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Butoxyethanol Ingestion with Prolonged Hyperchloremic Metabolic Acidosis Treated with Ethanol Therapy

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ABSTRACT

Background: Severe toxic ingestions of butoxyethanol (CAS No. 111-76-2) are rare despite the prevalence of this glycol ether in products such as glass and surface cleaners. Manifestations of acute butoxyethanol toxicity include metabolic acidosis, hemolysis, hepatorenal dysfunction, and coma, but vary widely in reported cases. Furthermore, the optimal therapeutic approach is not yet established. Much of the toxicity of butoxyethanol has been ascribed to its aldehyde and acid metabolites which are similar to those produced by oxidative metabolism of methanol and ethylene glycol. Although the roles of alcohol dehydrogenase inhibition with ethanol or fomepizole and hemodialysis are clear in the case of toxic ingestions of methanol and ethylene glycol, they remain poorly defined for butoxyethanol poisoning. Case Report: We report the case of a 51-year-old female who ingested up to 8 ounces of Sanford Expo White Board Cleaner® (butoxyethanol and isopropanol). She developed prolonged hyperchloremic metabolic acidosis and mental status depression and was treated with ethanol therapy but not hemodialysis. This patient recovered without apparent sequelae. The kinetics of butoxyethanol metabolism in this case are described and the potential therapeutic options are discussed.

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INTRODUCTION

2-Butoxyethanol (also known as butoxyethanol [BE], ethylene glycol monobutyl ether, butyl cellusolve CAS No. 111-76-2) is a solvent widely used in household and industrial cleaning products. It is commonly found in glass and surface cleaners in concentrations ranging from 2–16%.[1] Despite its widespread use, serious BE poisonings are infrequent and the manifestations of acute BE toxicity in the few reported cases of human exposure vary widely.[2–6] Reported toxic effects in humans include rapid onset mental status depression and coma, anion gap metabolic acidosis, hypotension, hemolysis, and disseminated intravascular coagulation (DIC). Less commonly, hepatic and renal dysfunction and respiratory dysfunction including acute respiratory distress syndrome (ARDS) have also been noted.[3,4]

Butoxyethanol is oxidatively metabolized via an aldehyde intermediate to butoxyacetic acid (BAA) in a manner analogous to methanol and ethylene glycol.[7,8] As with methanol and ethylene glycol, some of the toxic effects, notably the acidosis and hemolysis, are believed to be secondary to these metabolites. Although it has been suggested that BE undergoes an oxidative *O*-dealkylation to form ethylene glycol, this ether linkage is quite stable and data regarding metabolism of BE to ethylene glycol in humans are conflicting.[5,9,10] Proposed management strategies for BE intoxication mirror those for other toxic alcohol exposures. Specifically, inhibition of alcohol dehydrogenase (ADH) to halt the production of potentially toxic aldehyde and acid metabolites has been recommended.[6,10,11] However, inhibition of ADH by ethanol or fomepizole after ingestion of BE has not been proven to be of therapeutic benefit and there may be potential disadvantages to these therapies. Hemodialysis has been used in some cases of BE intoxication to remove both the parent compound and metabolites, as well as to correct acid–base abnormalities.[2,5,6] The indications for hemodialysis remain poorly defined for acute BE intoxication.

We report a case of BE ingestion with a rapid onset of hyperchloremic metabolic acidosis persisting for over 44 hours. This patient was treated with ethanol therapy but not hemodialysis and recovered without apparent sequelae.

