (hippuric acid, *N*-benzoylglycine), which, in turn, is rapidly excreted by the kidneys via glomerular filtration and tubular secretion (Figure).[12,38,39] One mole of hippurate contains one mole of waste nitrogen. Thus, 1 mole of nitrogen is removed per mole of benzoate when it is conjugated with glycine (one half as much nitrogen as is excreted in urea).[40] Thus, although not as efficient, hippurate can serve as an alternative vehicle for removal of waste nitrogen. When 10 g/day of sodium benzoate was administered to 6 patients with cirrhosis and chronic por-

Table 2. Portal-Systemic Encephalopathy Score

Component	Description	Score	Importance factor	Maximum points
1	Mental status (West Haven Criteria)	0–4	3	12
2	EEG findings (mean cycle frequency and observation of triphasic or slow delta waves)	0–4	1	4
3	Blood ammonia concentration	0–4	1	4
4	Number connection test time	0–4	1	4
5	Degree of asterixis	0–4	1	4

EEG=electroencephalogram.

tosystemic encephalopathy, urinary hippurate elimination increased from 0.21±0.3 mg/dL to 34±18 mg/dL compared with only trace increases observed with lactulose.[41]

The effect of cirrhosis and/or kidney disease in the generation and elimination of hippurate is unknown, but dialysis has been shown to increase excretion from about 20% in controls to almost 50% in dialysed patients.[42] Unlike patients with inborn errors of metabolism, the ability of benzoate to remove nitrogen is theoretically limited in situations in which liver conjugation is impaired. Additionally, the effect of significant kidney dysfunction on the efficacy and safety of sodium benzoate is unknown but likely impaired, given that urinary ammonia excretion is tightly regulated by tubular urine flow.[10]

Efficacy

The largest study evaluating the effectiveness of sodium benzoate versus lactulose was a prospective, randomized, double-blind study involving 74 consecutive patients with cirrhosis or surgical portosystemic anastomosis and HE of fewer than 7 days' duration.[43] Patients were randomly selected to receive lactulose that was dose-adjusted for 2 or 3 semi-formed stools per day (n=36) or sodium benzoate in dosages of 5 g by mouth twice daily (n=38). All patients received tap water enemas, maintenance of fluid and electrolytes, protein restriction, antibiotics, diuretics, and therapeutic paracentesis, if required. Patients were excluded if they had received treatment with lactulose for 24 hours or more before entry into the study or had active gastrointestinal bleeding, sepsis, severe hyponatremia, azotemia, or a history of neurologic disease other than HE. Sixty-four (86%) patients had West Haven Criteria grade 3 or 4 encephalopathy. Both medications were administered as solutions given orally or administered via nasogastric tube.

Response was determined based on assessment of mental status, degree of asterixis, blood ammonia concentration, electroencephalogram (EEG) findings, and cognitive function (determined by the time to complete the number connection test). Each of these tests was given a score ranging from 0 to 4 and arbitrarily weighted in proportion to its importance. Mental status was assigned a factor of 3 and all other categories a factor of 1. A portal-systemic encephalopathy (PSE) sum was calculated with these scores (Table 2). The maximum PSE score of 28 is indicative of severe HE. The PSE index (PSEI) is expressed as the ratio of the patient's PSE score to the maximum PSE score of 28.

In this study, PSE sums were not always comparable because asterixis and trail making tests could not be performed in comatose patients, and EEGs were not always performed. Thus, to allow for improved comparison of response to therapy, the PSEI was used.

Visual, auditory, and somatosensory evoked potentials and a battery of psychometric tests for cognition and memory also were performed and evaluated. Therapeutic success was defined as sustained improvement of 1 grade in mental status in less than 48 hours or improvement of more than 2 grades in mental status. Partial response was defined as improvement in mental status by at least 2 grades without normalization. Therapeutic failure was defined as no change in mental state after 48 hours of therapy, sustained deterioration of 1 grade in mental status during 48 hours of therapy, deterioration of 2 grades in mental state, and death in coma despite treatment.

