γ-Hydroxybutyrate Serum Levels and Clinical Syndrome After Severe Overdose

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Study objective: We discuss a prospective case series of patients who present with a severe γ-hydroxybutyrate intoxication with confirmatory serum and urine γ-hydroxybutyrate levels.

Methods: Patients with a clinical suspicion of γ-hydroxybutyrate–like drug overdoses and a Glasgow Coma Scale score of 8 or lower were identified from July 1998 through January 1999. Serial serum specimens and a single urine specimen were collected. The levels of γ-hydroxybutyrate were performed by gas chromatography–mass spectrometry.

Results: All 16 suspected severe γ-hydroxybutyrate overdose patients had significant serum or urine levels of γ-hydroxybutyrate. Serum levels ranged from 45 to 295 mg/L, with a median of 180 mg/L (interquartile range [IQR] 235 to 118 mg/L). Patients who developed a Glasgow Coma Scale score of 3 had serum levels that ranged from 72 to 300 mg/L, with a median of 193 mg/L (IQR 242 to 124 mg/L). The time of awakening ranged from 30 minutes to 190 minutes, with a median of 120 minutes (IQR 150 to 83 minutes). Quantitative serum γ-hydroxybutyrate levels did not correlate with the degree of coma or the time to awakening. Urine levels ranged from 432 to 2,407 mg/L, with a median of 1,263 mg/L (IQR 1,550 to 796 mg/L). Mild transitory hypoventilation occurred in 5 of the 16 patients.

Conclusion: All of our patients with clinically suspected severe γ-hydroxybutyrate overdose were confirmed to have significant serum and urine levels of exogenous γ-hydroxybutyrate. They presented with severe coma that lasted 1 to 2 hours. Transient hypoventilation occurred in one third of these patients.

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INTRODUCTION

γ-Hydroxybutyrate is a naturally occurring molecule in the central nervous system and has a structure similar to that of γ-amino butyric acid.[1] When ingested, γ-hydroxybutyrate rapidly crosses the blood-brain barrier and, in low doses, produces euphoria. Higher doses consistently produce an alteration in the level of consciousness. These effects have led to its popularity as a recreational drug in the so-called rave scene and have inevitably led to cases of overdose and other medical problems.[2] The Drug Abuse Warning Network has estimated that γ-hydroxybutyrate–related emergency department (ED) visits increased from 55 in 1994 to 1,282 in 1998.[3]

Patients with a γ-hydroxybutyrate overdose present with a rapidly decreasing level of consciousness, relatively intact ventilation, and normal blood pressure. Physical examination of these patients usually reveals generalized hypotonia and minimal to no reflexes, nonreactive pupils of variable size, occasional myoclonic movements, and no response to verbal or painful stimuli. These patients are commonly rated a 3 to 5 on the Glasgow Coma Scale. Some patients present with confused agitation that alternates with profound coma. Hypoventilation and even apnea have been noted in several case reports of suspected γ-hydroxybutyrate–like drug overdose.

γ-Butyrolactone and 1,4-butanediol are 2 available precursors that are readily absorbed, are quickly metabolized to active γ-hydroxybutyrate, and result in similar effects. γ-Butyrolactone is metabolized in the serum by various lactonases, and 1,4-butanediol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase.[4] We describe the clinical features of patients with laboratory-confirmed γ-hydroxybutyrate intoxication.

MATERIALS AND METHODS

All patients in this study were treated in the ED of San Francisco General Hospital, a county ED with 75,000 visits yearly. The Committee on Human Research for the University of California–San Francisco approved this study.

Patients with a strong clinical suspicion of a γ-hydroxybutyrate–like drug overdose and a Glasgow Coma Scale score of 8 or lower were included in this study from July 1998 through January 1999. Patients with a traumatic cause of an altered mental status or with clinically obvious ethanol intoxication were excluded. Research assistants were on call with a 20- to 30-minute response time and aided in the collection of the clinical information, as well as the blood and urine samples. The attending physician on duty dictated the clinical management of the patient.

