

## ADVERSE EVENTS, INCLUDING DEATH, ASSOCIATED WITH THE USE OF 1,4-BUTANEDIOL

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## ABSTRACT

**Background** 1,4-Butanediol is an industrial solvent that, when ingested, is converted to  $\gamma$ -hydroxybutyrate, a drug of abuse with depressant effects, primarily on the central nervous system. After reports of toxic effects of  $\gamma$ -hydroxybutyrate and its resultant regulation by the federal government, 1,4-butanediol and  $\gamma$ -butyrolactone, another precursor of  $\gamma$ -hydroxybutyrate and an industrial solvent, began to be marketed as dietary supplements. We investigated reports of toxic effects due to the ingestion of 1,4-butanediol and reviewed the related health risks.

**Methods** From June 1999 through December 1999, we identified cases of toxic effects of 1,4-butanediol involving patients who presented to our emergency departments with a clinical syndrome suggesting toxic effects of  $\gamma$ -hydroxybutyrate and a history of ingesting 1,4-butanediol and patients identified through public health officials and family members. We used gas chromatography–mass spectrometry to measure 1,4-butanediol or its metabolite,  $\gamma$ -hydroxybutyrate, in urine, serum, or blood.

**Results** We identified nine episodes of toxic effects in eight patients who had ingested 1,4-butanediol recreationally, to enhance bodybuilding, or to treat depression or insomnia. One patient presented twice with toxic effects and had withdrawal symptoms after her second presentation. Clinical findings and adverse events included vomiting, urinary and fecal incontinence, agitation, combativeness, a labile level of consciousness, respiratory depression, and death. No additional intoxicants were identified in six patients, including the two who died. The doses of 1,4-butanediol ingested ranged from 5.4 to 20 g in the patients who died and ranged from 1 to 14 g in the nonfatal cases. In some cases there was evidence of addiction and withdrawal.

**Conclusions** The health risks of 1,4-butanediol are similar to those of its counterparts,  $\gamma$ -hydroxybutyrate and  $\gamma$ -butyrolactone. These include acute toxic effects, which may be fatal, and addiction and withdrawal. (N Engl J Med 2001;344:87-94.)

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**T**HE industrial solvent 1,4-butanediol, when ingested, is rapidly converted to  $\gamma$ -hydroxybutyrate, a neuromodulator with depressant effects, primarily on the central nervous system.  $\gamma$ -Hydroxybutyrate is a metabolite of  $\gamma$ -aminobutyric acid (GABA), which is an inhibitory neurotransmitter (Fig. 1). 1,4-Butanediol and  $\gamma$ -hydroxybutyrate occur endogenously in humans in trace amounts.<sup>1</sup>  $\gamma$ -Hydroxybutyrate was marketed to bodybuilders in

the 1980s as a purported aid to muscle building and fat loss. Because of its euphoric and sexual effects, it became a drug of abuse. Reports of the drug's toxicity resulted in warnings about health risks and a federal prohibition of the manufacture, sale, and use of  $\gamma$ -hydroxybutyrate outside the context of clinical trials supervised by physicians and approved by the Food and Drug Administration (FDA).<sup>2,3</sup>

Subsequently,  $\gamma$ -butyrolactone, another precursor of  $\gamma$ -hydroxybutyrate and an industrial solvent, and 1,4-butanediol began to be marketed as "natural," "nontoxic" dietary supplements. Reports of toxic effects and deaths led the FDA to issue warnings about both compounds and to designate both as illicit and unapproved new drugs.<sup>4,5</sup> 1,4-Butanediol was declared a class I health hazard, with toxic effects including vomiting, respiratory depression, loss of consciousness, seizures, and death.<sup>5</sup>

