Suspected GHB Overdoses in the Emergency Department

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Abstract

Blood specimens from 146 suspected gamma-hydroxybutyrate (GHB) overdose cases, presenting to an emergency department in Washington State over a 12-month period, were analyzed for GHB and other drugs. Of these 146 patients, GHB was confirmed in approximately one-third of the patients ($N = 54$), sometimes in potentially toxic concentrations. These patients were aged between 17 and 59 years (median 28 years), and 83% were male. Blood GHB concentrations ranged from 29 to 490 mg/L (mean 137 mg/L; median 103 mg/L). In 36 (67%) of the 54 patients, other drugs were additionally detected. Ethanol was measured in 22 (41%) patients, with concentrations ranging from 0.01 to 0.26 g/100 mL (median 0.04 g/100 mL). Other commonly co-administered drugs included 3,4-methylenedioxymethamphetamine, marijuana, methamphetamine, cocaine, and citalopram. Frequently observed clinical symptoms on admission for the GHB overdose group included copious vomiting, ataxia, lack of gag reflex, respiratory depression, mild acute respiratory acidosis, unconsciousness, and sudden altered states of consciousness. Many patients required intubation, and several became combative and required restraints. The majority of patients were discharged within 6 h of hospital admission. However, despite presenting with similar clinical symptoms on admission, GHB was not confirmed in 92 of the 146 overdose patients, suggesting that GHB overdose cases may frequently be indistinguishable from other drug overdoses or medical conditions.

Introduction

Gamma-hydroxybutyrate (GHB) was first used clinically as an anesthetic in the 1960s; however, its use was discontinued as it lacked analgesic properties and had an unpredictable duration of action, producing dramatic swings between consciousness and unconsciousness (1). Since then, GHB has been recreationally used by bodybuilders as an alternative to anabolic steroids to enhance muscle growth and by others for its intoxicating effects such as euphoria, reduced inhibitions, and sedation (2–6). Analogues of GHB, namely gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), convert to GHB within the human body following oral administration and are also recreationally abused. On February 18, 2000, GHB was placed in Federal Schedule I of the Controlled Substance Act, with GBL cited as both a list I chemical and a controlled substance analogue and 1,4-BD falling under the controlled substance analogue section (7,8). This scheduling has included a provision for medically formulated GHB to be placed in Federal Schedule III, and GHB is now available in the U.S. for the treatment of cataplexy associated with narcolepsy.

The primary effects of GHB are those of a central nervous system (CNS) depressant. Clinical and adverse effects range from relaxation and euphoria, confusion, dizziness, drowsiness, nausea and vomiting, agitation, nystagmus, memory impairment, and somnolence to uncontrollable shaking or seizures, combativeness, sinus bradycardia, respiratory depression, and unarousable unconsciousness (2,3,9–13). The onset of effects is extremely rapid, and unconsciousness can occur within 10–20 min. In Washington state, there has been an increasing number of patients presenting to emergency departments with signs of GHB intoxication or overdose. Unconsciousness may last anywhere from 1 to 6 h, and in extreme cases, death may occur.

Blood specimens from 146 suspected GHB intoxications were sent to the Washington State Toxicology Laboratory (WSTL) to confirm the presence of GHB and other drugs. The drug results and presenting clinical symptoms of these patients are presented here.

Methods

Blood was obtained from suspected GHB overdose cases presenting to the emergency department of a major Seattle hospital over a 12-month period. Hospital records were reviewed for information regarding the circumstances, presenting vital signs, clinical signs and symptoms, and time spent in the emergency department. Suspected GHB-overdose patients with symptoms of unconsciousness, coma, vomiting, cessation of breathing, bradycardia and/or respiratory depression, were included. Upon presentation, a blood specimen was drawn by

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qualified medical personnel, either by venous puncture (vacutainer) or through a heparin lock. Because the hospital was unable to analyze for GHB, specimens were submitted to the WSTL for GHB confirmation, in addition to a comprehensive drug screen. Twenty milliliters of blood was collected in two 10-mL gray-top blood tubes that contained sodium fluoride and potassium oxalate. On receipt of blood specimens at the laboratory, samples were stored at 4°C until tested.