Case Report

A 51-year-old female was observed to ingest up to 8 ounces of Sanford Expo White Board Cleaner for Dry Erase Surfaces® (H_2O 40–70%, BE 10–30%, Isopropanol 10–40%) in a suicide attempt. On arrival in the emergency department 100 minutes later, she vomited and became increasingly lethargic over the next 3 hours. Initial vital signs were recorded as: heart rate 117/min, BP 138/84 mm Hg, respirations 24/min, T 37.3°C, and room air O_2 saturation of 98%. She was lavaged via nasogastric tube and received 50 g of activated charcoal and 10 ounces of magnesium citrate. Laboratory tests (drawn 100 minutes after ingestion) included CO_2 13 mEq/L, Na^+ 143 mEq/L, K^+ 3.6 mEq/L, Cl^- 115 mEq/L, anion gap 15 mEq/L, BUN 5.0 mmol/L (14 mg/dL), and Cr 71 μmol/L (0.8 mg/dL), glucose 5.1 mmol/L (92 mg/dL), Ca^{++} 2.0 mmol/L (8.2 mg/dL), and PO_4^{3-} 0.77 mmol/L (2.4 mg/dL). Arterial blood gases on room air showed pH 7.31, P_{CO_2} 23 mm Hg, P_{O_2} 83 mm Hg, and bicarbonate 12 mEq/L with a urine pH of 5.5. Serum lactate was not measured. Ethanol, methanol, and ethylene glycol were not detected. Isopropanol was 3 mg/dL, acetone was 3 mg/dL, and the osmolal gap was 1 mOsm/kg. Because of the rapid onset of her metabolic acidosis, the patient received a loading dose of 500 mL 10% ethanol intravenously (IV) followed by an infusion at 1.3 mL/kg/h, thiamine 100 mg IV, pyridoxine 50 mg IV, and folate 50 mg IV (approximately 4 hours after ingestion). At this point, she became obtunded and hypotensive (BP 91/54 mm Hg) and was intubated and admitted to the intensive care unit (ICU). In the ICU, her mild hypotension resolved with normal saline 1 L IV. A hyperchloremic metabolic acidosis (CO_2 ranging from 13–16 mEq/L, Cl^- ranging from 111–115 mEq/L) with an anion gap ranging from 11–15 mEq/L persisted over 44 hours. Hemodialysis was considered but not performed and the decision was made to continue with the ethanol infusion and supportive care only. During this time, her blood ethanol concentrations increased from 21 to 51 mmol/L (97–236 mg/dL), and therefore the IV ethanol infusion rate was gradually decreased to 0.75 mL/kg/h. On hospital day 3, blood ethanol concentrations unexpectedly dropped from therapeutic levels to levels below the limits of detection for several hours. At this point, she received 350 mL ethanol 10% IV as a repeat loading dose and her infusion rate was increased to 70 mL/h. Coincident with this time interval, CO_2 concentrations began to normalize and by the end of the day, her acidosis and hyperchloremia were corrected. Her hypotension then resolved (hospital day 2), she was extubated (hospital day 3), and the ethanol infusion was discontinued (hospital day 4). There was no evidence of ARDS, renal dysfunction, oxalate crystalluria, or hemolysis during her hospital course. Her aspartate transference was mildly elevated on the 2nd and 3rd hospital days (peak 45 IU/L) but other liver function tests

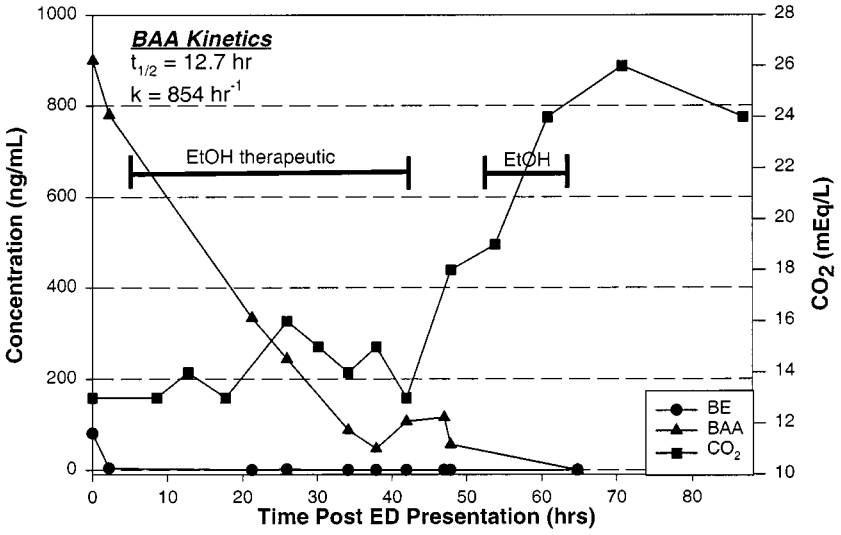

Figure 1. Butoxyethanol (BE; circles), butoxyacetic acid (BAA; triangles) and TCO_2 (squares) concentrations plotted versus time. Note the simultaneous decrease in BAA and increase in TCO_2 concentrations. The bars show periods of time when blood ethanol concentrations were therapeutic.

were normal. She was discharged 5 days after ingestion without apparent sequelae.

Serum BE, butoxyacetic acid (BAA), and TCO_2 concentrations were determined and are plotted vs time in Figure 1.