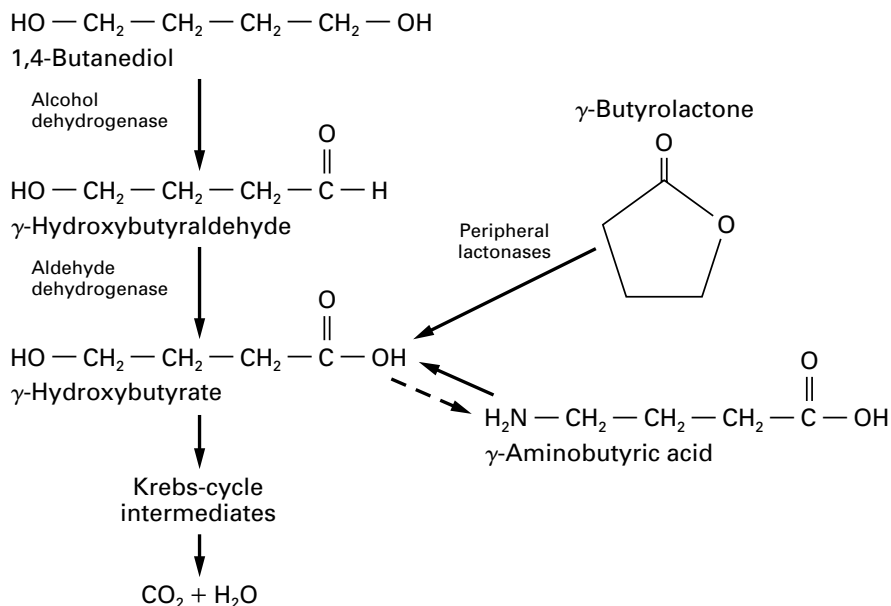
The toxic effects of 1,4-butanediol on humans have been described only in abstracts,<sup>6,7</sup> one case report,<sup>8</sup> one report of mass intoxication at a "rave party,"<sup>9</sup> and one 1948 German-language report of coma in seven patients, two of whom died, who had been given 15 g of 1,4-butanediol as a laxative.<sup>10</sup> We assessed nine episodes of toxic effects of 1,4-butanediol in eight patients, two of whom died. The toxic effects of 1,4-butanediol and the health risks associated with it are similar to those of  $\gamma$ -butyrolactone and  $\gamma$ -hydroxybutyrate, which is the active metabolite of all three compounds; some users ingest these compounds interchangeably.

## METHODS

From June 1999 through December 1999, we identified six cases of toxic effects of 1,4-butanediol in patients who presented to our emergency departments with a clinical syndrome suggesting the toxic effects of  $\gamma$ -hydroxybutyrate and a history of ingesting 1,4-butanediol; we identified three other cases through public health officials and family members who provided historical data, hospital records, and autopsy reports. The study was approved by the relevant institutional review board, and consent was obtained from the patients or their representatives when necessary.

We used gas chromatography–mass spectrometry to measure the concentrations of 1,4-butanediol and  $\gamma$ -hydroxybutyrate in the body fluids of the patients and in the products containing 1,4-butanediol.<sup>11</sup> We calculated the approximate doses of 1,4-butanediol taken by each patient on the basis of reports by the patients or by others

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**Figure 1.** Metabolism of 1,4-Butanediol.

1,4-Butanediol is metabolized in the liver and the brain, first by alcohol dehydrogenase to  $\gamma$ -hydroxybutyraldehyde (an intermediate) and then by aldehyde dehydrogenase to  $\gamma$ -hydroxybutyrate.  $\gamma$ -Butyrolactone is metabolized to  $\gamma$ -hydroxybutyrate by lactonases in the blood.  $\gamma$ -Hydroxybutyrate is a metabolite of  $\gamma$ -aminobutyric acid. It is catabolized in the brain and peripheral organs, enters the Krebs cycle, and is eliminated from the body as carbon dioxide and water. The dashed arrow indicates limited conversion of  $\gamma$ -hydroxybutyrate back to  $\gamma$ -aminobutyric acid at physiologic levels; this pathway may be important in cases of high concentrations of  $\gamma$ -hydroxybutyrate, such as those seen in cases of ingestion.

who were present at the time of ingestion, using the concentrations of 1,4-butanediol listed on the products' packaging or detected by gas chromatography–mass spectrometry in the uningested portions of the products.

## CASE REPORTS

### Patients 1 and 2

Patient 1 was a previously healthy 32-year-old man who ingested approximately 200 ml of a dietary supplement called Thunder Nectar for its purported ability to increase libido; his 29-year-old wife (Patient 2) ingested 110 to 140 ml of the same product (Table 1). They had obtained it from a friend who had purchased it at a sports-nutrition store and told them it was nontoxic. The bottle was unlabeled; they received no dosage instructions. The woman's last memory was that 15 minutes after drinking the Thunder Nectar, she felt "lightheaded" and sat down in a chair. She awoke seven hours later, on the floor with her husband, covered with vomitus and with evidence of fecal incontinence. Her husband was dead. An autopsy revealed only pulmonary edema. There was no evidence of aspiration.

### Patient 3

Patient 3 was a 42-year-old woman who ingested 30 to 60 ml of a dietary supplement called NRG3 to treat insomnia. She had a history of depression, for which she was taking sertraline. Her boyfriend reported that she was talking with him three hours after taking the NRG3 and was sleeping when he left one hour thereafter; she was dead when he returned eight hours later. The blood concentrations of sertraline were within the range of postmortem blood

concentrations in patients taking therapeutic doses.<sup>12</sup> An autopsy revealed only pulmonary edema. There was no evidence of aspiration.