GHB was analyzed by gas chromatography–mass spectrometry (GC–MS) as previously described (14), using diethylene glycol as an internal standard. Blood was slightly acidified with 0.1N H_2SO_4, then extracted twice in ethyl acetate. The analytes were derivatized to their TMS derivatives using BSTFA/1% TMCS. The assay had a limit of quantitation of 1 mg/L, defined as the lowest concentration at which the assay was determined to be linear. Calibration was determined to be linear up to 100 mg/L in blood, and the correlation coefficient was typically better than 0.990. Specimens with GHB concentrations above 100 mg/L were reanalyzed after dilution with blank matrix to within the linear range of the assay. All specimens underwent blood alcohol analysis for ethanol, methanol, acetone, and isopropanol by headspace GC with flame ionization detection. The limit of detection for ethanol was 0.005 g/100 mL. Methanolic extracts of blood specimens underwent a screen for drugs of abuse and several prescription drug classes using an enzyme multiplied immunoassay technique (EMIT). The EMIT procedure screened for cocaine metabolites (cutoff limit 100 ng/mL), opiates (10 ng/mL), amphetamines (100 ng/mL), carboxy-tetrahydrocannabinol (10 ng/mL), methadone (100 ng/mL), phencyclidine (10 ng/mL), propoxyphene (100 ng/mL), barbiturates (100 ng/mL), benzodiazepines (50 ng/mL), and tricyclic antidepressants (100 ng/mL). Additionally, *n*-butylchloride and ethyl acetate extracts of the blood specimens underwent separate screens for basic compounds and weak acidic and neutral compounds, respectively, using GC–MS.

Results

Over a 12-month period, 146 cases of suspected GHB overdose were admitted to the emergency department. These patients were aged between 14 and 59 years (median 25 years), and 60% of the patients were male. A GHB overdose or intoxication was suspected based on the clinical symptoms on each patient admission. Such symptoms included confusion, disorientation, copious vomiting, ataxia, decreased heart rate and blood pressure, sinus bradycardia, respiratory depression, apnea, and sudden altered states of consciousness.

However, of these 146 patients, GHB was detected in only 54 (37%) cases. These patients were aged between 17 and 59 years (median 28 years), and 83% were male. Blood GHB concentrations ranged from 29 to 490 mg/L (mean 137 mg/L; median 103 mg/L). The distribution of GHB concentrations in these GHB-related overdoses is shown in Figure 1. In 36 (67%) of these 54 patients, other drugs were additionally detected. Ethanol was measured in 22 (41%) patients, with concentrations ranging from 0.01 to 0.26 g/100 mL (median 0.04 g/100 mL). Other commonly co-administered drugs included 3,4-methylenedioxymethamphetamine (MDMA) ($N = 10$), marijuana ($N = 6$), methamphetamine ($N = 5$), cocaine ($N = 5$), and citalopram ($N = 4$).

The circumstances of a typical GHB overdose patient are presented here. Paramedics brought an 18-year-old male into the emergency department, at approximately 4:00 am. The patient had ingested an unknown quantity of "NRG3" in a suicide attempt. The exact time of ingestion was unknown. The patient was admitted to the critical care unit, and clinical symptoms included coma, CNS depression, respiratory depression, unresponsiveness to pain, absence of gag reflex, anion gap metabolic acidosis, mild hypothermia, and vomiting. Arterial blood gases were measured, and the patient had a pCO_2 of 46 and an arterial pH of 7.18 (respiratory acidosis). His pupils ranged between 2 and 4 mm and alternated between being reactive and unreactive. Treatment administered to the patient included charcoal, intubation, 10% ethanol drip, and fluoxetine. At approximately 9:00 a.m., the patient was still comatose but was breathing on his own. He regained consciousness shortly thereafter. Venous blood was collected shortly after admission, and GHB was detected at a concentration of 490 mg/L. GHB was also detected in a urine sample at a concentration of 928 mg/L. Blood was additionally positive for fluoxetine and ethanol (0.05 g/100 mL); however, both of these were administered to the patient while in the emergency room.

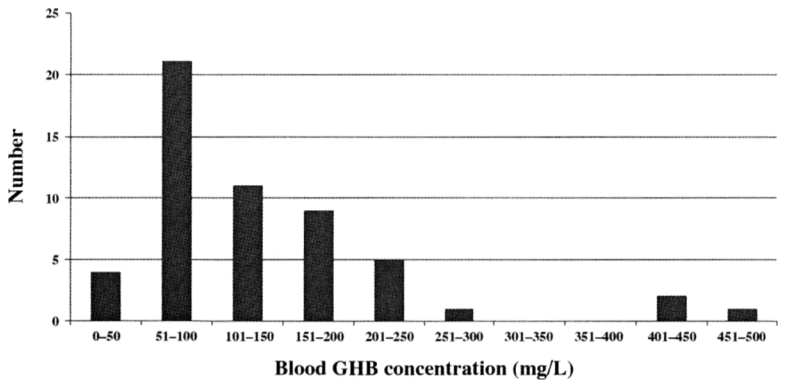

Figure 1. Distribution of GHB blood concentrations in 54 GHB-related overdoses.

