

# Gamma Hydroxybutyric Acid (GHB) Intoxication

Phillip E. Mason, MD, William P. Kerns II, MD

## Abstract

Gamma hydroxybutyric acid (GHB) is a naturally occurring analog of gamma-aminobutyric acid (GABA) that has been used in research and clinical medicine for many years. In the past decade it has become very popular as a dietary supplement and recreational drug. Acute overdose leads to profound alteration of mental status and variable amounts of respiratory depression. With proper management, most patients recover fully within six hours. However, respiratory arrest and death have been reported in severe GHB intoxication. In addition to acute

overdose, there is a GHB withdrawal syndrome that is similar to sedative/hypnotic and ethanol withdrawal. Recently several congeners of GHB, gamma butyrolactone and 1,4-butanediol, have emerged as drugs of abuse and show toxidromes similar to GHB. Emergency physicians should be familiar with the presentation and management of GHB-related emergencies. **Key words:** GHB; gamma hydroxybutyric acid; drug abuse; overdose; toxidromes. *ACADEMIC EMERGENCY MEDICINE* 2002; 9:730–739.

Gamma-aminobutyric acid (GABA) was discovered as the predominant inhibitory central nervous system (CNS) neurotransmitter in 1956. This prompted a search for a GABA analog that would cross the blood–brain barrier for possible therapeutic use. During this search, gamma-hydroxybutyric acid (GHB) was found in the brain and subsequently synthesized in the laboratory in 1964.<sup>1,2</sup>

Since its discovery, GHB has played many roles in the laboratory. It was used to create an absence seizure model.<sup>3,4</sup> GHB was also shown to have tissue-protective effects in the setting of myocardial infarction, stroke, sepsis, small bowel ischemia, hypovolemic shock, ionizing radiation, and oxygen free radicals.<sup>2,5,6</sup> Despite promising beneficial effects in basic science research, GHB has not found widespread clinical use. In the 1960–70's, GHB was used as a general anesthetic agent but fell out of favor due to an association with abnormal electroencephalographic (EEG) patterns in animals.<sup>7,8</sup> GHB has been found to be equivalent to benzodiazepines in the management of alcohol withdrawal.<sup>9–12</sup> There is evidence that its prodrug, gamma-butyrolactone (GBL), may decrease alcohol cravings in animals and humans.<sup>13</sup> However, the only Food and Drug Administration (FDA)-approved indication for GHB is the treatment of narcolepsy, where trials have shown amelioration of symptoms and improved sleep patterns.<sup>14–19</sup>

While GHB has been present in labs and therapeutic trials for years, it has recently become a public health issue as a drug of abuse.

## METABOLISM

Most references to GHB in clinical medicine pertain to its exogenous administration in therapeutic or illicit settings. However, GHB does exist naturally in brain tissue with concentrations in human and monkey striatum ranging from 11 to 25  $\mu\text{M}$ .<sup>5,6,20–23</sup> It is also found in heart, liver, kidney, muscle, and brown fat, where its function is unknown.<sup>6,20</sup> Endogenous GHB is formed in the brain primarily from GABA by the action of GABA aminotransferase and succinic semialdehyde reductase.<sup>6,20,22,24</sup>

The primary pathway for GHB elimination involves conversion to succinic semialdehyde that is subsequently converted to succinate. Succinate then enters the Krebs cycle and is ultimately expired as carbon dioxide (Fig. 1).<sup>20,22–24</sup> A small fraction of GHB is metabolized to succinate via a beta oxidation pathway in the liver before entering the Krebs cycle.<sup>25</sup> A negligible amount of GHB is eliminated in the urine.<sup>26–30</sup>

## PHARMACOKINETICS

The pharmacokinetics of GHB have been determined from a mixture of human and animal studies. The oral bioavailability of GHB in rats is 59–65%.<sup>27,31</sup> Peak blood levels of GHB occur 15–45 minutes after oral administration to humans.<sup>26,28–30,32</sup> Initial clinical and EEG effects occur 15–20 minutes after oral administration, with peak clinical effect occurring 30–60 minutes post-ingestion.<sup>3,26,28,33</sup> GHB is lipid-soluble and has essentially no protein binding, allowing it to readily cross the blood–brain barrier.<sup>2,5,26</sup> Distribution to target tissues occurs rapidly and follows a two-compartment model with a volume of distribution ( $V_D$ ) of 0.4 L/kg and 0.6 L/kg.<sup>34</sup> Pharmacokinetic studies demonstrate dose-dependent elimination of GHB with an average half life of 20–53 minutes in healthy human subjects.<sup>26,29,30,32</sup>

From the Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC.

