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CASE REPORT

Repeated Ingestion of 2-Butoxyethanol: Case Report and Literature Review

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ABSTRACT

Background: Ethylene glycol monobutyl ether (2-butoxyethanol) is not commonly associated with significant human poisoning. Exposures are usually through occupational contact and typically involve inhalation injury. Animal studies report severe hemolysis occurring in rats and mice. Rare published human cases give varied descriptions of the clinical course associated with 2-butoxyethanol poisoning including reports of metabolic acidosis, ethylene glycol production, oxaluria, renal failure, and anemia. We report a case of two separate ingestions (80 to 100 grams) of a glass cleaner concentrate containing 22% 2-butoxyethanol, and its primary metabolite butoxyacetic acid. *Case Report*: An 18-year-old male ingested 360–480 mL of 22% 2-butoxyethanol on two separate occasions. Approximately 10 hours after the first ingestion, the patient developed severe CNS depression, metabolic acidosis, hematuria, and mild elevation of hepatic enzymes. He was treated initially with ethanol therapy but continued to deteriorate and was started on hemodialysis. Approximately 10 days after discharge, the patient ingested 480 mL of the same product and received ethanol and hemodialysis within four hours of ingestion. During his second admission the patient did not develop the delayed severe CNS depression or profound metabolic acidosis. Clinically significant hemolytic anemia, oxaluria, ethylene glycol production, and renal failure were not noted in either episode. The patient recovered on both occasions without sequelae. *Conclusion*: Hemodialysis may be an effective treatment intervention for managing severe acute 2-butoxyethanol intoxication; however, further investigation is warranted.

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INTRODUCTION

Ethylene glycol monobutyl ether, also known as 2-butoxyethanol (BE), is a member of a family of glycol ethers that are used in a variety of industrial and household products. BE is found in a number of resins, varnishes, and hydraulic fluids. It is also a principal constituent of many household products including floor polishes and glass, leather, and upholstery cleaners.

Toxicity information for human ingestions of BE-containing products is limited. The medical literature on BE poisoning contains primarily case reports of adult ingestions (1–7). Unintentional pediatric exposures to glass cleaners containing 0.5% to 9.9% BE does not appear to pose a serious health risk (1).

The clinical features of reported human BE intoxication in humans reported include metabolic acidosis, CNS depression and coma, renal injury, hemolytic anemia, non-hemolytic anemia, thrombocytopenia, DIC, hematuria with or without oxaluria, ARDS and hypotension (3–7). Animal studies of BE intoxication have demonstrated the potential for significant hemolytic anemia, but this has not been a consistent or clinically significant finding in human case reports of BE exposure (8–17). Liver injury also occurs in animals following exposure to BE (8,9). The toxicological effects associated with BE poisoning have been attributed primarily to butoxyacetic acid (BAA), a major metabolite of BE (4,8–12).

CASE REPORT

First Ingestion

An 18-year-old male voluntarily consumed between 360 mL and 480 mL of a glass cleaner containing 22% 2-butoxyethanol. The patient presented to the hospital approximately three hours later complaining of mild epigastric discomfort. Physical examination was unremarkable. Initial laboratory values including CBC, electrolytes and hepatic function tests were normal. Creatinine was 1.2 mg/dL (106.1 μmol/L), which was the upper limit of normal. Arterial blood gas results were pH 7.34, pCO_2 36.4 mm Hg, pO_2 100 mm Hg, and bicarbonate 19.5 mmol/L. A urine drug screen, and serum salicylate, acetaminophen and serum ethanol levels were negative. The serum osmolality concentration measured using freezing-point depression methodology was 297 mOsm/kg H2O. Intravenous isotonic saline was administered at a rate of 200 mL/hour and the patient was admitted to the Intensive Care Unit for medical observation.