Patients with therapeutic failure who were receiving sodium benzoate were started on lactulose. Those receiving lactulose with therapeutic failure were continued on lactulose. Recovery was achieved in 30 (80%) patients receiving sodium benzoate and 29 (81%) taking lactulose (P>.1), leading the investigators to conclude that sodium benzoate is a safe and effective alternative to lactulose for treatment of acute PSE.

The rates of recovery in mental status and asterixis were also similar in the 2 treatment groups. The duration of therapy before complete clinical recovery was 11.6±6.4 days in the sodium benzoate group and 12.8±9.1 days in the lactulose group (P>.1). Ammonia levels eventually normalized in 34 (94%) of 36 patients treated with sodium benzoate and in 31 (94%) of 33 patients treated with lactulose; however, not surprisingly, the grade of encephalopathy did not correlate with arterial ammonia. Significant improvement (P<.001) in

Table 3. Changes in Portal-Systemic Encephalopathy Parameters Before and After Treatment[43]

	Sodium benzoate (n=38)		Lactulose (n=36)	
Parameter	**Before* (n)**	**After* (n)**	**Before* (n)**	**After* (n)**
Mental status (0–4)	3.3±0.13 (38)*	0.13±0.34** (30)	3.6±0.4 (36)	0.1±0.3** (29)
Asterixis (0–4)	3.6±0.5 (23)	0.1±0.2** (30)	3.5±0.6 (24)	0.2±0.6** (29)
Number connection test (0–4)	3.9±0.25 (18)	2.1±1.1† (12)	3.8±0.8 (17)	1.9±1.3† (12)
Arterial ammonia (0–4)	2.1±0.9 (38)	1.1±0.8† (30)	1.9±0.6 (36)	0.9±0.3† (29)
EEG (0–4)	1.6±0.8 (11)	1.4±0.4† (8)	1.8±0.9 (13)	1.5±0.8† (10)
PSE index	0.61±0.08	0.2±0.01**	0.68±0.06	0.19±0.02**

EEG=electroencephalogram; PSE, portal-systemic encephalopathy.
*All values expressed as mean ± standard deviation; figures in parentheses indicate the number of patients in whom the tests could be performed.
**Values significantly different before and after treatment (P<.01).
†Values significantly different before and after treatment (P<.05).

the scores of cognition, memory, and PSEI was observed with both sodium benzoate and lactulose therapy (Table 3). Therapy failed in 9 (24%) patients treated with sodium benzoate and 7 (19%) patients treated with lactulose. Eight patients receiving sodium benzoate and 7 patients receiving lactulose died, and 1 patient who failed sodium benzoate therapy responded to lactulose. The results suggest that sodium benzoate may be an alternative to lactulose for the treatment of acute HE in cirrhotic patients. Critics of the study argue that the real efficacy of sodium benzoate in managing hyperammonemia is difficult to establish because management also included other therapeutic measures such as protein restriction, bowel cleansing, and/or management of precipitating events that may have influenced ammonia levels.[44]

A noncontrolled trial by Campollo and colleagues evaluated the safety and efficacy of sodium benzoate during 6 months of treatment in 18 patients with HE.[45] Patients received a mean daily dose of 6.4 g of sodium benzoate administered as an 8% solution. Three patients dropped out of the study within 1 month due to gastrointestinal intolerance. Patients were evaluated using the PSEI (Table 2).