Received July 11, 2001; revision received December 3, 2001; accepted December 6, 2001.

Address for correspondence and reprints: Phillip E. Mason, MD, Department of Emergency Medicine, Carolinas Medical Center, 1000 Blythe Boulevard, Charlotte, NC 28232. e-mail: phillipmason@yahoo.com.

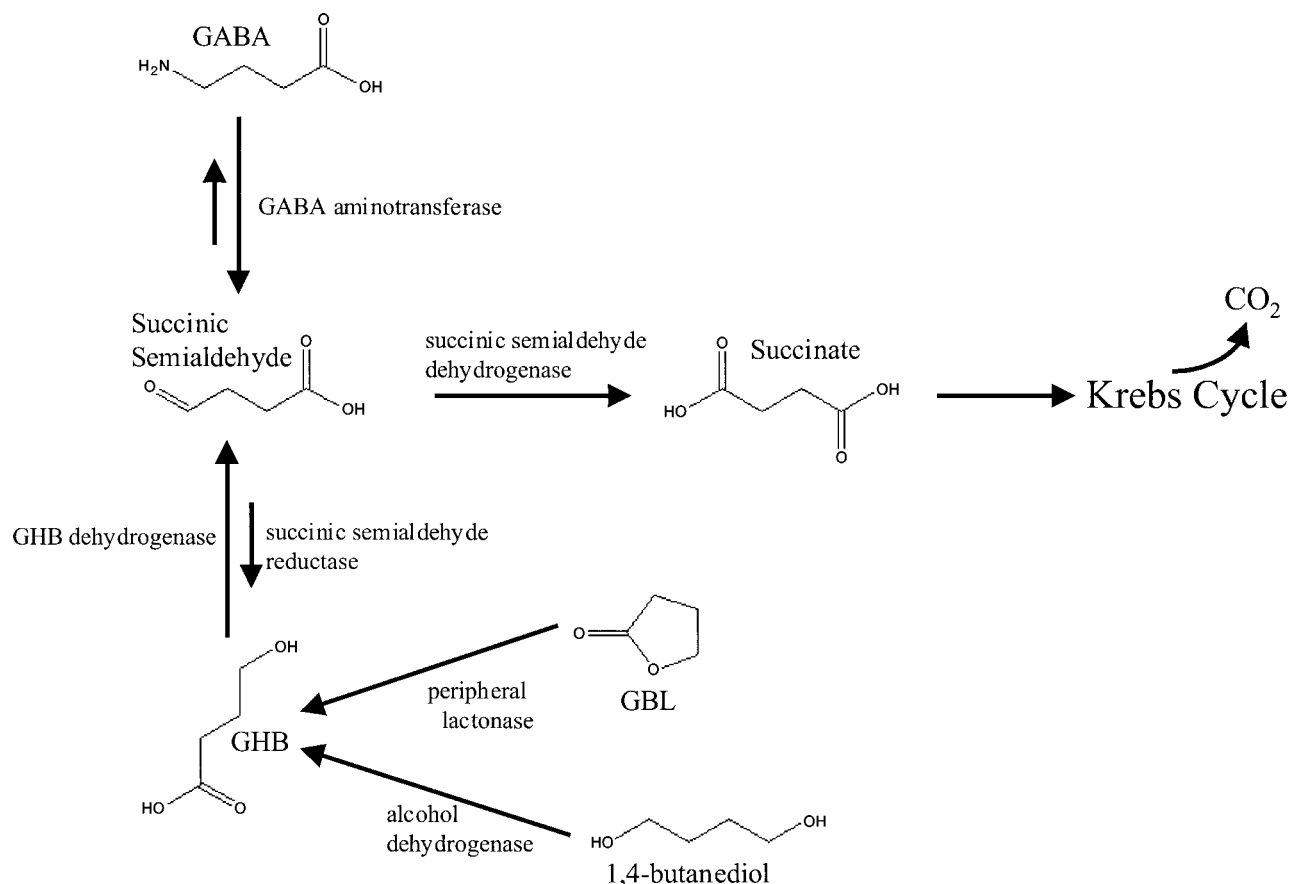


Figure 1. The primary pathway for gamma hydroxybutyric acid (GHB) elimination. GABA = gamma aminobutyric acid; GBL = gamma butyrolactone.