Approximately 10 hours post-admission the patient was noted to be more lethargic, weak, and hyperventilating. A serum ethylene glycol sample collected at this time was negative (Mayo Medical Laboratories, Rochester, Minnesota). Laboratory values obtained approximately 16 hours post-ingestion included an elevated lactate level of 5.9 mEq/L (0.65 mmol/L) and an arterial blood gas sample with pH 7.46, pCO_2 6.4 mm Hg, pO_2 120 mm Hg, and bicarbonate 4.3 mEq/L (Base excess—13.9). Renal function tests showed a slight elevation of creatinine to 1.5 mg/dL (136.6 μmol/L) and urinalysis revealed moderate ketones. Aspartate aminotransferase (AST) was 75 U/L (normal, <45 U/L). Repeat serum osmolality remained within normal limits at 291 mOsm/kg H2O. A chest radiograph was unremarkable.

The patient was given a single 50 mEq intravenous bolus of sodium bicarbonate immediately following the initial finding of metabolic acidosis.

The patient's clinical status deteriorated and he was transferred to a tertiary care hospital where hemodialysis, was started approximately 24 hours post-ingestion. Dialysis was performed at a flow rate of 200 mL/min with Fresenius-8 Polysulphone Membrane Dialyzer with a 3K + bath for 4.5 hours. No ultrafiltration was performed. During the course of dialysis the acidosis resolved as evidenced by the return of bicarbonate to normal. Creatinine decreased to 1.1 mg/dL (97.2 μmol/L). Urinalysis was remarkable for protein, moderate ketones, and intact red blood cells (>10 RBC per HPF). Liver enzymes remained elevated with an AST of 60 U/L, alanine aminotransferase (ALT) 134 U/L, total bilirubin 3.4 mg/dL (58.1 μmol/L) with the fraction of direct bilirubin 0.5 mg/dL (8.6 μmol/L). Orally administered ethanol therapy was started 30 minutes after dialysis was initiated, however serum ethanol concentrations were not measured during dialysis. Serum ethanol concentrations of 16 mg/dL and 153 mg/dL were measured at 2.5 and 7 hours post-dialysis, respectively. The mean serum ethanol concentration during the 29.5-hour treatment period was 58 mg/dL (12.6 mmol/L). Treatment also included intravenous doses of thiamine (100 mg every 12 hours), folic acid (50 mg every 12 hours), and pyridoxine (50 mg every 6 hours).

Four hours following dialysis the patient was alert, oriented, and hemodynamically stable. Approximately 60 hours after the ingestion hepatic and urinalysis abnormalities resolved. The patient remained afebrile, neurologically intact, and hemodynamically normal for the remainder of his hospital stay. Serum samples

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collected 25 hours after his initial exposure and 2 hours after hemodialysis was started had no ethylene glycol, methanol, isopropanol, and acetone (MedTox Laboratories Inc., St. Paul, Minnesota). Quantitative analysis for butoxyacetic acid (BAA), the major metabolite of 2-BE, was performed using previously published analytical methodology (18,19). The highest BAA concentration was 4.86 mmol/L, collected approximately 16 hours post-ingestion and 7 hours prior to hemodialysis (Table 1).

Second Ingestion

Ten days following his initial hospital discharge the patient was re-admitted with a second ingestion of 480 mL of the same BE-containing window cleaner. The patient denied any physical complaints on presentation approximately six hours after this ingestion. Vital signs were within normal limits. The physical examination revealed a hemodynamically stable patient patient who was neurologically intact. The remainder of the examination was unremarkable. Initial laboratory testing revealed a pH 7.40, $PaCO_2$ 31.5 mm Hg, PaO_2 99.6 mm Hg, and bicarbonate 19.3 mEq/L. Creatinine was 1.3 mg/dL (114.92 μmol/L) and hepatic laboratory tests were normal.