### Patient 4

Patient 4 was a 22-year-old man who ingested 90 to 120 ml of a dietary supplement called Serenity, reportedly to increase his "energy." One hour later, friends found him unconscious. When the paramedics arrived, he was vomiting and unresponsive to painful stimuli, and he had bradycardia, hypotension, respiratory depression, and urinary incontinence. He was intubated and received mechanical ventilation, recovered fully within hours, and was discharged.

### Patient 5

Patient 5 was a 26-year-old man who, while talking on the telephone to his brother, told him that he had just ingested a dietary supplement called NRG3; he mentioned no amount. His brother noticed dysarthria, heard him fall to the floor, and was unable to elicit any further response. Paramedics found him unconscious, with food burning on the stove and smoke throughout the house. In the emergency department, he had tachycardia and hypertension. He was intubated to protect the airway and received mechanical ventilation. He recovered several hours later and was transferred for psychiatric evaluation for possible drug dependence.

The patient had a history of depression and abuse of multiple substances, including two years of ingesting increasing and ultimately around-the-clock doses of 1,4-butanediol and  $\gamma$ -butyrolactone supplements for bodybuilding and  $\gamma$ -hydroxybutyrate–related addiction (we refer to addiction to one or more of these compounds as " $\gamma$ -hydroxybutyrate–related addiction"). Cessation of the supplements caused withdrawal symptoms including auditory hallu-

TABLE 1. CLINICAL CHARACTERISTICS AND COURSE OF NINE EPISODES OF 1,4-BUTANEDIOL TOXICITY IN EIGHT PATIENTS.\*

PATIENT No.	SEX/AGE (Yr)	WEIGHT (kg)	PATIENT NAME	PRODUCT CONCENTRATION OF BD (SOURCE)	PERCENT CONCENTRATION OF BD (SOURCE)	AMOUNT INGESTED	CLINICAL FINDINGS	CLINICAL COURSE	LABORATORY TEST RESULT†
1	M/32	67	Thunder Nectar	10 (GC-MS)	200 ml (20 g)‡	200 ml (20 g)‡	Vomiting; fecal incontinence; loss of consciousness	Vomiting; fecal incontinence; loss of consciousness	Blood: GHB 432 mg/liter Urine: GHB 5430 mg/liter, BD 845 mg/liter
2	F/29	NA	Thunder Nectar	10 (GC-MS)	110–140 ml (11–14 g)	110–140 ml (11–14 g)	Dizziness; loss of consciousness; vomiting; fecal incontinence; amnesia	Not treated	Blood: GHB 837 mg/liter, BD 220 mg/liter Urine: GHB 1161 mg/liter, BD 1756 mg/liter Stomach contents: GHB 201 mg/kg, BD 579 mg/kg
3	F/42	57	NRG3	18 (label)	30–60 ml (5.4–10.8 g)§	30–60 ml (5.4–10.8 g)§	NA	Found dead	Urine: GHB 415 mg/liter, BD undetectable
4	M/22	NA	Serenity	7 (label) 6 (GC-MS)	90–120 ml (6.3–8.4 g)	90–120 ml (6.3–8.4 g)	Vomiting; urinary incontinence; loss of consciousness; pulse, 50; RR, 10; SBP, 100 mm Hg; SaO <sub>2</sub> , 92%; GCS, 3; temperature, 95.9°F	Naloxone, intubation, ventilation, charcoal; extubation after 4 hr and full recovery	Urine: GHB 1161 mg/liter, BD 1756 mg/liter Stomach contents: GHB 201 mg/kg, BD 579 mg/kg
5	M/26	NA	NRG3	18 (label) 5 (GC-MS)	NA	NA	Dysarthria; loss of consciousness; periorbital contusion; HR, 110; BP, 180/80 mm Hg; respiratory depression	Naloxone, dextrose, intubation and ventilation for 3 hr, then extubation, transfer	Urine: GHB 415 mg/liter, BD undetectable
6	F/37	NA	InnerG	5 (label) 7 (GC-MS)	90 ml (4.5 g)	90 ml (4.5 g)	Agitation; ataxia; urinary incontinence; ankle fracture; GCS, 11; labile level of consciousness	Physical restraints, droperidol; followed by withdrawal symptoms of hypervigilance and insomnia	Urine: GHB 716 mg/liter, BD undetectable
Second episode			Zen	14 (label) 16 (GC-MS)	NA	NA	Severe agitation; hitting face on floor; frontal and nasal contusions; avulsion of tooth; GCS, 11; RR, 10	Sedation, intubation, ventilation; subsequent severe 4-day withdrawal requiring high doses of sedatives	Serum: GHB 317 mg/liter Urine: GHB 5140 mg/liter, BD undetectable
7	M/51	NA	InnerG	5 (label)	60 ml (3 g)	60 ml (3 g)	Loss of consciousness while driving; arousable by vigorous stimuli; lethargy; amnesia	Observation, full recovery	None
8	M/29	NA	Concentrated industrial BD diluted by patient	20 (patient's report)	5–7.5 ml (1–1.5 g)	5–7.5 ml (1–1.5 g)	Diaphoresis; confusion; agitation; ataxia; myoclonus; RR, 12 and shallow; labile level of consciousness	Naloxone, lorazepam; observation and supportive care, full recovery	None

