Articles

Acute Poisoning From γ-Hydroxybutyrate in California

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We report a series of 5 representative patients in California who experienced adverse reactions from the illicitly marketed substance γ-hydroxybutyrate (GHB). The drug is a putative neurotransmitter marketed as a growth hormone releaser for bodybuilders. The most commonly reported symptoms included abrupt drowsiness, dizziness, and a "high." Other effects were headache, nausea, vomiting, myoclonic jerking, and short-term coma. There have been no reported deaths. If product use is discontinued, full recovery with no long-term side effects is universal. No clear dose-response effect was observed; this may be attributable to differences in susceptibility, wide variations in doses taken by the same person, or the coingestion of other substances. Case interviews confirm that, despite being banned by the US Food and Drug Administration, GHB is still widely available in the underground drug market. Athletes and bodybuilders may take drugs for which there are claims of improved performance or body image. Physicians should be alert for signs of GHB poisoning in emergency department and clinic patients.

(Chin MY, Kreutzer RA, Dyer JE: Acute poisoning from γ-hydroxybutyrate in California. West J Med 1992 Apr; 156:380-384)

On August 7, 1990, the San Francisco Regional Poison Control Center notified the US Food and Drug Administration (FDA) and the California Department of Health Services (DHS) of acute poisonings with gastrointestinal, respiratory, and central nervous system symptoms associated with the consumption of the illicitly marketed substance γ-hydroxybutyrate (GHB).[1] The drug is a putative neurotransmitter that was sold to bodybuilders as a "dramatic new growth hormone releaser." It was also marketed as a health aid to dieters and persons with insomnia. Three months later, on November 8, 1990, the FDA warned consumers to discontinue use of the illegally marketed substance. The state health departments of California and Florida issued similar warnings and banned the sale of GHB in their states. By November 30, 1990, there were 25 reported cases of acute poisoning related to GHB in California (17 from San Francisco); 15 cases in Georgia; 7 in Florida; 3 in South Carolina; 2 each in Arizona and Minnesota; and 1 each in Texas, Ohio, Virginia, and the District of Columbia.[1]

A paper summarizing the San Francisco cases has recently been published.[2] We describe in greater detail the histories of representative patients in whom adverse reactions were associated with the use of GHB. We compare the findings with information in the published literature and examine some of the issues implied by the case series. Table 1 summarizes some of the known product names and distributors of GHB.

Biochemistry and Metabolism

The natural metabolic role of GHB is not well understood, and the psychophysiologic effects are described in an extensive body of literature that is wide-ranging but inconclusive.

γ-Hydroxybutyrate (chemical formula $HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2OH$) is a four-carbon molecule that is found naturally in the central nervous system and, in higher concentrations, in peripheral tissues.[3] It has a structure much like γ-aminobutyric acid (GABA), which is better understood than GHB and acts as an inhibitory neurotransmitter in vivo. γ-Aminobutyric acid is catabolized by transamination to succinate semialdehyde, which is then oxidized to succinate[4] (Figure 1). Brain tissue is capable of reducing succinate semialdehyde to GHB. Concentrations of both GHB and GHB-oxidizing enzymes are 15 to 20 times higher in kidney, heart, skeletal muscle, and brown fat than in the central nervous system.[5] The significance of this finding is not known, however.

γ-Hydroxybutyrate exhibits the properties of a neurotransmitter in humans and has a wide range of purported pharmacologic effects.[6] Hippocampal receptors for GHB have been isolated; synaptic transmission and regulation have been demonstrated.[6] Nevertheless, some investigators think that GHB has not yet fulfilled all the criteria needed to be considered a bona fide neurotransmitter because its effects have not been associated with specific neuronal tracts. Research in this area continues.[6,7] γ-Hydroxybutyrate crosses the blood-brain barrier. Some studies have shown that it can double brain dopamine and dynorphin levels and that this pharmacologic effect can be blocked experimentally by naloxone, dextro-amphetamines, and caffeine.[8,9] Because it in-

TABLE 1.—*Products and Distributors of γ-Hydroxybutyrate*

Common Product Names	*Currently Known Distributors*
γ-Hydroxybutyric acid	Biosky
Sodium oxybate	Biotonic Formulary
Sodium oxybutyrate	Hi-Tech Bodybuilding
γ-Hydroxybutyrate sodium	
γ-OH	
4-Hydroxy butyrate	
γ-Hydrate	
Somatomax PM	

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ABBREVIATIONS USED IN TEXT

DHS = California Department of Health Services
FDA = US Food and Drug Administration
GABA = γ-aminobutyric acid
GHB = γ-hydroxybutyrate
REM = rapid-eye-movement

creases the level of dopamine in certain areas of the brain, GHB has been used experimentally to treat auxiliary symptoms of narcolepsy (such as myoclonus and cataplexy) associated with dopamine deficiency.