Intravenous ethanol 10% at a rate of 1.5 mL/kg/hour was empirically started with the intent to maintain a serum ethanol concentration of approximately 100 mg/dL (22 mmol/L). The patient underwent hemodialysis beginning approximately eight hours post-admission, prompting an increase in his ethanol infusion rate to 2.5 mL/kg/hour until dialysis was completed. The serum ethanol concentrations were 88 mg/dL at the start of dialysis and 74 mg/dL at the end of the dialysis period. Dialysis was performed utilizing the previously employed parameters and dialyzer. The mean serum ethanol concentration during the 28-hour treatment period was 109 mg/dL (23.7 mmol/L). The patient's measured serum osmolality was 318 mOsm/kg H2O providing a calculated osmolal gap of 27 mOsm (8 mOsm when taking into account the ethanol). The patient was also maintained on the same intravenous doses of thiamine, folate, and pyridoxine as during the first ingestion. The remainder of the patient's hospital stay was uneventful without any evidence of hemodynamic, neurologic, renal, or hepatic abnormalities. Ethylene glycol was not detected in pre-dialysis serum samples collected six hours post-ingestion. The highest reported BAA concentration following the second ingestion was 2.07 mmol/L, but this was collected 22 hours post-ingestion and two hours after hemodialysis was started (Table 1).

DISCUSSION

Oral ingestions of BE have not been commonly reported in the literature. Our case was unusual in that we were able to observe the effects of two separate ingestions of concentrated BE in the same patient. Early treatment with dialysis and possibly ethanol therapy may explain why our patient experienced a less severe clinical course after the second ingestion.

The gastrointestinal absorption of BE is rapid and complete. BE is oxidized in the liver via alcohol and aldehyde dehydrogenases to the primary metabolite

Table 1. 2-Butoxyethanol (BE) and butoxyacetic acid (BAA) serum concentrations.

Estimated oral dose of BE	Day	Time	Unbound BAA (mM)	Unbound BE (mM)
80–100 grams (1st ingestion)	1	1800–1900	NR	NR
	2	1050	4.86	0.00038
	2	2030	3.64	0.00080
	2	2225	2.98	0.00020
	2	2300	2.87	0.00141
	3	0100	2.54	0.00113
100 grams (2nd ingestion)	1	2100	NR	NR
	2	0325	NR	NR
	2	0712	2.07	0.108
	2	1059	0.742	0.051
	2	1800	0.447	0.015
	3	0608	0.091	0.002

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butoxyacetic acid (BAA) (9–12). BAA is then excreted in the urine (4,6,9–17). BAA is believed to be responsible for the toxicologic manifestations of BE poisoning (9–12,20). This metabolic pathway is a saturable process demonstrating Michaelis–Menten kinetics. Prolonged BE elimination observed in the setting of a BE overdose has been attributed to the saturable metabolic pathways of BE elimination (4). Conjugation of BE with glucuronide or sulfide to produce oxyethanol–glucuronide and butoxyethanol sulfate is believed to be primary detoxifying pathways of the parent compound (11). The fraction of BE converted to the glucuronide and sulfate conjugates has been shown to increase significantly with pyrazole inhibition of BE metabolism to BAA by alcohol dehydrogenase (9,11).

The occurrence of profound hemolytic anemia in animal models of BE poisoning has been well described. In vitro and in vivo studies have ascribed these potent hemolytic properties to BAA and not BE (9,11,12,21). Human erythrocytes have been shown in in vitro studies to be resistant to the hemolytic effects of BAA even at concentrations several times higher than those producing hemolysis in animals (10,12,21). These studies have consistently demonstrated that BAA concentrations ≥ 8 mM are required for pre-hemolytic changes to occur in human red blood cells. Despite these studies, two separate reports of attempted suicidal ingestions of BE described a decline in hemoglobin and evidence of hematuria following the ingestions (4,6). Mechanisms such as hemodilution may be an explanation for declining hemoglobin concentrations but together with hematuria may represent a true hemolytic process (3). Haufroid et al. noted that occupational exposure to BE in workers demonstrated an effect on hematocrit and mean corpuscular hemoglobin concentration (22) but concerns about the methodology create doubts about the validity of the reported results.