ANALYTICAL METHODS

Butoxyethanol (BE), butoxyacetic acid (BAA), pentanol (internal standard, IS), pentafluorobenzyl bromide (PFBBr), pentafluorobenzoyl chloride (PFBCl), methylene chloride, sodium hydroxide, and tetrabutylammonium hydrogen sulfate were purchased from Aldrich Chemical Company (Milwaukee, WI). Stock solutions of BE and BAA were prepared in distilled deionized water at concentrations of 900 ng/mL and 1000 ng/mL, respectively. The stock solution of IS was prepared in distilled deionized water at a concentration of 1800 ng/mL. The buffer used consisted of 0.2 M NaOH and 0.1 M tetrabutylammonium hydrogen sulfate adjusted to a pH of 10. Plasma controls were prepared by dilution of BE and BAA stock solutions 1:10 with pooled, filtered, banked plasma for final concentrations of 90 ng/mL BE and 100 ng/mL BAA.

The analytical method used was an adaptation of that of Bormett.[12] Briefly, a 500 µL aliquot of patient or control plasma was rendered protein-free with a Millipore YM-30 centrifree filter (Millipore; Bedford, MA). In a 15-mL conical tube, an aliquot of protein-free centrifree supernatent (200 µL), internal standard (200 µL), buffer (500 µL), CH_2Cl_2 (1 mL), and PFBBr (50 µL) were combined. The tube was vortexed (10 sec) and heated at 60°C in a dry heat block for 1 minute. The tube was then vortexed for 10 seconds and heated for an additional 1 minute. This cycle was repeated 10 times for a total heating time of 10 minutes. The tubes were then centrifuged (5 min; 1500 g) and the organic (lower) layer transferred to a clean 15-mL conical tube. PFBCl (50 µL) was added and the tubes were capped, vortexed, and incubated in a dry heat block at 60°C for 15 minutes. A 3-µL aliquot of the solution was injected into the gas chromatograph.

A Hewlett-Packard Model 5890 gas chromatograph, equipped with a Model 5970 mass selective detector was used. The column was a Hewlett-Packard Ultra-II with a 25-m length and 0.25-mm internal diameter. The injector and detector were maintained at 250°C and 280°C, respectively, and the solvent delay was 5.0 minutes. The initial oven temperature was 100°C which was held for 0.3 minutes followed by a ramp at 15°C/min to 180°C, then an immediate ramp at 30°C/min to 300°C. The final temperature was held for 0.5 minutes. An oven equilibration time of 0.5 minutes was included in each cycle. The total run time was 10.13 minutes. The mass selective detector was operated in positive-ion chemical ionization mode using methane as the reagent gas with a dwell time of 50 ms/ion. A methane line feed pressure of 5 psi was used for all experiments. The chemical ionization ratio

(median of 0.3) was set using the stock Hewlett-Packard autotune protocol.

Retention times were 5.89, 6.97, and 7.22 minutes for the derivatized IS, BE, and BAA, respectively. The detector was operated in scan mode and the peaks of interest quantitated using selected ion extraction during data analysis. Quantitation was performed using the ratio of the area-under-the-analyte peak to the area-under-the-IS peak. The ions selected for analysis were: *m/z* 239 (BE), 283 (IS) and 313 (BAA). Within run precisions (n = 3) were 18.9% and 32.7% for BE and BAA, respectively. Between run precisions (n = 3) were 11.1% and 12.5% for BE and BAA, respectively. The assay was linear from 2 to 1800 ng/mL with a detection limit of 2 ng/mL for both analytes.

RESULTS AND DISCUSSION

Butoxyethanol is a monoalkyl glycol ether that is metabolized by ADH to butoxyaldehyde and BAA.[7,8] In rats, BE metabolism to BAA appears to follow Michaelis-Menten kinetics, indicating potential saturation of metabolic pathways in a manner similar to ethanol.[13] Kinetic data in humans are limited, but reported $t_{1/2}$ measurements (although, strictly speaking, not the appropriate parameter for Michaelis-Menten kinetics during zero order elimination) for BE range from 40 minutes in cases of low-level respiratory exposure to 210 minuutes in an overdose case with coingestion of ethanol.[2,14] The reported $t_{1/2}$ of the primary metabolite BAA in humans exceeds that of the parent compound, ranging from 1.7 to 9.6 hours.[2,14] In ADH-inhibited rats, BE is converted to sulfate and glucuronide conjugates.[8] It is unclear if this nonoxidative conjugative pathway exists in humans.