\*BD denotes 1,4-butanediol, GHB  $\gamma$ -hydroxybutyrate, GC-MS gas chromatography–mass spectrometry, NA not available, RR respiratory rate, SBP systolic blood pressure, SaO<sub>2</sub> arterial oxygen saturation, GCS Glasgow Coma Scale (range, 3 to 15, with 3 denoting not responsive to any stimulus and 15 denoting fully responsive), HR heart rate, and BP blood pressure.

†Toxicologic screening tests of blood and urine were negative in the patients in whom the tests were performed (Patients 1, 3, 4, 5, and 6), with the exception of a positive test for cannabinoids in Patient 1. No ethanol was detected in the blood of the patients tested (Patients 1, 3, 4, 5, and 6). Routine laboratory studies were normal in all patients tested (Patients 4, 5, and 6). In Patients 1, 5, and 6,  $\gamma$ -hydroxybutyrate was measured by conversion to  $\gamma$ -butyrolactone under acidic conditions, then by liquid–liquid extraction of  $\gamma$ -butyrolactone and quantitation by GC-MS; the lower limit of detection was 5 to 10 mg per liter. 1,4-Butanediol was measured directly by GC-MS after liquid–liquid extraction; the lower limit of detection was 200 mg per liter. In Patient 3, liquid–liquid extraction under acidic conditions was used for both  $\gamma$ -hydroxybutyrate and 1,4-butanediol, with subsequent trimethylsilyl derivatization and then GC-MS quantitation; the limit of quantitation for  $\gamma$ -hydroxybutyrate and 1,4-butanediol was 50 mg per liter.

‡The amount was equivalent to 300 mg per kilogram of body weight.

§The amount was equivalent to 95 to 189 mg per kilogram.

cinations, insomnia, vomiting, tachycardia, diaphoresis, tremor, depression, anxiety, and agitation.

#### Patient 6

Patient 6 was a 37-year-old woman who had two episodes of  $\gamma$ -hydroxybutyrate–related toxic effects. In the first, she ingested 90 ml of a dietary supplement called InnerG. Paramedics found her one and a half hours later, yelling and thrashing on the ground, disoriented and incontinent of urine. In the emergency department, she alternated abruptly between screaming and thrashing and lying motionless. She was very easily startled, briefly followed commands and abruptly became extremely agitated, and was oriented to person only. She was sedated and physically restrained. On awakening, she was oriented, but she had hypervigilance and insomnia, symptoms consistent with early  $\gamma$ -hydroxybutyrate–related withdrawal. She declined treatment for withdrawal and was discharged.

The patient had a history of depression, substance abuse — including the use of 1,4-butanediol and  $\gamma$ -butyrolactone supplements for one year — and  $\gamma$ -hydroxybutyrate–related addiction. She reported having ingested approximately 30 ml of InnerG every four hours, around the clock, for four weeks; she had increased her dose that evening “for energy.” She described using approximately eight different brands of 1,4-butanediol and  $\gamma$ -butyrolactone supplements during the previous year, which she took to treat insomnia and, subsequently, depression. This led to the around-the-clock doses and apparent addiction. Cessation of the supplements caused withdrawal symptoms of anxiety, chest tightness, palpitations, and tremor within four to six hours. She had been hospitalized for nine days three and a half months earlier, during which time she had had auditory, visual, and tactile hallucinations, paranoid delusions, severe insomnia, agitation, and tremor for five days after she discontinued the use of the dietary supplements. She had also presented twice for 1,4-butanediol intoxication and once for  $\gamma$ -butyrolactone intoxication during the six months before this presentation, once after being stopped by police for erratic driving. Blood ethanol and toxicologic screening tests were repeatedly negative, and she stated that she had not used ethanol or drugs during this six-month period.