The role of GHB as an agent to increase muscle mass is ambiguous. Growth hormone release is known to be greater during slow-wave sleep, a pattern of sleep that is facilitated by GHB. This short-term effect (half-life approximately one to two hours) has been demonstrated by some investigators.[10] It is not clear what long-term effects this may have on actual muscle growth or mass.

The clinical effects of GHB are well documented—short-term amnesia and hypotonia with an oral dose of 10 mg per kg, and drowsiness and sleep with 20 to 30 mg per kg. γ-Hydroxybutyrate promotes rapid-eye-movement (REM) sleep in depressed and narcoleptic patients and induces non-REM sleep in normal persons.[11] Studies on the effects of anesthetic use in humans indicate that an intravenous dose of 50 to 70 mg per kg produces hypnosis but little analgesic effect.[12] The same dose may cause mild hypotonia, bradycardia, and bradypnea, as well as nausea, vomiting, and Cheyne-Stokes respiration. Typically, an intravenous dose of 65 mg per kg induces sleepiness within five minutes descending into a comatose state that lasts one to two hours or more, after which there is rapid awakening.[13] Higher doses may lead to severe cardiac and respiratory depression and other neurodepressive sequelae.[14,15] Studies in animals show that when plasma levels of GHB exceed 500 μg per ml, myoclonic seizures almost always result. (In humans, oral doses in mg per kg approximate plasma levels expressed in μg per ml.) No published trials have been carried out in humans at this dosage.

γ-Hydroxybutyrate may potentiate other endogenous opiates or exogenous narcotics, and it is potentiated by alcohol, benzodiazepines, and other neuroleptics.[15,16] While dextroamphetamine, naloxone, trimethadone, and valproate antagonize the electroencephalographic changes produced by GHB, no clinically effective GHB antagonists are consistently described in the published literature.

In light of these many important effects, it is important that physicians be familiar with the clinical picture that GHB poisoning presents.

Methods

As of November 28, 1990, 25 cases of GHB toxicity had been reported to poison control centers in California. Because of the nature of poison control center telephone consultations, information for retrospective follow-up is not always available. Follow-up information was obtained for only 14 of the 25 cases. In 10 of the 14 traceable cases, the patient or the physician was contacted successfully. All 10 contacts ultimately cooperated by either answering a telephone questionnaire or granting DHS access to the medical chart (Table 2). Five of these cases were previously summarized as index cases.[2*] This report gives more detailed information on five cases (two previously summarized and three new cases) that illustrate the spectrum of serious illness seen.

*Alfredo Quattrone, PhD, and Alan Slagle, PharmD, provided information on some of the index cases.