Demographic, clinical, and historical information was collected anonymously by using a standardized reporting instrument. The circumstances of the overdose, mode of transportation, out-of-hospital treatment, and history of other drug use were collected. Vital signs, including room air pulse oximetry and Glasgow Coma Scale score, were recorded every 30 minutes. An initial rectal temperature was recorded. Thirty milliliters of blood was collected in citrate-free blood tubes on arrival of the patient in the ED and every 30 minutes until the patient was alert or admitted to a hospital bed. Awakening was defined as achieving a Glasgow Coma Scale score of 15. A spot urine specimen was collected within 30 minutes of arrival. Blood samples were centrifuged and the serum and urine samples frozen at –16°C (4°F) until analysis.

Laboratory tests that were recommended but not required by the protocol included serum alcohol level, serum electrolyte levels, arterial blood gas level on room air, and a urine toxicology screen that included qualitative tests for barbiturates, amphetamines, benzodiazepines, and cocaine. Ketamine and dextromethorphan levels were not included in this screening.

The assay for γ-hydroxybutyrate concentration used the method of Ferrara et al,[5] which involves acid-catalyzed condensation of γ-hydroxybutyrate to γ-butyrolactone, extraction into chloroform, and analysis by gas chromatography–mass spectrometry with

selected-ion monitoring. Half the samples were split and analyzed by 2 laboratories using similar methods (Joseph J. Muto, BS, and Daniel T. Anderson, MS, Forensic Science Laboratories, Department of the Coroner, County of Los Angeles, CA). Mean levels were plotted for duplicate analyses. The mean SD for these paired samples was 30 mg/L.

The analysis included percentages, proportions, and SDs to describe the patient's characteristics. Pearson correlation coefficient was used to examine the correlation of serum levels to clinical features.

RESULTS

The age of the 16 study patients ranged from 20 to 39 years, with a median age of 25 years. Eleven were male patients; 15 patients came from 1 of several local clubs, and 12 came by ambulance. All 16 patients with a suspected severe γ-hydroxybutyrate overdose had increased levels of γ-hydroxybutyrate in their serum or urine, demonstrating exogenous use.

γ-Hydroxybutyrate levels and other data will be presented as the median (upper interquartile range [IQR] to lower IQR).

Fifteen patients had serum analyzed, and their initial levels ranged from 45 mg/L to 295 mg/L, with a median of 180 mg/L (IQR 235 to 118 mg/L). Patients who developed a Glasgow Coma Scale score of 3 had serum levels that ranged from 72 to 300 mg/L, with a median of 193 mg/L (IQR 242 to 124 mg/L).

For ease of display, we established a common known reference point (the time of awakening, Glasgow Coma Scale score=15) as time zero, which allowed plotting of serial serum levels versus time (Figure 1). This figure illustrates declining levels, with the patients regaining consciousness as levels decrease into the range of 75 to 150 mg/L. The rate of γ-hydroxybutyrate level decline was variable, as is expected for a zero-order process for