Two months after the first episode, the woman was brought to the emergency department after ingesting an unknown amount of a dietary supplement called Zen. Paramedics had found her moaning and banging her face on the floor at her apartment. She was intubated and received mechanical ventilation for three days, during which she had severe symptoms of  $\gamma$ -hydroxybutyrate–related withdrawal. Physical restraints and extremely high doses of sedatives (propofol, diazepam, and lorazepam) were used during the first two days to control refractory agitation. She was discharged on day 8 after enrolling in an intensive treatment program for mental illness and substance dependence, from which she withdrew after approximately two weeks. During the next two and a half months, she was brought to the emergency department twice more because of 1,4-butanediol intoxication. She subsequently completed an inpatient treatment program for substance dependence for her  $\gamma$ -hydroxybutyrate–related addiction, and she then continued outpatient treatment.

#### Patient 7

Patient 7 was a 51-year-old man who ingested 60 ml of InnerG before exercising. Approximately one hour later, he lost consciousness while driving. Police found him “asleep” at a traffic light, arousable only with vigorous stimuli. His lethargy and amnesia resolved within two hours, and he was discharged. He reported purchasing InnerG as a replacement product for Revivarant ( $\gamma$ -butyrolactone), which he had taken for four months to increase athletic and sexual performance.

#### Patient 8

Patient 8 was a 29-year-old man who was found on the ground by police approximately three hours after ingesting 5 to 7.5 ml of his own dilution of a highly concentrated, industrial 1,4-butanediol product that he had purchased from a chemical-supply company; neighbors had reported seeing him wandering around, partially unclothed and disoriented. An initial examination revealed respiratory depression, diaphoresis, twitching of the arms and legs, and a depressed level of consciousness; 30 minutes later he was agitated, for which he received lorazepam. He was asymptomatic at the time he was discharged, approximately five hours later.

The patient had a history of alcohol addiction, which he had been treating with 5 to 7.5 ml of 1,4-butanediol every four hours for six months. He had learned from the Internet about the use of  $\gamma$ -hydroxybutyrate in clinical trials for alcohol addiction and had seen Web sites marketing 1,4-butanediol supplements for the treatment of alcohol and drug addiction. He purchased highly concentrated, industrial 1,4-butanediol as a cheaper alternative to dietary supplements.

## RESULTS

The clinical manifestations and adverse outcomes of the toxic effects of 1,4-butanediol in these patients included vomiting, urinary and fecal incontinence, confusion, ataxia, agitation, combativeness, an extremely labile level of consciousness, respiratory depression, and death. The treatment given was supportive, including protection of the airway and sedation for the control of agitation. The approximate doses of 1,4-butanediol ingested by the patients who died ranged from 5 to 20 g (88 to 300 mg per kilogram of body weight) and were 1 to 14 g in those who survived. In Patient 3, the reported course of events suggests the possibility of additional unwitnessed ingestion, and the presence of  $\gamma$ -hydroxybutyrate in the contents of the stomach suggests the possibility of redistribution of the compound from the blood.

1,4-Butanediol was undetectable in the body fluids of the patients with nonfatal cases, presumably because of the smaller doses they ingested, the compound's rapid conversion to  $\gamma$ -hydroxybutyrate, and the limits of detection of the assays used (Table 1). The  $\gamma$ -hydroxybutyrate concentrations in the blood, serum, and urine of all the patients in whom they were measured far exceeded normal concentrations; endogenous  $\gamma$ -hydroxybutyrate occurs in trace amounts in normal subjects, and postmortem blood concentrations in the absence of known ingestion average from 12 to 25 mg per liter.<sup>13,14</sup> No other toxic substances were detected in the six patients whose body fluids were tested, and the other two patients did not report ingesting other toxic substances. We conclude that 1,4-butanediol was the cause of the toxic effects in all the patients and of death in Patients 1 and 3.

## DISCUSSION

To understand the health risks associated with 1,4-butanediol, one must consider it in the context of the use and effects of its active metabolite,  $\gamma$ -hydroxybutyrate, and its fellow precursor compound,  $\gamma$ -butyrolactone (Fig. 1).  $\gamma$ -Hydroxybutyrate is an endogenous metabolite of GABA, which is the predominant inhibitory neurotransmitter in the brain.  $\gamma$ -Hydroxybutyrate exerts complex neuromodulatory effects on the dopaminergic and GABAergic systems, and there are