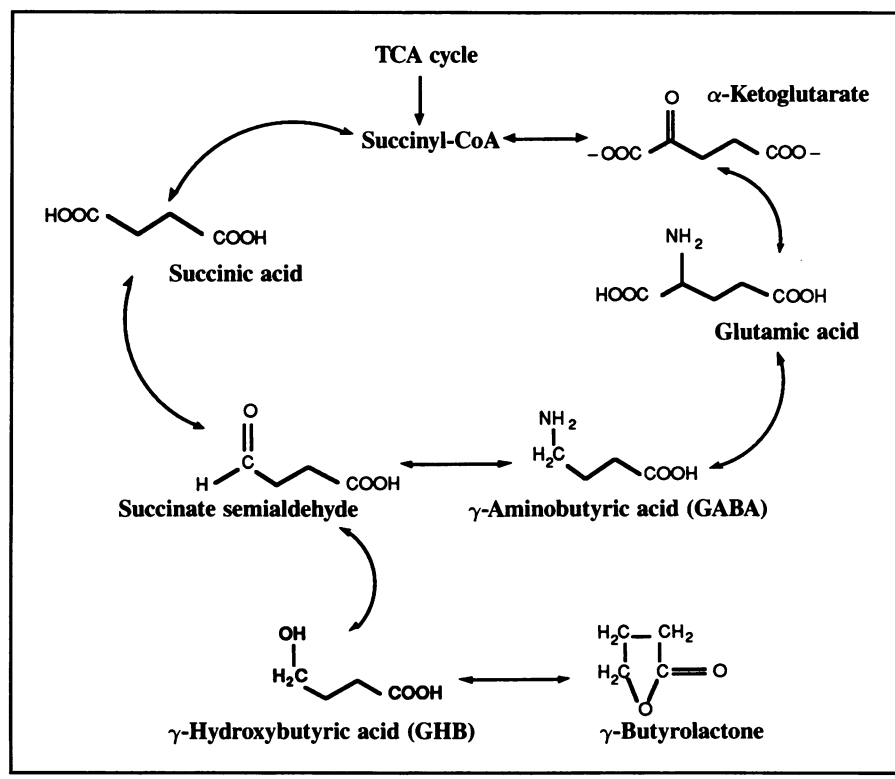

Figure 1.—The biochemical pathway of γ-hydroxybutyrate metabolism is shown. CoA = coenzyme A, TCA = tricarboxylic acid

TABLE 2.– *Summary of 10 Abstracted Cases Reported to California Poison Control Centers*

Case	Dose	Adverse Reaction: Drowsiness	Dizziness	"High"	Headache	Confusion	Nausea	Vomiting	Diarrhea	Incontinence/ Urgency	Trouble Breathing	Uncontrollable Shaking	Temporary Amnesia	Seizure	Coma	Other*	Other Substances Ingested
1	Unknown	X	X	X	X	--	--	--	--	X	--	--	X	--	--	--	--
2	~2 tsp	X	X	X	--	X	--	--	--	--	X	X	--	--	--	X	Hydrocodone bitartrate and acetaminophen
3	Unknown	X	X	X	X	X	X	X	X	X	--	--	--	--	--	--	Alcohol
4	~1 tsp	X	--	X	X	--	X	--	--	--	X	X	--	--	--	--	--
5	Unknown	X	--	--	--	X	--	X	--	--	--	X	--	X	X	--	Alcohol
6	~1 tsp	X	--	X	--	--	--	--	--	--	--	--	X	X	--	--	--
7	4 tsp in 8 h	X	X	X	--	X	--	--	--	X	X	X	--	X	X	--	--
8	2 tsp	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--
9	1 tsp	X	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--
10	1.5 tsp	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Diphenhydramine hydrochloride

*Hallucinations, moaning, or babbling.

Report of Cases

Case 1

A previously healthy 39-year-old woman bought GHB from a health food store and took a 1-teaspoon dose in September 1990. Within 10 minutes she experienced numbing of the legs, dizziness, and a tight chest. She was helped to bed and did not take GHB again for three weeks. Then she began taking a half-teaspoon of GHB granules in juice almost daily and did so for a month.

In one instance she took three or four doses during the course of a single day. The last dose, taken at bedtime, triggered the reported adverse response. She experienced a "high" (similar to the high she had experienced from past marijuana use), the "jabbers" (pressured speech and ebullience), intense drowsiness, confusion, difficulty breathing, and uncontrollable twitching in her arm. Her children reported that, when they found her, her eyes were rolled back, her body was tense, and she was hallucinating. Her medical chart indicates she was twitching for 45 minutes. She had no previous history of seizures.

She was seen in an emergency department and admitted to hospital overnight. Her pulse, blood pressure, and respirations were normal. A physical examination was unremarkable except for alternating wakeful and sleepy states with irregular leg twitches. Laboratory values included a leukocyte count of 10.8×10^9 per liter (10,800 per μl), hemoglobin 133 grams per liter (13.3 grams per dl), hematocrit 0.40 (40.3%), and thrombocyte count 258×10^9 per liter (258×10^3 per μl). Electrolyte levels were sodium 142, potassium 3.6, and chloride 104 mmol per liter. Bicarbonate, creatinine, and blood urea nitrogen levels were not noted in her chart, and no blood gas determinations were done. She was taking ibuprofen and a combination product containing hydrocodone bitartrate and acetaminophen (Vicodin) around the time she ingested GHB. Although she drinks alcoholic beverages and had previously used illicit drugs, she denied ingesting alcohol or using drugs when taking GHB. She experienced a full recovery with no lasting symptoms.