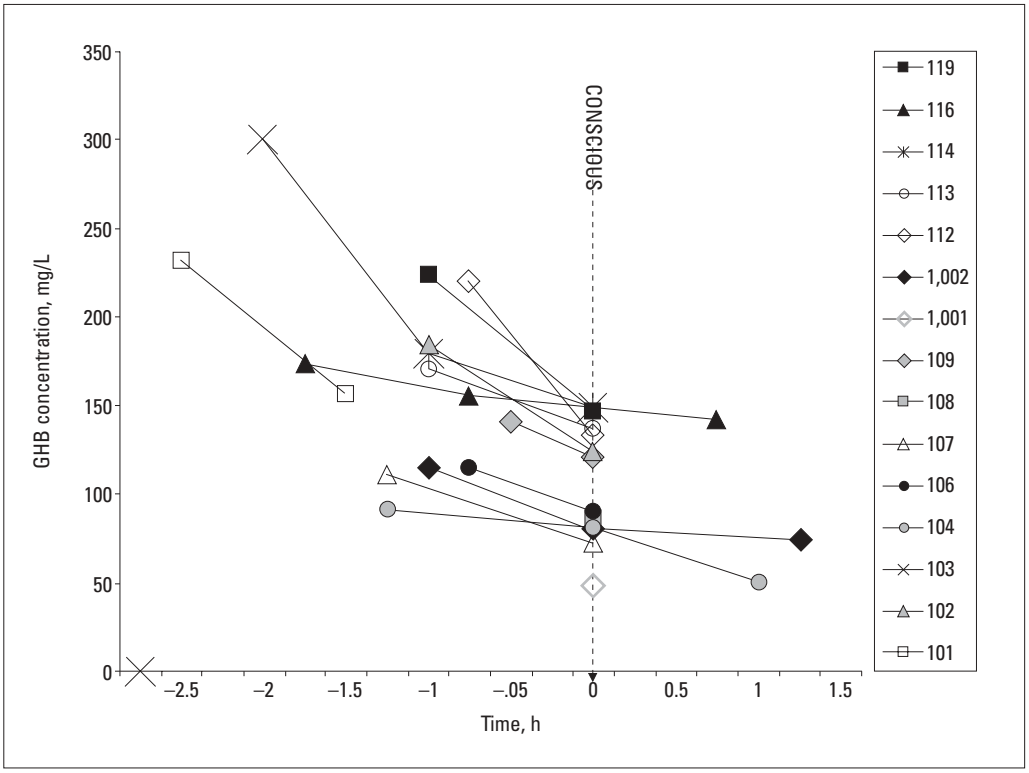

Figure 1.
γ-Hydroxybutyrate concentration after acute overdose (normalized to time=0 on regaining consciousness). ***GHB,*** *γ-Hydroxybutyrate.*

which the metabolic capacity has been exceeded (Figure 1).

All the available urine samples were positive for γ-hydroxybutyrate. The urine levels ranged from 432 to 2,407 mg/L, with a median of 1,263 mg/L (IQR 1,550 to 796 mg/L). The urine levels did not correlate with serum levels.

Five of the patients with elevated serum or urine γ-hydroxybutyrate had negative serum ethanol levels and no other drugs apparent on their toxicology screen. Four patients with γ-hydroxybutyrate only had a nadir Glasgow Coma Scale score of 3. Seven of the 16 patients had serum ethanol levels measured. Alcohol levels ranged from 12 to 295 mg/dL, with a median of 104 mg/dL (IQR 129 to 45 mg/L). The toxicology screen was positive in 2 patients. One patient had evidence of amphetamine and ethanol. The other patient's results were positive for opiates, benzodiazepines, amphetamines, cocaine, and ethanol.

The Glasgow Coma Scale measurement for our patients was 8 or below by definition, but the majority (11) developed a Glasgow Coma Scale score of 3 during their observation. The interval from arrival in the ED to awakening (Glasgow Coma Scale score=15) was calculated on the 14 patients who were not intubated and sedated. The peak serum γ-hydroxybutyrate level did not correlate with the time to awakening (Pearson correlation coefficient –0.04, P=.88, df=11). The time of awakening ranged from 30 to 190 minutes, with a median of 120 minutes (IQR 150 to 83 minutes) (Figure 2).

There were no patients with an initial recorded respiratory rate lower than 10 breaths/min. The room air pulse oximetry was less than 90% in 3 patients and was 95% to 100% in 13 others. Arterial blood gases were measured in 10 patients. The PCO_2 was 35 to 45 mm Hg in 5 patients, 45 to 55 mm Hg in 4 patients, and 56 mm Hg in 1 patient. The 2 patients who received endotracheal intubation had a Glasgow Coma Scale score of 3, with transient oxygen saturation below 90%.

There were a number of minor complications. Two patients were intubated. One self-extubated at 40 minutes. Another patient experienced a witnessed aspiration pneumonia during a difficult and unsuccessful intubation attempt by the paramedics. This patient was admitted and treated for aspiration pneumonia without endotracheal intubation.

