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Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia

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Summary: Intravenous sodium benzoate and sodium phenylacetate have been used successfully in the treatment of acute hyperammonaemia in patients with urea cycle disorders. They provide alternative pathways for waste nitrogen disposal and help maintain nitrogen homeostasis. However, we report three patients with hyperammonaemia who received inappropriate doses of intravenous sodium benzoate and sodium phenylacetate that resulted in severe complications. Ambiguous medical prescriptions and inadequate cross-checking of drug dosage by physicians, nurses and pharmacists were the main causes of these incidents. All the patients presented with alteration in mental status, Kussmaul respiration and a partially compensated metabolic acidosis with an increased anion gap. Two patients developed cerebral oedema and hypotension and died. The third survived after haemodialysis. Plasma levels of benzoate and phenylacetate were excessively high. The possible mechanisms of toxicity, management and safety measures are discussed.

Intravenous sodium benzoate and sodium phenylacetate have been used successfully in the treatment of episodic hyperammonaemia in patients with urea cycle disorders (Brusilow et al 1984). These drugs provide alternative pathways to ureagenesis for waste nitrogen disposal and help maintain nitrogen homeostasis in these patients. Sodium benzoate is conjugated with glycine to form hippurate, while sodium phenyl acetate is conjugated with glutamine to form phenylacetylglutamine. Both of these metabolites are rapidly excreted in urine via glomerular filtration and tubular secretion. The recommended dose of intravenous sodium benzoate and sodium phenylacetate is 250 mg/kg each infused over 90 min, followed thereafter by 250 mg/kg each infused over 24 h. Theoretically, administration of 250 mg/kg per day of each drug

will lead to an excretion of 24 mg/kg per day of hippurate nitrogen or 44 mg/kg per day of phenylacetylglutamine nitrogen (Brusilow and Maestri 1996).

These investigational drugs have been used in the treatment of patients with urea cycle defects for almost 20 years and the effectiveness and safety of this therapy is widely accepted. The success of the drugs in decreasing plasma ammonium levels in these disorders has led to their wider application to the treatment of hyperammonaemia from other causes (Mendenhall et al 1986; Tse et al 1991). Known side-effects of the drugs include nausea and vomiting during the infusion and hypokalaemia secondary to urinary loss enhanced by the excretion of the non-absorbable anions (hippurate and phenylacetylglutamine) (Batshaw et al 1982). Hyperchloraemic acidosis may occur as a consequence of arginine-HCl administration. No serious side-effects have been reported when the drugs are used in the recommended doses. However, we report here three cases of hyperammonaemic patients who received excessive doses of intravenous sodium benzoate and sodium phenylacetate, resulting in devastating complications.

MATERIALS AND METHODS

We reviewed the hospital charts of three patients who received accidental overdose with intravenous sodium benzoate and sodium phenylacetate. All three patients had known urea cycle defects and were being treated for intercurrent acute hyperammonaemia at the time the overdose occurred. Two cases occurred at one hospital and the third at a separate hospital. The clinical courses, relevant laboratory results including blood gases, electrolytes and ammonium levels, details of drug dosage, and drug and drug metabolite levels were summarized.

Plasma ammonium was measured by a cation-ion exchange method (Brusilow 1991). In our laboratory, the normal plasma ammonium levels are less than 30 μmol/L. Where possible, blood for determination of drug levels and drug metabolites was obtained. Plasma benzoate, hippurate, phenylacetate and phenylacylglutamine were determined by reversed-phase high-pressure liquid chromatography (Batshaw et al 1982).

PATIENT 1

J.H., a 3-year-old girl with known ornithine transcarbamylase deficiency, presented with a 2-day history of upper respiratory tract infection. Subsequently, she became irritable with decreased mental alertness. At the time of admission her diet was protein restricted (1 g/kg per day natural protein) and she was taking 2.5 g/day of sodium benzoate and sodium phenylacetate and 3.6 g/day of citrulline. On admission her weight was 11.6 kg. Initial laboratory results showed a plasma ammonium of 82 μmol/L. Serum electrolytes were sodium 141 mEq/L, potassium 4.0 mEq/L, chloride 103 mEq/L, bicarbonate 21 mEq/L and glucose 67 mg/dL. At that time her quantitative amino acids showed glutamine 1056 μmol/L (337–673), glycine 296 μmol/L (87–323), alanine 948 μmol/L (136–440), citrulline 0 μmol/L (10–34), ornithine 108 μmol/L (22–94), arginine 20 μmol/L (15–115); normal laboratory values are shown in parentheses. Because of altered mental status, a priming intra-