Our case did not definitively show a hemolytic process despite having a BAA serum concentration of 4.86 mM 16 hours after his first ingestion. Based on previously reported studies, such a BAA concentration would be expected to produce rapidly fatal RBC hemolysis in BAA sensitive mammals (10,12,21,23). During our patient's first hospitalization, there was a rise in indirect bilirubin, but complete blood counts and differentials showed no evidence of hemolysis throughout his hospital course.

Significant ketonuria has not been reported following acute BE intoxication in humans. Following the first ingestion, our patient's urinalysis was positive test for ketones, and resolved 15 hours later. Although this finding may be consistent with alcoholic ketoacidosis, our patient's history made this diagnosis unlikely. The significance of ketonuria in acute BE ingestion is unknown. It is possible that BE or its metabolites may interfere with the urine dipstick assay, or that a ketone metabolite may be produced from BE causing ketonuria. Oxaluria, renal insufficiency, and metabolic acidosis were observed in a patient who ingested 250–500 mL of 12% BE 12 hours prior to presentation (20). The idea was proposed that saturation of BE metabolism may lead to another metabolic pathway which produces ethylene glycol and subsequently, oxalic acid (20). An ethylene glycol concentration of 110 mg/dL (1772 μmol/L) has been reported in a woman who ingested an unknown quantity of a disinfectant cleaner containing 6.5% BE (5). The method used to quantify ethylene glycol in this case was not described and BE or BAA concentrations were not measured. Oxaluria-associated and ethylene glycol has not been reported in animal models of BE poisoning (24–27). Crystaluria and clinically significant renal insufficiency were not reported in either hospitalization described in this case report, and ethylene glycol was not detected in the pre-dialysis serum collected 10 and 6 hours following the respective ingestions of glass cleaner.

Other clinical features of BE intoxication that have been previously described include hypotension, hepatic injury, and acute respiratory distress syndrome (3,4,6,7). Our case showed only mild, transient liver dysfunction during his first admission and no elevation of enzymes during the second hospitalization for BE poisoning. Cardiovascular and pulmonary complications were not evident in our patient. Burkhart et al. reported severe neurological deficits in a patient following resuscitation after ingestion of a liquid containing butoxyethanol (7). Our patient had no neurological sequelae despite ingestion of a similar amount and concentration of a BE-containing liquid.

An osmolal gap may be used as a diagnostic tool in ethylene glycol, methanol, or ethanol ingestions. Our patient did not have an osmolal gap that could be attributed to a non-ethanol alcohol. Lund and colleagues found in an in vitro study that BE does not appear to affect measurements of osmolality (28).

Treatment modalities for BE ingestions have been based on the hypothesis that inhibition of the metabolic pathway enzymes will prevent the conversion to toxic metabolites. Inhibiting alcohol and aldehyde dehydrogenase with pyrazole and cyanamide, respectively, prevented toxicity in rats exposed to lethal quantities of BE (9). Other animal studies have shown ethanol therapy may prevent BAA-induced toxicity by inhibiting its

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formation from BE (29,30). To our knowledge, no human studies evaluating the efficacy of ethanol or 4-methylpyrazole (fomepizole) therapy in BE-poisoned patients have been published. Based on the toxicokinetics of BE, the use of ethanol or fomepizole in the treatment of BE poisoning warrants further study. Burkhart et al. used hemodialysis for the treatment of refractory acidosis (7). We found hemodialysis to be beneficial in our patient with metabolic acidosis and declining clinical condition during his first presentation. Following his second exposure to BE, a relatively benign hospital course was observed when hemodialysis was initiated early.

In conclusion, much more information is needed regarding the pathophysiology, clinical effects, and appropriate treatments for 2-butoxyethanol poisoning.

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