Case 2

The patient, a previously healthy 26-year-old woman who is a bodybuilder, acquired GHB from a friend at the gymnasium where she trained. On October 28, 1990, she took the dose recommended on the bottle (one scoop or about 1 teaspoon) and went to sleep; she was ill the next morning. Four days later, she attended a party and drank a glass of wine. Afterward, she took GHB again; she was ill that night and for the next two days. She experienced vomiting, drowsiness, headache, nausea, diarrhea, confusion, dizziness, a "high" ("felt like Quaaludes or Valium"), and intermittent lack of bladder control. She did not go to a hospital and was not seen by a physician. She had no history of medical problems. At the time she took GHB, she was taking birth control pills and was otherwise "totally drug free." Since discontinuing GHB, she has been asymptomatic.

Case 3

The patient, a 28-year-old woman, was at a nightclub when she ingested GHB with some mixed drinks. She experienced confusion and uncontrollable shaking, followed by a seizure and then coma. A witness stated that she was banging her head on a wall before becoming unconscious. The patient vomited and was suctioned before being transported to hospital. Paramedics reported that she alternated between combativeness and unresponsiveness during transport.

She arrived in the emergency department with good respiratory effort but long apneic periods. On admission, she was restrained, intubated, ventilated, lavaged, and given activated charcoal. Laboratory values included a leukocyte count of 10.9×10^9 per liter (10,900 per μl), hemoglobin 119 grams per liter (11.9 grams per dl), hematocrit 0.37 (36.9%), and thrombocyte count 306×10^9 per liter (306×10^3 per μl). Blood chemistry values included sodium 143, potassium 3.9, bicarbonate 30, and chloride 110 mmol per liter; creatinine 88.4 μmol per liter (1.0 mg per dl); and blood urea nitrogen 3.57 mmol per liter (10 mg per dl). Initial arterial blood gas determinations with 95.5% oxygen saturation were pH 7.56, HCO_3 19.8 mmol per liter, Pco_2 21.9 mm of mercury, and Po_2 292.8 mm of mercury. Radiographic, electroencephalographic, computed tomographic, and magnetic resonance imaging scans were unremarkable. Past medical problems included anemia, asthma, and migraine headaches. The patient's toxicologic screen was negative, but her blood alcohol level was 80 mg per dl. No

adverse effects have been observed since she stopped taking GHB.

Case 4

A 47-year-old man bought GHB at a health food store after receiving a mailer advertising its effectiveness as a soporific. He said he took 1 teaspoon with a potassium supplement and water "every once in a while" for approximately two months. One day he took 1 teaspoon every two hours for a total dose of 4 teaspoons. Approximately a half hour after his last dose, his wife found him immobile and having difficulty breathing. Other symptoms included heavy drowsiness, confusion, a "high," urinary urgency, uncontrollable shaking (paramedics noted seizure), dizziness, and coma. The patient noted that on other occasions GHB had made him more talkative. In the emergency department he was initially lethargic but later became awake and alert. His physical examination, laboratory work, electrocardiogram, and contrast computed tomographic scan were normal, and he was released three hours later. A follow-up neurologic examination two weeks later was normal, with no focal findings and a normal electroencephalogram. The patient has had no symptoms since discontinuing GHB use.

This patient may have had a seizure 20 years ago after drinking excessively and taking a "few pills." He was seen by a physician at that time and had a normal electroencephalogram. He took no medications, is not aware of any other seizures in his life, and has no family history of seizures. His neurologist noted that his general health has been excellent and he has had no significant head injuries or fainting spells.

Case 5

The patient, a 23-year-old man, took 1 teaspoon of GHB as a growth hormone releaser. Four hours later, he was brought into the emergency department vomiting and unresponsive except to pain. His pupils were small and sluggish. On admission his blood pressure was 150/90 mm of mercury, pulse 60 beats per minute, and respirations 16 per minute. The physical examination was unremarkable and the laboratory findings undiagnostic. At this time a complete blood count revealed a leukocyte count of 12.3×10^9 per liter (12,300 per μl), hemoglobin 148 grams per liter (14.8 grams per dl), hematocrit 0.425 (42.5%), and thrombocyte count 196×10^9 per liter (196×10^3 per μl). Electrolyte levels were sodium 145, potassium 4.0, bicarbonate 5, and chloride 108 mmol per liter; creatinine 88.4 μmol per liter (1.0 mg per dl); blood urea nitrogen 5.35 mmol per liter (15 mg per dl); and glucose 11.4 mmol per liter (206 mg per dl). Arterial blood gas determinations with 97% oxygen saturation were pH 7.44, Pco_2 43 mm of mercury, Po_2 83 mm of mercury, and HCO_3 29 mmol per liter. Repeat electrolyte measurements four hours later indicated no significant changes except for an elevated bicarbonate of 32 mmol per liter. There was no evidence of alcohol or drugs in his blood or urine. The patient was discharged asymptomatic six hours after admission.