Overall, many of these 54 patients admitted taking GHB or its analogues. Substances mentioned included V35, Blast, G3, NRG3, Renewtrient, 1,4-butanediol, a "clear liquid", and GHB. Approximately 40% of patients fell unconscious or were found unresponsive at a club, dance club, or rave. Other patients were brought in from the street, bars, parties, or from their homes. On admission to the emergency department, two-thirds were noted to be unconscious or unresponsive. Other common symptoms noted upon admission were drowsiness, agitation, ataxia, vomiting, sweating, lack of gag reflex, respiratory depression, and sudden altered states of consciousness; 34 patients required intubation. The average

heart rate measured was 83 bpm (N = 49; range 48–135); however, one-third of the patients were described as bradycardic and one-third were described as tachycardic. The average body temperature measured was 95.9°F (N = 47; range 91.4–100.6°F). Numerous patients were noted to have mild acute respiratory acidosis. The average blood pH was 7.39 (N = 29; range 7.30–7.51), and the average pCO_2 measured was 38.6 (N = 28; range 28–57). Overall, patients took between 1.5 and 6 h to be discharged from the emergency department (N = 46; average 3 h).

Interestingly, GHB was not detected in 92 (63%) of the 146 suspected GHB overdose patients, despite the observations of similar clinical symptoms upon presentation. These patients were aged between 14 and 54 years (median 23 years), and 53% were female. In 70 (76%) of these 92 patients, drugs other than GHB were detected. Ethanol was measured in 44 (48%) patients, with concentrations ranging from 0.01 to 0.39 g/100 mL (median 0.20 g/100 mL). Other co-administered drugs included marijuana (N = 17), MDMA (N = 12), methamphetamine (N = 6), meprobamate (N = 3), sertraline (N = 3), cocaine (N = 2), methadone (N = 2), and ketamine, oxycodone, olanzapine, tramadol, and trazadone were detected in one case each.

Discussion

In many emergency departments, the differential diagnosis of a typical GHB overdose or ingestion is extremely broad (i.e., somnolent or comatose, with or without respiratory compromise) and may, in fact, be indistinguishable from other drug overdoses or medical conditions. In a study by Chin et al. (15), the authors retrospectively reviewed medical records from 88 patients presenting to an emergency department for GHB ingestion. They found that patients who overdosed on GHB presented with a markedly decreased level of consciousness. Co-ingestion of ethanol or other drugs was common, as were bradycardia, hypothermia, respiratory acidosis, and emesis. Typically, the patients regained consciousness spontaneously within 5 h of the ingestion. Information about GHB use was simply gained from patient records, and GHB confirmation in blood was only performed in three patients.

In the present study, GHB was confirmed in 54 cases. Clinical symptoms on admission appeared to be similar to those observed by Chin et al. (15) and included copious vomiting, agitation, mild hypothermia, lack of gag reflex, mild acute respiratory acidosis, respiratory depression, and unresponsiveness or unconsciousness. The majority of patients required intubation, and several patients became combative and required restraints.

GHB concentrations detected in the present study were similar to those previously reported in known non-fatal GHB overdose cases, whereas several patients had concentrations equal to or approaching those reported in fatal GHB overdoses. In one report of non-fatal GHB overdoses, three patients arrived simultaneously at an emergency department 1 h after ingesting GHB, each having a Glasgow Coma Score (GCS) of 3 (16). GHB was detected in the serum of one patient at a concentration of 101 mg/L. In another report, an unconscious female was admitted to an emergency department after suddenly losing consciousness at a house party (17). The patient had a GCS of 6 and showed signs of bradycardia and respiratory depression. A serum specimen was positive for GHB at a concentration of 125 mg/L and for 0.13 g/100 mL ethanol. Following a 4.5-g dose of 1,4-BD, another female was found disoriented, incontinent of urine, and yelling and thrashing on the ground (13). In hospital, the patient showed signs of aggression, agitation, ataxia, and a labile level of unconsciousness. GHB was detected in the patient's serum at a concentration of 317 mg/L. In one report of a GHB-related fatality, an individual took large swigs from a "Gatorade" bottle that was being passed around at a bar. The subject passed out, lost bladder and bowel control, and subsequently died. Postmortem blood was positive for 400 mg/L GHB and 0.22 g/100 mL ethanol. In another study, a male consumed a 20-g dose of 1,4-BD. He was later found dead on the floor covered in vomitus and with signs of fecal contamination. Postmortem blood was positive for GHB at a concentration of 432 mg/L. A female became violently ill at a party after consuming a drink suspected of containing both GHB and GBL (18). She fell into a coma and subsequently died in the hospital. Antemortem blood collected in the hospital was positive for 510 mg/L GHB. A postmortem GHB concentration of 761 mg/L was detected in femoral blood in yet another reported fatal GHB intoxication case (19).

In the present study, however, numerous patients were potentially misdiagnosed as GHB intoxications or overdoses. The combined use of other drugs such as ethanol, illicit drugs, and sedative drugs such as meprobamate may also result in similar clinical signs and symptoms on hospital admission and subsequently may result in the misdiagnosis of these cases as GHB related.

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