Extreme γ-Butyrolactone Overdose With Severe Metabolic Acidosis Requiring Hemodialysis

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γ-Hydroxybutyrate (GHB) and its precursor γ-butyrolactone (GBL) are commonly abused drugs with a narrow therapeutic index. Therefore, overdoses occur readily with recreational use, and severe poisoning can occur after deliberate self-poisoning. We report the sequelae in a patient who ingested a massive dose of GBL, with suicidal intent. Severe metabolic acidosis and an asystolic cardiac arrest were successfully treated with standard resuscitation, supportive care, and continuous venovenous hemodiafiltration. Plasma GHB concentrations were the highest reported to date. The acidosis was attributed to rapid systemic absorption of GBL, followed by rapid metabolism to GHB. [Ann Emerg Med. 2011;58:83-85.]

INTRODUCTION

γ-Hydroxybutyrate (GHB) has been used to increase muscle bulk, as an anxiolytic or hypnotic, or for treatment of alcohol dependence. Most commonly, it is used for recreational purposes. Regulation of GHB in Australia resulted in increasing recreational use of the industrial solvents γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), which are precursors of GHB (Figure).

Given the narrow therapeutic index and synergistic effect of ethanol, overdose of GHB or GBL is a relatively common presentation to the hospital. Severe manifestations of overdose are central nervous system depression, hypoventilation, bradycardia, myoclonus, and seizures. These effects are usually short lived with supportive care, which is the management priority in acute GHB overdose. Fatalities caused by GHB overdose are reported, often associated with delayed presentation or out-of-hospital collapse. Agitation or delirium has also been reported, particularly during the offset of severe poisoning.

We report a case of severe metabolic acidosis in a patient with deliberate self-poisoning with GBL that required treatment with continuous venovenous hemodiafiltration. The GHB plasma concentrations observed in this survivor are, to our knowledge, the highest reported.

CASE REPORT

A 39-year-old man who had been drinking alcohol during the day was heard to collapse at his home and found unresponsive next to a half-empty 600-mL bottle that his roommate believed to contain GHB. Paramedics arrived within 10 minutes and found the patient to be hypoventilating, rapidly progressing to apnea and cyanosis (pulse oximetry 74% on room air). The pulse rate decreased from 70 to 39 beats/min, but the patient was normotensive 130/70 mm Hg. The Glasgow Coma Scale score was 3 of 15, pupil diameter was 7 mm bilaterally, and the capillary blood glucose level was 171 mg/dL (9.5 mmol/L). Paramedics instituted bag-valve-mask ventilation, and the patient was immediately transferred to the hospital.

On arrival to the hospital, immediate tracheal intubation (without requirement for induction agents) and ventilation restored oxygenation. Blood pressure was 178/80 mm Hg, pulse rate 86 beats/min, and Glasgow Coma Scale score 3 of 15. Admission testing included an arterial blood gas, which revealed pH 6.75, pCO₂ 70 mm Hg, pO₂ 483 mm Hg, base excess –23 mEq/L, and lactate level 26.1 mg/dL (2.9 mEq/L), consistent with a severe combined metabolic and respiratory acidosis. The patient experienced an asystolic cardiac arrest that responded to cardiopulmonary resuscitation, including 7 minutes of chest compressions, 3 1-mg boluses of epinephrine, 50 mL sodium bicarbonate 8.4%, and 10 mmol magnesium intravenously. During resuscitation, there was brief episode of a broad-complex tachycardia with return of spontaneous circulation, which rapidly resolved to sinus rhythm. Postresuscitation, the patient was initially tachycardic (120 beats/min) and hypertensive (199/115 mm Hg), but the blood pressure soon decreased to 105/50 mm Hg, requiring an epinephrine infusion at 1.2 mg/hour. A detailed clinical examination revealed fixed and dilated pupils but no new abnormalities.
Results of laboratory investigations included a blood alcohol concentration of 0.19% (190 mg/dL; 42 mmol/L), acute kidney injury (creatinine level 1.42 mg/dL [126 μmol/L]), mild hepatocellular dysfunction, leucocytosis (16.2 × 10⁹/L), and prolonged activated partial thromboplastin time (77 seconds) but a normal prothrombin time. A urine drug screen result was negative, although it did not measure GHB or related compounds. An ECG demonstrated T-wave flattening in leads II, III, aVF, V5, and V6.

The patient was transferred to the ICU, epinephrine was discontinued, and vasopressin, norepinephrine, hydrocortisone, and antibiotics were commenced. During the following several hours, an increased anion gap (38 mEq/L) metabolic acidosis persisted, with pH 6.82 to 6.99. There was only a minor contribution from lactate (26.1 to 44.1 mg/dL [2.9 to 4.9 mmol/L]), and the osmolar gap was calculated to be 9 mOsm/kg (reference range 0 to 10 mOsm/kg) after multiplying the blood ethanol concentration by a factor of 1.25 with the method of Purssell et al.³ To correct the severe persistent acidemia and remove any circulating unmeasured acids, continuous venovenous hemodiafiltration was commenced 8 hours postadmission. Throughout the following hours, hemodynamics quickly improved, allowing cessation of vasopressors, and acidemia resolved (pH 7.36, pCO₂ 35 mm Hg, HCO₃⁻ 19 mEq/L). Continuous venovenous hemodiafiltration was ceased and acidemia did not recur.