venous dose of 250 mg/kg of sodium benzoate and sodium phenylacetate with 2 ml/kg of 10% arginine-HCl was ordered to be given over 90 min, followed by the same dose over 24 h. Her plasma ammonium level decreased to 44 μmol/L and 54 μmol/L at 4 and 7 h, respectively, after starting treatment. Plasma amino acids 4 h after starting treatment showed glutamine 745 μmol/L (337–673), glycine 85 μmol/L (87–323), alanine 998 μmol/L (136–440), citrulline trace (10–34), ornithine 237 μmol/L (22–94), arginine 776 μmol/L (15–115). However, during this time she became more irritable and somnolent, and developed tachypnoea with Kussmaul respiration. A repeat venous blood gas 7 h after starting the intravenous drugs showed a pH of 7.21 and pCO_2 of 5 torr. Serum electrolytes at that time were sodium 146 mEq/L, potassium 3.7 mEq/L, chloride 104 mEq/L and bicarbonate 4 mEq/L, with a calculated anion gap of 42. She was transferred to the intensive care unit, where her condition worsened. Her plasma ammonium levels increased to 158 μmol/L and 232 μmol/L at 22 and 26 h, respectively, despite continuous infusion of both medications. Serum electrolytes at 26 h were sodium 152 mEq/L, potassium 2.9 mEq/L, chloride 107 mEq/L and bicarbonate 16 mEq/L, with a calculated anion gap of 32. Haemodialysis was required to correct her acid–base balance and hyperammonaemia. Plasma ammonium decreased below 100 μmol/L and her anion gap normalized within 24 h. Plasma ammonium levels were normal by 48 h.

Plasma taken 4 h after the priming dose was ordered, and at the time of the increased anion gap, revealed levels of benzoate and phenylacetate far above those reported for the recommended doses (Table 1). Retrospective review of the medical record revealed that the patient had received three priming doses intravenously followed by an incorrect maintenance infusion dose. In total the patient received 915 mg/kg of sodium benzoate and sodium phenylacetate over 12 h. The written orders were ambiguous and the abnormal dose went unrecognized by pharmacists, nurses and physicians. She recovered from the event and was discharged home after 17 days of admission. She is now 19 years of age with an overall DQ of 35. She continues to have occasional episodes of hyperammonaemia despite treatment with a protein-restricted diet (0.75 g/kg per day) supplemented with sodium phenylbutyrate (500 mg/kg per day) and citrulline.

PATIENT 2

S.P., a boy aged 6 years and 8 months with known late-onset ornithine transcarbamylase deficiency, presented with vomiting and a possible viral illness. His weight on admission was 21 kg. Prior to admission the patient was on a protein-restricted diet with citrulline supplementation. However, the family was noncompliant. His initial plasma ammonium was 326 μmol/L. Serum electrolytes were sodium 141 mEq/L, potassium 4.7 mEq/L, chloride 103 mEq/L, bicarbonate 23 mEq/L, with an anion gap of 20. Plasma amino acids were not obtained. He was admitted and treated with a priming dose of 250 mg/kg of sodium benzoate and sodium phenylacetate with 2 ml/kg of 10% arginine-HCl infused over 2 h. This resulted in a decline of the plasma ammonium to 78 μmol/L one hour after com-

Table 1 Drug levels and metabolites obtained in patients 1 and 3

Time (h)	*BA* (mmol/L)	*PA* (mmol/L)	*HA* (mmol/L)	*PAG* (mmol/L)
Patient 1				
0	0.002	ND	0.007	ND
4	10.60	10.0	0.292	ND
12	1.80	2.71	0.294	0.097
Patient 3				
6	5.07	8.19	0.399	0.341
9	5.58	9.07	0.395	0.341
13	3.37	7.67	0.362	0.292
15	2.53	8.16	0.412	0.319
19	0.321	7.59	0.566	0.475
28	0.034	1.79	0.189	0.677
Normal values				
0	0	0	0	0
3	2.6	3.4	0.25	0
12	1.5	4.5	0.35	0
17	0.2	3.5	0.25	0.40
20	0	3.0	0.15	0.50
27	0	2.2	0.15	0.50
32	0.4	1.5	0.15	0.45

For comparison, values are shown from a single patient who received 250 mg/kg over 90 min followed by 250 mg/kg over 24 h
BA, benzoate; PA, phenylacetate; HA, hippurate; PAG, phenylacetylglutamine; ND, not determined.