$\gamma$ -hydroxybutyrate-specific receptors in the brain; the nature and clinical importance of these effects and receptors, however, are not fully understood.<sup>15</sup> At physiologic levels,  $\gamma$ -hydroxybutyrate also undergoes limited conversion back to GABA.<sup>1,16</sup> There may be higher rates of conversion in the presence of the very high concentrations of  $\gamma$ -hydroxybutyrate that result from ingestion; the clinical manifestations of this increased conversion back to GABA, however, are not known.  $\gamma$ -Hydroxybutyrate also affects the cerebral glucose metabolism, temperature regulation, blood flow, and sleep patterns.<sup>17</sup>

$\gamma$ -Hydroxybutyrate was developed in 1960 as an anesthetic and has been studied outside the United States as a potential treatment for opiate withdrawal, alcohol addiction, and narcolepsy. The clinical use of  $\gamma$ -hydroxybutyrate in the United States is limited to trials in patients with narcolepsy.<sup>18</sup> The toxic effects include vomiting, incontinence, hypothermia, bradycardia, hypotonia, tremor, myoclonus, seizure-like activity, agitation, combativeness, somnolence, labile level of consciousness, coma, respiratory depression, apnea, and death.<sup>19-21</sup> Although classified by the federal government as a schedule I drug,  $\gamma$ -hydroxybutyrate continues to be widely used at "rave" concerts, parties, and clubs and is readily accessible through Internet sources, kits, and "recipes" for home synthesis in which the primary ingredient is  $\gamma$ -butyrolactone.

$\gamma$ -Butyrolactone is a lactone-ring analogue of  $\gamma$ -hydroxybutyrate (Fig. 1). It does not occur endogenously in humans.<sup>22</sup> When ingested,  $\gamma$ -butyrolactone is rapidly converted to  $\gamma$ -hydroxybutyrate and thus has similar pharmacologic and toxic effects.<sup>23</sup> However, because  $\gamma$ -butyrolactone and  $\gamma$ -hydroxybutyrate differ in their tissue distribution and in their bioavailability after oral ingestion,  $\gamma$ -butyrolactone appears to have greater potency and more prolonged action than  $\gamma$ -hydroxybutyrate.<sup>24,25</sup> Toxic effects of  $\gamma$ -butyrolactone have been reported after the ingestion of solvents and dietary supplements.<sup>26-29</sup> From April 1998 to April 1999, the FDA received 119 reports of toxic effects, including 2 deaths; 19 patients required intubation, and 9 reported addiction or withdrawal.<sup>30</sup>

1,4-Butanediol is an aliphatic alcohol that occurs endogenously in trace amounts. When ingested, it is rapidly absorbed and converted to  $\gamma$ -hydroxybutyrate (Fig. 1).<sup>31</sup> The lowest lethal dose in humans is listed by the National Toxicology Program as 0.3 g per kilogram, although no sources are given.<sup>32</sup> Although studies in rats indicate that 1,4-butanediol may have direct pharmacologic effects similar to those of ethanol, the effects of its metabolite  $\gamma$ -hydroxybutyrate predominate clinically, and sedation and akinesia are induced at doses  $\frac{1}{10}$  as large as those of ethanol.<sup>33</sup> 1,4-Butanediol is metabolized by alcohol dehydrogenase. Ingesting 1,4-butanediol concurrently with ethanol may increase the risk of death or renal and hepatic damage,<sup>34</sup> potentiate the effects of ethanol,<sup>35</sup> or

through the competitive inhibition of alcohol dehydrogenase, delay the effects of 1,4-butanediol.<sup>8</sup>

Evidence of the lethality of  $\gamma$ -hydroxybutyrate-related compounds is mounting. The Drug Enforcement Administration has documented 71 deaths associated with  $\gamma$ -hydroxybutyrate; a  $\gamma$ -hydroxybutyrate-related compound was the sole intoxicant in 15 of these cases (Drug and Chemical Evaluation Section, Drug Enforcement Administration: personal communication). However, there have probably been more such deaths, given the lack of knowledge on the part of clinicians and forensic toxicologists about the toxic effects and lethality of  $\gamma$ -hydroxybutyrate, the masking of toxic effects by simultaneous intoxication with other substances, the need to engage in targeted analysis in order to detect  $\gamma$ -hydroxybutyrate-related substances in body fluids, and the general underreporting of cases of toxic effects. In another report, death resulted from apnea, aspiration, positional asphyxia, trauma after abrupt loss of consciousness, or simultaneous intoxication with other depressant drugs.<sup>36</sup>

The Dietary Supplement Health and Education Act of 1994 established that substances designated as neither foods nor drugs may be sold as dietary supplements without premarketing proof of safety or efficacy. Consequently, although the sale of  $\gamma$ -hydroxybutyrate was prohibited by the federal government in 1990, the Dietary Supplement Health and Education Act made possible the legal sale of its precursors as dietary supplements. Although it was already used as an industrial solvent,  $\gamma$ -butyrolactone thereafter began to be marketed as a "natural," "nontoxic" dietary supplement (Table 2) in health-food stores, sports-nutrition stores, and gyms and on the Internet. It was claimed that the supplements enhanced sleep, athletic performance, libido and sexual performance, muscle building, and fat loss and decreased insomnia, depression, stress, and the effects of aging.