Peak concentrations of troponin I and creatinine were 0.26 ng/mL and 1.63 mg/dL (144 μmol/L), respectively. Mild hemolytic anemia and thrombocytopenia were attributed to oxidative stress and critical illness. On weaning sedation, recurrent seizures occurred, requiring a midazolam infusion, but the patient was successfully extubated 60 hours postpresentation. Further history clarified that the patient was not receiving regular medications and that the only toxic exposure on the day of admission was liquid from the bottle. After psychiatric assessment, he was discharged home with community follow-up and has recovered well.

The concentration of GHB was determined with gas chromatography and mass spectrometry according to a previously reported method.⁴ The GHB plasma concentration obtained approximately 60 to 90 minutes postingestion was 2,498 mg/L (24 mmol/L); methanol, ethylene glycol, and propylene glycol were not detected. The GHB concentration in a subsequent plasma sample 2.5 hours later was 1,135 mg/L (11 mmol/L), which equates to a half-life of 2.2 hours. Analysis of a sample of the liquid consumed by our patient, using Fourier transform infrared spectroscopy and gas chromatography mass spectrometry, confirmed the presence of GBL.

**DISCUSSION**

To our knowledge, this is the first case of profound metabolic acidosis associated with GHB, GBL, or 1,4-BD overdose. Even though GHB was suspected, the presentation was atypical and the acidemia persisted, which contributed in part to the cardiac arrest. Hemodiafiltration was commenced because of persistent acidemia despite bicarbonate treatment in a patient with an unconfirmed ingestion. GHB is a low-molecular-weight compound with a relatively small volume of distribution and minimal protein binding and so should be efficiently eliminated by hemodiafiltration.⁶ Therefore, we believe that hemodiafiltration remains a treatment option for patients with severe acidemia caused by poisoning with GHB or related compounds.

The GHB concentration of our patient recorded at admission is the highest to be reported in a survivor of GHB, GBL, or 1,4-BD overdose. Indeed, similar concentrations of GHB (up to 2,937 mg/L but usually much lower) have been reported in fatal cases.⁷ However, there is poor correlation between clinical severity and measured concentration, as demonstrated by comparing postmortem GHB concentrations to those measured in surviving patients or impaired drivers.⁸ Acidemia may have impaired hepatic and renal function, decreasing the clearance of GHB and therefore prolonging acidemia. The apparent half-life was 2.2 hours in our patient, which is prolonged compared with the 30 minutes reported in volunteers.⁹

The mechanism of metabolic acidosis from GBL ingestion has not been established. Respiratory acidosis is a well-described effect of GBL, 1,4-BD, and GHB poisoning and is accompanied by sedation, coma, and respiratory failure. We observed a high-anion-gap metabolic acidosis in our patient, with a relatively minor contribution of lactate. On the basis of
in vitro studies, the osmolar gap was predicted to be increased, but it was normal in our patient, which suggests the presence of a circulating unmeasured anion; methanol, ethylene glycol, and propylene glycol were not detected in our patient. We propose that it was GHB itself and that metabolic acidosis occurred because of the massive ingestion of GBL. Spontaneous hydrolysis of GBL to GHB occurs in vitro during a number of days at pH 2.8 to 12. However, once GBL is absorbed it is rapidly metabolized to GHB by the plasma enzyme lactonase. Further, given that the pKa of GHB is 4.72, it rapidly dissociates to the anion and hydrogen ion, causing acidosis (Figure).

We also hypothesize that acidosis is more likely to occur with GBL compared with 1,4-BD and GHB. Baboon studies have demonstrated that GBL is absorbed more rapidly and extensively than GHB because of its lipophilicity. As discussed above, GBL is metabolized rapidly to GHB by a lactonase enzyme in vivo, with a reported Michaelis constant (Km; the concentration at which the enzymatic reaction proceeds at 50% of the maximum rate) of 27 mmol/L, which is higher than the plasma concentration of GHB in our patient. In contrast, 1,4-BD is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase, both of which are saturable. There are no human data about this reaction, but rat experiments with 1,4-BD and alcohol dehydrogenase demonstrate a far lower Km of 0.61 mmol/L. Therefore, GBL overdoses are more likely to be associated with a high plasma concentration of GHB and acidosis. In contrast, this is unlikely to occur in 1,4-BD overdose because of slow bioactivation to, and subsequent rapid metabolism of, GHB.

In summary, this case demonstrates the potential for significant toxicity of GBL in overdose and propensity to cause acidosis with massive ingestion. An unprecedented high plasma concentration of GHB is reported, which was accompanied by severe metabolic acidosis, a previously unreported complication of this overdose. The acidosis contributed to a cardiac arrest and did not appear to resolve until treatment with hemodialfiltration. Clinicians should be alert to the possibility of GBL causing metabolic acidosis and of dialysis as a potentially effective rescue therapy.

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