After 6 months of sodium benzoate treatment, PSEIs improved significantly (0.31±0.03 vs 0.23±0.04; P<.02), and mean ammonia levels were significantly lower (163±22 µg/mL vs 107±16 µg/mL; P<.02). Significant fluid retention did not develop in any patient, but 3 (16%) patients in the safety analysis set reported gastrointestinal complaints. However, it is important to note that PSEI is no longer used to assess HE. Instead, the combination of clinical assessment of mental status (commonly using the West Haven Criteria), psychometric testing (with number connection tests, digit symbol tests, block design tests, and other such tests), and EEG analysis is often recommended for evaluating the severity of HE.[1]

In a double-blind crossover study of 8 male patients with cirrhosis complicated by chronic stable HE, sodium benzoate (10 g/day) was compared with sodium phenylacetate (10 g/day).[46] Phenylacetate binds glutamine to form phenylacetylglutamine, which removes as much waste nitrogen as urea and about twice as much as hippurate.[47] Each patient served as his own control, with 4 patients randomly selected to initially receive sodium benzoate and 4 randomly selected to receive sodium phenylacetate.

Each course of treatment was given for 7 days followed by a 3-day washout prior to crossover. Baseline PSEI was established for 3–8 days on standard therapy prior to randomization. Encephalopathy was deemed stable and clinically evaluated using West Haven Criteria as grade 1 in 4 patients and mild grade 2 in 4 patients. Standard therapy consisted of a low-protein diet alone in 3 patients, neomycin and a low-protein diet in 2 patients, and a low-protein diet and lactulose in 3 patients.

Patients remained on standard therapy throughout the duration of the study. Mean baseline PSEIs were similar in the 0.34–0.37 range for each standard therapy. The addition of sodium benzoate to standard therapy resulted in improved mental status in 5 (63%) patients, reduced serum ammonia levels in 7 (88%) patients (mean reduction of 54.4±25.5 µg/dL), and improved PSEIs in 7 (88%) patients to a mean PSEI of 0.187±0.044 (47% reduction compared with standard therapy; P<.001). In contrast, phenylacetate provided no significant benefit beyond that seen with standard therapy. Four of the patients did not experience complete clinical remission with either agent and were further treated with combination sodium benzoate/phenylacetate therapy; 2 of the 4 patients showed further improvement in mental status and PSEI.

Using post-treatment scores that represented the maximum improvement seen in patients, 6 patients receiving sodium benzoate monotherapy and 2 patients receiving

the combination of sodium benzoate and phenylacetate achieved improvements in mental status (from 2.63±0.37 to 0.38±0.37; *P*=.0007), number connection tests (from 2.50±0.33 to 1.5±0.19; *P*=.02), and blood ammonia levels (from 275±56 µg/dL to 113±50 µg/dL; *P*=.0001). The authors concluded that, when added to diet restriction and neomycin or lactulose, sodium benzoate may be superior to phenylacetate but that the combination may be better than either agent used alone.

Efrati and colleagues used a different approach to evaluate the effects of sodium benzoate levels, administering a 20-g glutamine challenge to 6 stable patients with cirrhosis (but without overt HE) both before and after 5 days of sodium benzoate treatment to assess the effect on ammonia levels and psychometric performance without the influence of confounding events (eg, precipitating factors, protein restriction, or use of lactulose, lactitol, or neomycin).[44] The study group consisted of 6 hospitalized men (Child-Pugh class A=1; Child-Pugh class B=3; Child-Pugh class C=2). Baseline ammonia levels were drawn in the morning after overnight fasting. Patients were then given glutamine (20 g by mouth), with ammonia levels measured at 30 and 60 minutes after the glutamine load. A number connection test and Posner attention test (which evaluates attentional and memory dysfunction) were then performed immediately after the last blood sample. After this baseline evaluation, patients were started on sodium benzoate, receiving 2.5 g by mouth twice daily on Day 1 and then 5 g by mouth twice daily thereafter.

The oral glutamine challenge and psychometric testing were repeated after 5 days of treatment. Blood ammonia levels increased after the glutamine load both before sodium benzoate treatment (from 66±12 µg/dL to 123±34 µg/dL and 179±53 µg/dL after 30 and 60 min, respectively; analysis of variance [ANOVA] *P*=.0004) and after treatment (from 102±27 µg/dL to 185±49 µg/dL and 250±39 µg/dL after 30 and 60 min, respectively; ANOVA *P*=.00001).