pletion of the priming infusion. Since he was unable to take his oral medication, a 24 h infusion of the same dose of each medication was ordered. At 16 h of this infusion, he was found to be obtunded and unresponsive to painful stimuli and had Kussmaul respiration. His plasma ammonium was 113 μmol/L. A venous gas showed a pH of 7.38, pCO_2 of 9 torr and a calculated bicarbonate of 5 mEq/L. Serum electrolytes were sodium 151 mEq/L, potassium 2.7 mEq/L, chloride 97 mEq/L and bicarbonate <5 mEq/L. The calculated anion gap was 52 mEq/L. An overdose of intravenous sodium benzoate and sodium phenylacetate was suspected at that time and the infusion was stopped at approximately 18 h. He was then treated with intravenous fluids and sodium bicarbonate. However, his plasma ammonium increased to 915 μmol/L. At that time his venous blood gas showed a pH of 7.35 and a pCO_2 of 12 torr. His serum electrolytes were sodium 152 mEq/L, potassium 3.5 mEq/L, chloride 101 mEq/L and bicarbonate 6 mEq/L. The calculated anion gap was 49 mEq/L. Haemodialysis was started and his acid–base balance and ammonium levels were normalized after two rounds of dialysis. Despite this, his neurological status worsened, a CT scan of his brain showed cerebral oedema and he had fixed and dilated pupils. He was pronounced dead on the third day of admission.

A review of the medical record revealed that the patient had received the entire 24 h continuous infusion dose repeating every 3 h resulting in a total dose of 1750 mg/kg of sodium benzoate and sodium phenylacetate over an 18 h period.

Again medical orders were ambiguous and the excessive doses were not recognized by pharmacists, nurses or physicians. He had received seven times the desired dose within 18 h until the time his clinical condition deteriorated and the infusion was stopped. Drug levels were not available.

PATIENTS 3

D.D., a boy aged 2 years and 9 months with known neonatal-onset ornithine transcarbamylase deficiency, was admitted following 1 week of upper respiratory tract infection and 2 days of emesis and irritability. At the time of his illness his diet consisted of 1.28 g/kg per day of protein, of which 0.5 g/kg per day was given as essential amino acids (UCD2, Milupa). Additionally, he was taking 600 mg/kg per day of phenylbutyrate and 3 g/day of citrulline. On admission he was alert and active with stable vital signs. His weight was 13 kg. The initial plasma ammonium was 84 μmol/L. A venous blood gas showed a pH of 7.38, and pCO_2 of 35 torr. Serum electrolytes were sodium 142 mEq/L, potassium 4.4 mEq/L, chloride 110 mEq/L, bicarbonate 22 mEq/L and a calculated anion gap of 14. Quantitative plasma amino acids showed glutamine 1446 μmol/L (337–673), glycine 390 μmol/L (87–323), alanine 2198 μmol/L (136–440), citrulline 0 (10–34), ornithine 50 μmol/L (22–94), arginine 39 μmol/L (15–115). Because of continued vomiting, a priming dose of 250 mg/kg sodium benzoate, 250 mg/kg sodium phenylacetate and 2 ml/kg 10% arginine-HCl was started. Maintenance with the same doses and medications was ordered to run over 24 h after the priming dose was completed. Six hours after starting the priming dose, the patient's plasma ammonium had decreased to 32 μmol/L. Plasma amino acids at that time showed glutamine 806 μmol/L (337–673), glycine 60 μmol/L (87–323), alanine 995 μmol/L (136–440), citrulline 0 (10–34), ornithine 148 μmol/L (22–94), arginine 377 μmol/L (15–115). However, after 9 h of treatment he was noted to be lethargic and irritable and had Kussmaul respiration. Serum electrolytes at that time were sodium 137 mEq/L, potassium 4.2 mEq/L, chloride 97 mEq/L, and bicarbonate 5 mEq/L. The calculated anion gap was 39 mEq/L. At that time it was discovered that he was receiving an incorrect maintenance dose. The medications were immediately stopped but despite vigorous fluid and electrolyte resuscitation he developed cerebral oedema and respiratory depression requiring ventilatory support. The patient developed disseminated intravascular coagulation, became hypotensive and died within 36 h of admission.

Drug levels (Table 1) revealed toxic levels of benzoate, phenylacetate and their metabolites. Review of the medical record revealed that the patient received a total of 750 mg/kg of the drugs over 10 h. The orders for the drugs were wrongly transcribed and the mistake was not recognized by pharmacists, nurses or physicians.