After the FDA issued a warning about the health risks of  $\gamma$ -butyrolactone and  $\gamma$ -butyrolactone supplements were voluntarily recalled in January 1999,<sup>4</sup> 1,4-butanediol began to be marketed as a "replacement product" (Table 2). Claims about the health benefits of 1,4-butanediol products echoed those for the earlier supplements, and new alleged benefits were added: the reduction of wrinkles, the reversal of baldness, the restoration of hair color, the elimination of cellulite, the sharpening of vision, and others. Despite the FDA's warning in May 1999 about 1,4-butanediol supplements,<sup>5</sup> extensive marketing continues on the Internet, and the use of all three compounds, sometimes interchangeably, has increased.<sup>36,37</sup>

The risk of toxic effects of  $\gamma$ -hydroxybutyrate-related compounds has been increased by claims that an overdose does not necessitate medical care; the resultant casual attitude toward overdoses has led to fatal delays in seeking medical attention.<sup>38</sup> Web sites such

**TABLE 2.** PRODUCTS CONTAINING 1,4-BUTANEDIOL,  $\gamma$ -HYDROXYBUTYRATE, OR  $\gamma$ -BUTYROLACTONE.

The active ingredient of 1,4-butanediol products is most commonly listed as tetramethylene glycol, butylene glycol, or suclo-B. Products are liquids unless otherwise noted. 1,4-Butanediol dietary supplements include the following: Rejuv@Nite, Ultradiol, Enliven, N-Force, Liquid Gold, Zen, Soma Solutions, BlueRaine, Thunder, Serenity, NRG3, Thunder Nectar, InnerG, SomatoPro (liquid or capsules), Weight Belt Cleaner, X-12, Rest-Q, Biocopia PM, Dormir, and Amino Flex.

1,4-Butanediol "nontoxic" and "organic" cleaners and solvents (all liquids) include the following: BlueRaine, Thunder, Serenity II, Mystik, Midnight, and Miracle Cleaning Products; ingredients of "cleaning products" may not be listed.

$\gamma$ -Hydroxybutyrate is available in liquid, powder, gel, and putty forms.

Street names for  $\gamma$ -hydroxybutyrate include the following: G, GHB, Scoop, Easy Lay, Great Hormones at Bedtime, Georgia Home Boy, Grievous Bodily Harm, Liquid Ecstasy, Liquid X, and G H Beers.

$\gamma$ -Hydroxybutyrate products illegally imported from Europe include the following: Alcover, Gamma-OH, Somatomax-PM, Somsanit, Anectamine, and Natural Sleep 500.

The active ingredient of  $\gamma$ -butyrolactone products is most commonly listed as furanone, furanone dihydro, lactone, or GBL. All products are liquids unless otherwise noted.  $\gamma$ -Butyrolactone supplements include the following: Gamma Ram, Furanone, Nu-Life, RenewTrient (liquid or capsules), Renewsolvent, Revivariant G, Jolt, Verve, Verve 5.0, GH Gold, Eclipse 4.0, Furan, G3, V3, GenX, Remedy GH, ReActive, Rest-Eze, Beta-Tech, Thunder, Furomax, Blue Nitro, Blue Nitro Vitality, Invigorate, Insom-X, GH Revitalizer, Gamma G, Remforce, Firewater, Revivariant, and Regenerize.

$\gamma$ -Butyrolactone "nontoxic" and "organic" cleaners and solvents (all liquids) include the following: Verve, Verve 5.0, and Miracle Cleaning Products; ingredients of "cleaning products" may not be listed.

as Lycaenum offering information about recreational drugs have played down the risks associated with an overdose in the absence of additional intoxicants. For example, Lycaenum advises that an overdose of  $\gamma$ -hydroxybutyrate "can cause anything from drowsiness to a short-term, harmless 'coma'"<sup>39</sup> and recommends that those coming to the aid of someone who has taken such an overdose "seek medical attention . . . unless you can positively verify that they are not under the influence of other drugs."<sup>40</sup> Many dietary supplements have carried similar instructions. In 1998, a clinical report of toxic effects of RenewTrient ( $\gamma$ -butyrolactone) cited a label that advised: "Unless drugs or alcohol have been taken with RenewTrient, the only treatment necessary is to SLEEP IT OFF!"<sup>27</sup> Regulatory efforts have reduced, but not eradicated, the supply of such dietary supplements and have stimulated shifts in the marketing tactics used on the Internet, where Web sites now advertise 1,4-butanediol and  $\gamma$ -butyrolactone as "all-natural solvents," "nontoxic cleaners," "ink jet cartridge cleaners," "chemical samples," and industrial supplies.