After sodium benzoate treatment, the basal values (102±27 µg/dL vs 66±12 µg/dL; *P*=.01) and peak increments of ammonia (166±56 µg/dL vs 102±40 µg/dL; *P*=.04) were significantly higher than before; the number connection test and Posner test results were not altered. The authors concluded that sodium benzoate may increase ammonia levels and that their data do not support use of this drug for managing HE in patients with cirrhosis. They suggested that when the urea cycle is fully functional, the addition of sodium benzoate may inhibit the production of urea by depleting coenzyme A–mediated processes in the urea cycle. However, there are potential confounders unrelated to sodium benzoate that may have been responsible for the elevated ammonia levels, including increased dietary protein versus the regimen prior to hospitalization, catabolism due to prolonged fasting or inadequate carbohydrate intake, bacterial overgrowth in the gut due to possible use of gastric acid suppression, or other precipitating events. In addition, ammonia levels may have decreased on their own after sodium benzoate was discontinued because the kidneys have been shown to respond to episodes of moderate hyperammonemia by reducing plasma release of ammonia, resulting in increased urinary excretion of ammonia.[9] Because these potential confounders were not addressed in the study, the results can only be taken at face value. The study emphasizes the potential limitations of using sodium benzoate, suggesting that it is not a therapeutic option for everyone with HE.

Dosage and Administration

Sodium benzoate is typically dosed for adults at 2–5 g orally twice daily.[38,39,43] It is supplied as a bulk powder that can be measured and mixed into a flavored beverage or food supplement. However, contact with the powder is discouraged because it is considered potentially hazardous in the event of skin contact (irritant), eye contact (irritant), or inhalation (Material Safety Data Sheet; available at http://www.sciencelab.com/msds.php?msdsId=9927413). Personal protection, including goggles, protective gown and gloves, and appropriate respiratory equipment and ventilation, has generally been recommended to prevent contact with the powder. However, one of the authors (RGG) has used sodium benzoate with approximately 1,000 patients who mixed a scoop of the powder into a soft drink, milk shake, or nutritional shake with no ocular, skin, or pulmonary adverse effects noted.

Perhaps the most practical approach for use of sodium benzoate is to have it compounded into 500-mg capsules or 10% (100 mg/mL) solution; sodium benzoate is soluble in water. Many compounding pharmacies can prepare and dispense these easy-to-use formulations for patients. Capsules help mask the unpleasant taste but can be problematic in patients who cannot swallow. It is recommended that the capsules not be opened unless appropriate contact and airborne precautions are followed. The 10% solution is a reasonable option for patients who have difficulty swallowing or have a gastrostomy tube; it avoids airborne concerns related to using the powder. It is recommended that the solution be mixed in a flavored beverage to mitigate the taste. Sodium benzoate also has been formulated into a sweet syrup by mixing it with dextrose.[41]

Drug Interactions

Penicillin competes with phenylacetylglutamine and hippurate for active secretion by renal tubules, which may affect the overall disposition of sodium benzoate.[48]

Probenecid is also known to inhibit the renal transport of many organic compounds, including aminohippuric acid, and may affect renal excretion of hippurate.[48] Several drugs and compounds have been reported to cause hyperammonemia by disrupting the metabolism of ammonia in the urea cycle. For example, salicylates, valproate,[49] carbamazepine, ribavirin, sulfadiazine, and pyrimethamine have been associated with causing hyperammonemia.[11] Salicylates can impair mitochondrial function in the liver. Glycine used for irrigation to distend the bladder and clear the surgical site during transurethral resection of the prostate has been found to stimulate ammonia production.[50] However, this is not to say that dietary glycine should be avoided. On the contrary, the availability of glycine is important for mediating the glycine benzoyl-CoA transferase reaction and is important in hippurate synthesis in vivo.[51] The administration of steroids has been found to increase blood ammonia levels through increased protein catabolism.[48]