In our patient, parent BE was detected only in the first blood sample (drawn 100 minutes after ingestion) reflecting rapid metabolism. Blood BAA concentrations declined from a peak measured value of 900 ng/mL on presentation to nondetectable by 65 hours after ingestion. BAA concentrations appeared to exhibit a linear decline with a calculated $t_{1/2}$ of 12.7 hours, which is longer than previously reported values for this parameter (see Figure 1).[2,14]

The interpretation of blood BE and BAA concentrations in the reported cases of BE overdose is difficult. Reported blood concentrations of BE in cases with similar clinical symptoms and amounts ingested range from 5.28 μg/L to 432,000 μg/L—an 80,000-fold difference (see Table 1).[3,4] This variation in reported values questions the validity of analytical results in these cases. Plasma sample volumes from our patient were insufficient to compare our analytical technique to other published methods. Any comparison would be problematic since there is no established standard analytical method for the quantitation of butoxyethanol and metabolites. Samples from our patient were stored at −20°C until the assay was developed and validated. Stability of the analyte was not investigated and it is possible that off-gassing of analyte from stored plasma specimens may have resulted in falsely lowered plasma concentrations.

In every human case of ingestion (including the present one), a single patient has been used to derive kinetic parameters and the absolute ''dose'' of BE ingested is not accurately known. Therefore, it is not possible to perform rigorous statistical analyses for the derivation of ''normal'' absorption and elimination phases for BE and BAA. This is further complicated by the variety of analytical methods that have been employed for BE and BAA analysis including high-pressure liquid chromatog-

Table 1

Serum Butoxyethanol Concentrations from Reported Cases of Butoxyethanol Ingestion with Reported BE Concentrations Including Estimated Amount Ingested and Time of Sample Collection Relative to Ingestion

	Peak BE Level	Estimated Dose	Time After Ingestion
McKinney *et al.*	81 μg/L	24–72 g	2.5 h
Gijsenbergh *et al.*[2]	432,000 μg/L	25–30 g	1 h
Bauer *et al.*[3]	5.28 μg/L	45 g	10 h
Gaultieri *et al.*[4]	44.9 μg/L	79–106 g	16 h
Gaultieri *et al.*[4]	12,760 μg/L	106 g	10 h

raphy, gas chromatography with flame ionization, electron capture, and mass spectral detection.[15–18] None of these methods are appropriate for emergent determination of BE and BAA concentrations. Fortunately, BE and BAA concentrations are not necessary for effective management of acute intoxication.

Although metabolic conversion of BE to ethylene glycol has been suggested, the ether linkage in BE appears to be quite stable, making this transformation unlikely in humans. However, in cases of human BE intoxication, data regarding metabolism of BE to ethylene glycol are conflicting. Oxaluria and elevated creatinine presumed secondary to metabolism of ethylene glycol to oxalate were noted in one case; however, ethylene glycol concentrations were not determined.[5] Litovitz *et al*. report a case of BE ingestion where ethylene glycol levels of 110 mg/dL were measured at an unspecified time after ingestion.[9] However, details of the history are unclear and no chemical analysis of the product was conducted to determine whether it contained ethylene glycol. A third case reports ingestion of a BE-containing product with subsequent ethylene glycol level of 4.95 mmol/L (31 mg/dL), oxaluria, and renal insufficiency.[10] Again, no analysis of this product was performed to ensure it did not contain ethylene glycol. The remaining cases of ingestion of BE in humans report no oxaluria, nondetectable ethylene glycol levels, or no renal damage indicative of significant ethylene glycol poisoning.[2–4,6]

The acute toxicity of BE ingestion in humans usually involves the rapid onset of mental status depression, hypotension, and metabolic acidosis.[11,19] Elevated transaminases and renal function tests, acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC) have also been reported, although they were not seen in our patient. It is unclear which of these toxic effects are due to the parent compound and which may be ascribed to metabolites. In some animal models, BE has potent hemolytic effects.[7,8] This hemolysis is blocked by inhibitors of ADH, suggesting that the hemolysis is not due to parent BE, but rather the BAA metabolite.[7,20] Interestingly, human red blood cells seem to be resistant to the hemolytic effects of BAA *in vitro*.[21] Of the 9 reported cases of BE ingestion, hemolysis was reported in only 3 and was not seen in our case.[2,5,6]

In addition to the hemotoxic effects, metabolic acidosis has been consistently reported in cases of human exposure.[2–6,9,10] In some cases, elevated lactate concentrations were detected, but in most reports, details are insufficient to further characterize the metabolic acidosis. In the present case, a hyperchloremic metabolic acidosis with a minimally elevated anion gap was seen within 100 minutes of ingestion and persisted for 44 hours, resolving as serum BAA concentrations decreased. The hyperchloremia occurred prior to administration of chloride containing intravenous fluids. The patient's urine pH was 5.5 and lactate was not measured. There was neither a history of renal disease or ingestion of chloride-containing acid nor were other causes of elevated anion gap or non-anion gap metabolic acidosis identified. In most, but not all, reported cases of BE ingestion, the metabolic acidosis was accompanied by an elevated anion gap.[2,3,10] Only Burkhart reports chloride values, also elevated at 116 mEq/L. The etiology of this acid/base and electrolyte disturbance remains unclear.