Although the long-term effects are poorly understood, long-term, frequent use of 1,4-butanediol,  $\gamma$ -butyrolactone,  $\gamma$ -hydroxybutyrate, or combinations of these compounds can result in physical and psychological addiction and potentially severe withdrawal syndromes.<sup>30,41-44</sup> The active metabolite,  $\gamma$ -hydroxy-

butyrate, appears to be the addictive substance, but unmetabolized 1,4-butanediol may also have effects on addiction and withdrawal syndromes, although such effects have not yet been elucidated. Due to the rapid absorption and elimination of  $\gamma$ -hydroxybutyrate, around-the-clock ingestion with short dosing intervals appear to be necessary for the development of addiction. In eight patients who had severe withdrawal symptoms after around-the-clock dosage with  $\gamma$ -hydroxybutyrate-related products, symptoms began one to six hours after the last dose and lasted 5 to 15 days; one patient died.<sup>42</sup> Another addicted user took a fatal overdose of hydrocodone while attempting self-treatment for withdrawal symptoms.<sup>36</sup>

The signs and symptoms of withdrawal include anxiety, confusion, tremor, mild tachycardia and hypertension, agitation, insomnia, delirium, delusions, and auditory, visual, and tactile hallucinations. Because these symptoms typically begin within hours after the last dose was taken, acute toxic effects in addicted persons may rapidly develop into withdrawal. The treatment of withdrawal should include supportive care and administration of a benzodiazepine, possibly in high doses.<sup>41,42</sup> It appears to be critical to incorporate a psychiatric assessment and treatment for chemical dependence into the treatment of acute withdrawal.

$\gamma$ -Hydroxybutyrate-related compounds have been implicated in sexual assaults.<sup>45-48</sup> Low doses may cause increased libido, euphoria, suggestibility, passivity, and amnesia, all of which make victims more susceptible to sexual assault. Higher doses have predominantly sedative effects.<sup>48</sup> Driving while intoxicated with  $\gamma$ -hydroxybutyrate-related compounds carries substantial personal and public risks. Clinical reports document cases in which  $\gamma$ -hydroxybutyrate-intoxicated drivers were stopped by police for erratic driving, were found "asleep" at the wheel in traffic, lost consciousness while driving, and caused multiple collisions.<sup>27,43,49-51</sup> It may be difficult to recognize behavior that is facilitated by  $\gamma$ -hydroxybutyrate, because intoxication with  $\gamma$ -hydroxybutyrate may be mistaken for or masked by the effects of other intoxicants.

Routine toxicologic screening tests do not detect  $\gamma$ -hydroxybutyrate-related compounds; targeted analysis with gas chromatography-mass spectrometry is necessary for their detection and quantification. The conversion of precursors to  $\gamma$ -hydroxybutyrate and its metabolism are rapid. Five hours after a dose of 50 mg of  $\gamma$ -hydroxybutyrate per kilogram, there remains no detectable concentration in the blood; higher doses result in slightly slower elimination. A small fraction of  $\gamma$ -hydroxybutyrate passes through the kidneys without being metabolized and collects in the bladder, where it remains stable<sup>11,52</sup>; thus, it may be detected in urine after it has ceased to be detectable in blood.

1,4-Butanediol is toxic, addictive, and potentially lethal. Ingestion of the compound impairs one's ability to drive, and it may be abused to facilitate sexual

assault. The available methods for detecting it in body fluids are costly, time-consuming, and dependent on targeted analysis; this fact adds to its attractiveness for recreational use, because it is not detected by standard screening tests for drugs. Extensive industrial use of 1,4-butanediol, in conjunction with the flexibility and anonymity of Internet marketing, ensures a continued supply that is almost impossible to regulate. The increasing numbers of reports of toxic effects and addiction indicate that demand is also high.

Physicians of diverse specialties, including emergency physicians, internists, and psychiatrists, and forensic toxicologists should be informed about the issues surrounding the abuse of  $\gamma$ -hydroxybutyrate-related compounds so that they may recognize and effectively treat patients who are intoxicated with these substances, educate the public about the dangers of 1,4-butanediol and other  $\gamma$ -hydroxybutyrate-related products, and implement preventive strategies.

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