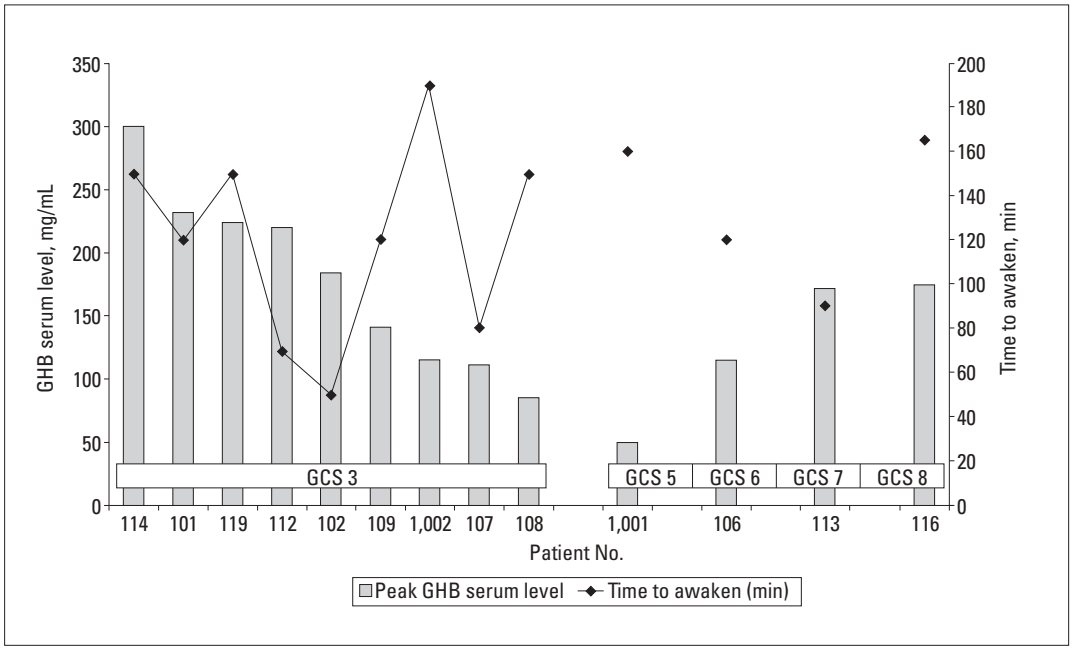

Figure 2.
Relationship of Glasgow Coma Score to peak γ-hydroxybutyrate serum level and time to awakening in nonintubated patients. ***GCS,*** *Glasgow Coma Scale score.*

Bradycardia without hypotension was noted in 5 of the 16 patients, and mild hypothermia (temperature <36.0°C [<96.8°F]) was noted in 6 patients. Both of these complications resolved spontaneously.

DISCUSSION

This is the first prospective series of patients experiencing γ-hydroxybutyrate overdose with confirmatory serum and urine γ-hydroxybutyrate levels. All of our patients with clinically suspected severe γ-hydroxybutyrate–like overdose had increased serum or urine levels of exogenous γ-hydroxybutyrate. Confirmatory levels are of little use to the physician but are useful in defining this subpopulation of overdose patients. It may also be useful for defining the appropriate body fluid for future rapid assays.

There are few human studies to correlate dosing and serum levels with clinical effects. One human study of intravenous γ-hydroxybutyrate anesthesia correlated drug levels with clinical effect.[6] Serum γ-hydroxybutyrate levels of 150 mg/L or less had "occasional eye opening and spontaneous movement," while levels higher than 260 mg/L correlated with profound coma. A 25- to 50-mg/kg oral dose of γ-hydroxybutyrate yielded serum levels of 35 to 98 mg/L and produced only mild transient drowsiness.[7] Serum γ-hydroxybutyrate levels decreased rapidly throughout several hours and were undetectable 8 hours after the administration of 75 to 100 mg/kg.[8]

There have been a few case reports of nonfatal γ-hydroxybutyrate overdoses that included serum γ-hydroxybutyrate levels. One patient with a Glasgow Coma Scale score of 3 had a serum γ-hydroxybutyrate level of 101 mg/L,[9] and another who presented with a mixed overdose of γ-hydroxybutyrate and ethanol had a γ-hydroxybutyrate level of 125 mg/L.[10] Another series of 8 patients without a recorded level of consciousness had a mean serum γ-hydroxybutyrate level of 184 mg/L.[11] Serum γ-hydroxybutyrate levels in the present study were similar to those of these studies (Figure 1). The γ-hydroxybutyrate levels in clinical overdose associated with awakening seem to be lower than those reported in the anesthesia literature.[6] The peak serum levels in clinical overdose probably occur before hospital arrival. The combination of other drugs and the different setting (anesthesia versus recreational use) would also have an effect on the expected serum level.