Because of the similarities of BE metabolism to other toxic alcohols such as methanol and ethylene glycol, similar management strategies have been proposed. These therapies center on inhibition of ADH by either ethanol or fomepizole, which block the formation of butoxyaldehyde and BAA, leaving the parent BE to be conjugated to the sulfate or glucuronide or excreted unchanged.[20] In rat models, these conjugates (but little unchanged BE) are excreted in the urine.[20] Similar metabolic pathways have not been observed in humans and the fate of BE in humans treated with ADH inhibitors is unclear.

Several practical issues arise when considering the use of ADH inhibition as a therapeutic option. In order to derive a benefit from ethanol or fomepizole therapy, it must first be assumed that the metabolites are more toxic than the parent compound. Animal data suggest that the hemolysis that is observed is not due to parent compound but to the metabolite, BAA. Inhibition of ADH by pretreatment with fomepizole or ethanol prevents or greatly attenuates BE-induced hemolysis in rodent models.[20,22] The resistance of human RBCs to BE-induced hemolysis and the fact that hemolysis is not consistently reported in human cases (and has never been reported to require transfusion therapy) bring into question the therapeutic value of ADH inhibition in human BE poisonings. It is assumed that the other aspects of BE toxicity such as mental status depression, hypotension, and acidosis are due to metabolite production. It is possible that the parent BE may contribute significantly to the observed toxicity and if this is the case, inhibition of ADH may prolong some aspects of toxicity while preventing others.

The timing of ADH inhibition therapy is also crucial if this therapy is to be effective in inhibiting further production of BAA. The reported half-life of BE is quite short (approximately 40 minutes in cases without ethanol coingestion). Therefore, by the time the patient presents to a health care facility for treatment, the window of efficacy for ADH inhibition may have either passed or be

greatly diminished. This is consistent with the present case in which we were only able to detect BE at nominal concentrations (81 ng/mL) in the first blood sample (drawn approximately 100 min after ingestion). Obviously, if little or no parent BE is present, ADH inhibition therapy will not be effective.

Ethanol therapy may also directly contribute to toxicity. In addition to additive mental status and respiratory depression and hypotension, the metabolism of therapeutically administered ethanol may alter the redox state of the liver, decreasing further metabolism of BAA or other alcohols and ketoacids. Our patient's metabolic acidosis began to resolve during a period when blood ethanol concentrations dropped below the therapeutic range. It is possible that a restoration of redox state occurred while ethanol concentrations were not detectable, allowing increased clearance of ketoacids. However, the acidosis continued to resolve after the patient received a second loading dose of ethanol and had documented therapeutic blood ethanol levels. Thus, it is difficult to determine if ethanol therapy adversely affected the resolution of acidosis in our patient. These issues regarding redox state may not apply to patients treated with fomepizole.

Blood ethanol concentrations varied dramatically over time in this patient despite few changes in ethanol infusion rate. On one occasion, ethanol concentrations dropped below detectable levels and required a second loading dose. Irregular and unpredictable ethanol kinetics mandate careful monitoring of blood ethanol concentrations to ensure therapeutic levels. Maintaining consistently therapeutic blood concentrations and consistent ADH inhibition has not been a practical issue with fomepizole.

The role of hemodialysis in cases of BE intoxication is also poorly defined. In the 9 reported cases of BE ingestion, 6 were treated with hemodialysis. Since metabolism of BE is quite rapid, the instances when extracorporeal drug removal of parent compound would be practical are limited to large ingestions with very early presentations. The role of hemodialysis in removing BE metabolites is unclear, although it does appear to speed correction of acid/base and electrolyte abnormalities.[6] In the present case, because of the mild degree of acidosis and lack of evidence of hemolysis, renal injury, and oxalate crystalluria, we opted to manage this patient without hemodialysis. It can be argued that early hemodialysis may result in earlier resolution of acidosis and other symptoms of toxicity, thereby reducing time in an intensive care setting; however, definitive recommendations for hemodialysis or ADH inhibition therapy cannot be made based on the existing data.

CONCLUSIONS

Patients ingesting butoxyethanol may present with rapid onset of coma, hypotension, and hyperchloremic metabolic acidosis. ADH inhibition therapy with ethanol or fomepizole therapy is unproven. Our patient was treated with ethanol therapy but not hemodialysis and recovered without apparent sequelae.

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