Safety Considerations

Reported adverse effects frequently associated with administration of sodium benzoate include gastrointestinal symptoms such as nausea (16–39%), vomiting (26%), and epigastric discomfort (16–26%).[43,45] Interestingly, dose reduction has not been shown to improve tolerability. Other adverse effects include an unpleasant salty taste and a burning sensation upon swallowing. However, many of these gastrointestinal adverse effects can be minimized by either administering sodium benzoate in capsule form or by mixing the solution in a soft drink or milk shake. Administration of an H_2-receptor antagonist also has been shown to control gastrointestinal symptoms.[43] Less common adverse effects that have been reported include tinnitus, vertigo, and headache. Electrolyte imbalance such as hypervolemic hyponatremia with worsening ascites is possible,[52] in which case sodium restriction is recommended.

The sodium content of sodium benzoate must be factored into the allotted dietary sodium limit; discontinuation of sodium benzoate may be necessary in patients with ascites or edema that is difficult to manage. Adjustments in diuretics may be required. As with lactulose, use of sodium benzoate may increase serum sodium levels or cause hypernatremia, especially in the setting of significant diarrhea and/or dehydration. In 38 patients who were receiving sodium benzoate, the mean serum sodium levels increased an average of 12%, from 123±22 mEq/L to 138±14 mEq/L.[43] The usual 5-g and 10-g sodium benzoate daily dosages provide approximately 800 mg/day and 1,600 mg/day of sodium, respectively. Monitoring of serum sodium levels and volume status is recommended.

Caution should be used in patients with congestive heart failure, hypernatremia, edema, or renal impairment. Serious but rare adverse events that have been reported include metabolic acidosis, disseminated intravascular coagulopathy, and urticaria/angioedema, although the latter is uncertain, as it may have been caused by other additives studied.[34,52] Sodium benzoate interacts with ascorbic acid to form benzene, a known carcinogen. The US Environmental Protection Agency (EPA) maximum contaminant level goal for benzene in drinking water is 0; the EPA maximum contaminant level allowed for benzene in drinking water is 5 ppb (0.005 mg/L).[53] The amount of benzene that may form in the combination of ascorbic acid with sodium benzoate at the doses used to treat HE is unknown. Thus, until more information is available, mixing powdered sodium benzoate with products containing ascorbic acid or swallowing sodium benzoate pills with drinks containing powdered sodium benzoate cannot be recommended.

Sodium benzoate is a common food additive classified by the FDA as generally regarded to be safe when used as a food preservative and limited to 0.1% by weight (0.1 g per 100 g or 100 mL). However, the FDA-approved daily dose of sodium benzoate/sodium phenylacetate is 5.5 g/m^2 of sodium benzoate for patients weighing more than 20 kg. The International Programme on Chemical Safety (IPCS), a joint venture of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, has established a provisional tolerable intake of 5 mg/kg body weight per day (400 mg per 80-kg person). Doses used to treat HE are 12.5–25 times greater than the limits established by the IPCS. Although studies evaluating the use of sodium benzoate at higher doses have shown that it is relatively safe,[43] its clinical significance and long-term safety remain unknown.

Conclusion

The avoidance of precipitating factors and the use of agents that reduce ammonia levels and other factors that contribute to HE remain the best therapeutic options in preventing and managing this condition. Rifaximin and lactulose are the 2 most effective therapeutic agents available at this time. However, lactulose is associated with many intolerable adverse effects that limit its usefulness. In clinical practice, additional agents may be required in combination with rifaximin and lactulose to optimize therapy and reduce morbidity and mortality, hospital admissions, and associated healthcare costs. Sodium benzoate appears to be a relatively safe and effective third- or fourth-line option that may be helpful in patients with portal systemic shunting or cirrhosis with minimal or episodic HE and good kidney function.

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