DISCUSSION

The recommended dose of intravenous sodium benzoate and sodium phenylacetate is 250 mg/kg each infused over 90 min, followed by 250 mg/kg each infused over 24 h

thereafter. We report three patients who accidentally received these drugs far in excess of these doses. Patients 1 had received 915 mg/kg over 12 h, patient 2 received 1750 mg/kg over 18 h, and patient 3 received 750 mg/kg over 10 h. Plasma levels of benzoate and phenylacetate were measured as 10.6 mmol/L and 10 mmol/L at 4 h after infusion in patient 1 and 5.58 mmol/L and 9.07 mmol/L at 9 h in patient 3. Using a priming infusion of 250 mg/kg over 90 min, plasma benzoate levels generally reach peak levels of 3 mmol/L at 4–6 h while phenylacetate reaches peak levels of 4 mmol/L at the same time (Table 1). Plasma hippurate and phenylacetylglutamine levels are generally below 600 μmol/L when treatment is with these doses (Brusilow et al 1984). The clinical presentation of toxicity was similar in all cases. The patients initially became agitated and confused even as the plasma ammonium decreased. Kussmaul respiration was prominent in all cases. Biochemical indices in blood showed that all patients developed a partially compensated metabolic acidosis with an increased anion gap (42, 52 and 27 in patients 1, 2 and 3, respectively). Accumulation of benzoate and phenylacetate may represent another cause of an increased anion gap. Plasma ammonium levels decreased in all patients after the priming dose but rebounded in patient 1 to 232 μmol/L and in patient 2 to 915 μmol/L once the intravenous drugs were discontinued. Mental status was depressed in all patients. Cerebral oedema was evident in patients 2 and 3 before they died. Hypotension and cardiovascular collapse were late signs of intoxication. Patients 2 and 3 died despite intensive therapy. Patient 1 survived after prompt haemodialysis.

Adverse reactions have been noted before in patients receiving sodium benzoate and sodium phenylacetate for the treatment of urea cycle defects (Brusilow et al 1984). These include nausea and vomiting. An increased anion gap may be observed due to the accumulation of benzoate, phenylacetate and their conjugation products in plasma, the sum of which may attain levels of 7 mmol/L. Other electrolyte changes that may be seen include hypernatraemia and hyperosmolarity (because of the high sodium content of the drugs), hypokalaemia as a result of increased urinary loss and hyperchloraemia due to the co-infusion of arginine-HCl. Finally, because of the structural similarity of benzoate and phenylacetate to salicylates, they have the potential to cause central hyperventilation and respiratory alkalosis.

Previous reports have implicated benzyl alcohol (which is converted to benzoic acid) as a cause of the 'gasping syndrome' and death in premature infants (Brown 1982; Gershanik et al 1982). While benzoic acid undoubtedly causes an increased anion gap metabolic acidosis, it also has been shown to interfere with various metabolic pathways (Tremblay and Qureshi 1993). High-dose benzoate sequesters coenzyme A, leading to a deficiency of acetyl-CoA. This results in inhibition of carbamoylphosphate synthetase and pyruvate carboxylase, thus affecting the urea cycle and gluconeogenesis (Cyr and Tremblay 1989; Cyr et al 1991). Carnitine deficiency through urinary loss of benzoylcarnitine further reduces acetyl-CoA and inhibits fatty acid oxidation (Baynen and Geelen 1982; Kalbag and Palekar 1988; Ohtani et al 1988; Van Hove et al 1995). There are two reports of adverse reactions to the use of phenylacetate in humans including emesis and neurotoxicity (Thibault et al 1994, 1995). The latter may be accounted for by the fact that phenylacetate has been shown to inhibit several neuronal-associated enzymes including choline acetyl-

transferase, dopa decarboxylase, 5-hydroxytryptophan decarboxylase and glutamic acid decarboxylase (Davidson and Sandler 1959; Fellman 1956; Hartman et al 1955; Petempska et al 1984). The formation of phenylacetyl-CoA decreases the availability of acetyl-CoA and inhibits fatty acid and sterol synthesis.

Intoxication with sodium benzoate and sodium phenylacetate should always be considered in patients receiving these intravenous medications. In the event of suspected overdose, the drugs should be discontinued and the patient should be carefully monitored for clinical and biochemical deterioration, with special attention to the anion gap. Haemodialysis is the treatment of choice. Supplementation with glycine and/or carnitine should also be considered as additional therapy. Clear and unambiguous orders and confirmation of dosages by physicians, nurses and pharmacists should be carefully observed.

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