Urine levels of γ-hydroxybutyrate have been reported after therapeutic use, in overdose, and postmortem.[8,9,12,13] Serial samples of urine have demonstrated a rapid decrease in γ-hydroxybutyrate concentrations throughout several hours, becoming undetectable in 12 hours.[8,9,12] Our study demonstrated significant urine γ-hydroxybutyrate levels simultaneous with increased serum levels when the patient was symptomatic. The concentrations of γ-hydroxybutyrate consistently detected in the urine and its longer duration of detection make this the body fluid of choice for qualitative testing of a γ-hydroxybutyrate–like drug.

This group of patients was young and primarily male. More than half our patients were found to be using γ-hydroxybutyrate in conjunction with other drugs, most commonly alcohol. This study has demonstrated that patients can develop a severe coma with γ-hydroxybutyrate alone.

Some of the limitations of the study included our inability to differentiate between the ingestion of γ-hydroxybutyrate, γ-butyrolactone, or 1,4-butanediol. Also, our study did not test for the presence of ecstasy (MDMA [3,4 methylenedioxymethamphetamine]), ketamine, or dextromethorphan.

All of our patients with clinically suspected severe γ-hydroxybutyrate–like overdose were confirmed to have increased serum and urine levels of γ-hydroxybutyrate. They presented with a coma that lasted 1 to 2 hours. A Glasgow Coma Scale score of 3 was possible with γ-hydroxybutyrate alone. Mild transient hypoventilation occurred in one third of the patients.

We thank the numerous University of California–San Francisco medical students who stayed up late to complete this study. We would also like to acknowledge the contributions of Joseph Muto, BS, and Dan Anderson, MS, of the Forensic Science Laboratories, Department of the Coroner, County of Los Angeles, for the analysis of our specimens.

Author contributions: KAS and JED conceived the study and designed the trial. KAS, JED, and RLC supervised the conduct of the trial and data collection. RLC and RL undertook recruitment of participating patients and managed the data, including quality control. KAS and RLC provided statistical advice on study design and analyzed the data. KAS drafted the manuscript, and all authors contributed substantially to its revision. KAS takes responsibility for the paper as a whole.

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REFERENCES

1. Nicholson KL, Balster RL. γ-Hydroxybutyrate: a new and novel drug of abuse. *Drug Alcohol Depend.* 2001;63:1-22.

2. Chin RL, Sporer KA, Cullison B, et al. Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med.* 1998;31:716-722.

3. Club drugs, 2001 update. Dawn Briefing. Substance Abuse and Mental Health Services Administration Web site. October 2002. Available at: http://www.samhsa.gov/oas/2k2/DAWN/clubdrugs2k1.pdf. Accessed March 15, 2003.

4. Zvosec DL, Smith SW, McCutcheon JR, et al. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med.* 2001;344:87-94.

5. Ferrara SD, Tedeschi L, Frison G, et al. Therapeutic gamma-hydroxybutyric acid monitoring in plasma and urine by gas chromatography-mass spectrometry. *J Pharm Biomed Anal.* 1993;11:483-487.

6. Helrich M, McAsian T, Skolnick S. Correlation of blood levels of 4-hydroxybutyrate with state of consciousness. *Anesthesiology.* 1964;25:771-775.

7. Palatini P, Tedeschi L, Frison G, et al. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol.* 1993;45:353-356.

8. Hoes MJ, Vree TB, Guelen PJ. Gamma-hydroxybutyric acid as hypnotic: clinical and pharmacokinetic evaluation of gamma-hydroxybutyric acid as hypnotic in man. *Encephale.* 1980;6:93-99.

9. Dyer J, Isaacs S, Keller K. Gamma-hydroxybutyrate (GHB) induced coma with serum and urine drug levels [abstract]. *Vet Hum Toxicol.* 1994;36:348.

10. Louagie HK, Verstraete AG, De Soete CJ, et al. A sudden awakening from a near coma after combined intake of gamma-hydroxybutyric acid (GHB) and ethanol. *J Toxicol Clin Toxicol.* 1997;35:591-594.

11. Mahon K, Tomaszewski C, Tayal V. Emergency department presentation of serum confirmed γ-hydroxybutyrate ingestions. *Acad Emerg Med.* 1999;6:395-396.

12. Stephens BG, Baselt RC. Driving under the influence of γ-hydroxybutyrate? *J Anal Toxicol.* 1994;18:357-358.

13. Suner S, Szlatenyi CS, Wang RY. Pediatric gamma-hydroxybutyrate intoxication. *Acad Emerg Med.* 1997;4:1041-1045.