Case 6

In addition to the cases reported to the California poison control centers, DHS reports the case of a 77-year-old man who died in October 1990 of massive gastrointestinal hemorrhage caused by esophageal varices and marked fatty metamorphosis of the liver. In addition to various other over-the-counter medications (tryptophan, Prostex, Motion Mate, and Nutrasleep), he was also taking GHB. He was advised to do so by a health food store clerk who suggested it would restore the muscle tone that the patient perceived he was losing. It is unclear whether the GHB played a role in his death.

Discussion

These cases illustrate the adverse reactions associated with the uncontrolled, self-directed use of GHB in varying doses. Table 2 summarizes the symptoms recorded in 10 abstracted cases reported to California poison control centers.

No reliable estimate of GHB consumption in the general population is available. The number of cases with adverse reactions reported is likely to be only a fraction of the actual number of such cases and even a smaller fraction of all users. Indeed, some patients who were contacted indicated that they had experienced unreported adverse reactions before the incident that precipitated the case report.

There appears to be a tremendous potential for abuse of GHB as an illicit drug. All interviewed patients reported a pleasurable sensation or "high." Several explicitly noted that one reason they continued taking the drug was because it made them "feel good." At least one said that, as of December 1990, some of her friends could still obtain GHB "underground" (prices range from $50 to more than $80 for a 100-gram bottle). In the eastern United States, GHB is already gaining popularity as an illicit street drug. In addition, GHB has been marketed for young people and athletes. The abuse of steroids among persons seeking improved body image or athletic performance is well documented[17,18] and has created a lucrative and growing market for these substances. Finally, the case of the 77-year-old man who was taking GHB to improve a body ravaged by age and disease illustrates that the vulnerable population may not be restricted to the young.

Researchers working with narcoleptic patients consider GHB a relatively harmless and effective drug. Several points, however, must be kept in mind. First, and perhaps most important, the therapeutic effects of GHB for a person with narcolepsy—the induction of major symptoms of narcolepsy at night, when they can be better controlled—are considered adverse effects in a normal person. Second, the side effects, termed "mild" by researchers comparing them to the extreme debilitation caused by narcolepsy, would be considered unacceptable in a normal person. Third, differences between normal and narcoleptic persons also may account for the different reactions to equivalent doses, although responses to equivalent doses vary considerably even for the same person. Fourth, the quality (reagent vs pharmaceutical grade) and quantity of GHB ingested is rigorously controlled and monitored in clinical trials. For casual users, however, there is no accurate method of assessing the amount or quality of GHB consumed. No doubt the actual size of a reported "1-teaspoon" dose varied widely.

Early suspicions that the adverse reactions were caused by contamination of retail lots seem unfounded. The symptoms experienced are compatible with documented physiologic effects of GHB. Toxicologic screens and the clinical course of the patients admitted to hospital seem to rule out the diagnosis of exposure to other known drugs. One lot of GHB recovered by the FDA was analyzed using capillary and

column gas chromatography. The results indicated that GHB was present as a sodium salt at 97% to 98% purity.

Conclusions

The drug GHB is a substance with documented clinical actions consistent with severe neurotoxicity. In many cases, intensive medical care has been required to counteract adverse reactions. Health professionals must understand that, despite FDA interdiction, this substance is still available to, marketed for, and used by bodybuilders, dieters, and persons suffering from insomnia. Patients should be told that compounds bought in health food or natural food stores may be drugs that can substantially alter body functions and adversely affect health. There are now over 40 reported cases of GHB poisoning in California (and additional cases in other states), and several of the persons involved in these cases procured the substance since it was banned on November 8, 1990.

The prognosis for those who experience GHB poisoning is quite good. There are no documented or anecdotal reports of long-term adverse effects or fatalities, nor any evidence for physiologic addiction. Current investigative efforts are directed toward interdiction, continued case surveillance with clinical description, additional study to understand how widespread GHB use may be, and efforts to disseminate accurate information regarding the adverse health effects of illicit GHB use.

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