## PHARMACOLOGY

In animals, CNS GHB levels increase by 100–500-fold after typical doses.<sup>5,6</sup> The principal clinical effect of exogenously-administered GHB is CNS depression. This neurodepressant effect may be mediated by a specific GHB receptor, binding to GABA receptors, modulation of GABA levels, or interactions with other neurotransmitters.

There is convincing evidence that a novel GHB receptor exists in the CNS. These high-affinity GHB receptors are localized to neuronal cells and, more specifically, to the synaptosomal membrane.<sup>20,35</sup> These receptors are saturated at the levels of GHB achieved after exogenous administration.<sup>35,36</sup> In human brain, the pons and hippocampus exhibit the highest density of GHB receptors, followed by the cerebral cortex and caudate.<sup>35</sup> The GHB receptor is selectively inhibited by the experimental antagonist NCS-382.<sup>20</sup>

In addition to its own receptor, GHB is known to bind to the GABA<sub>B</sub> receptor,<sup>37,38</sup> although with a much lower affinity.<sup>39</sup> Physiologic levels of GHB would not bind this receptor sufficiently to cause pharmacologic effect. However, supraphysiologic levels achieved after exogenous administration

could cause significant binding of the GABA<sub>B</sub> receptor, leading to membrane hyperpolarization and depression of the CNS.<sup>22,37–39</sup>

It has been hypothesized that GHB exerts its action by increasing the total CNS GABA pool. While there is evidence that GHB is converted to GABA *in vitro*, the extent of this conversion is minimal and unlikely to account for the physiologic effect of GHB.<sup>2,20,24,40–44</sup>

The GHB receptor is associated with dopaminergic neurons that may mediate the effects of GHB on the CNS.<sup>20,22,35</sup> Administration of GHB increases dopamine concentrations in the striatum and cortex in a dose-dependent fashion.<sup>5,6,20,22</sup> This increase occurs due to stimulation of tyrosine hydroxylase, the enzyme necessary for dopamine synthesis, and is not related to a decrease in the catabolism of dopamine.<sup>6</sup> Following increased dopamine formation, there is increased dopamine release as well.<sup>20</sup> There are studies suggesting that low doses of GHB inhibit while higher doses promote, the release of dopamine and that GHB inhibits dopamine release in awake animals while stimulating it in anesthetized animals.<sup>22</sup>

While GHB predominantly alters the CNS dopaminergic system, there is also evidence of in-

creased acetylcholine and 5-hydroxytryptamine levels after administration of GHB.<sup>6,20,43,45</sup> Some studies suggest that GHB interacts with CNS opioids as well.<sup>20,46–48</sup>

Oral doses of 25–30 mg/kg of GHB are used therapeutically in narcolepsy to induce physiologic sleep.<sup>16–19,33</sup> Studies correlating level of consciousness with oral dosing found that 50–70 mg/kg induces coma in adults, with children requiring higher doses to achieve a similar level of sedation.<sup>2,3,44</sup> GHB administered orally at doses of 25–50 mg/kg produced peak serum levels of approximately 50–90 µg/mL, while eight patients intoxicated with GHB had an average level of 184 µg/mL.<sup>26,29,30,32,49</sup> The median lethal dose (LD<sub>50</sub>) for GHB in rats is 1.7 g/kg, and is 3.3 g/kg in dogs, with death resulting from respiratory depression.<sup>2,50</sup>

### GHB AS A DRUG OF ABUSE

Gamma hydroxybutyric acid has been touted for use as a bodybuilding supplement and a sleep enhancing agent under many names, including Somatomax PM, Gamma OH, Grievous Bodily Harm, Georgia Homeboy, and Liquid X. The problem of intentional misuse for purposes of achieving a euphoric state was first reported in 1990, with a majority of cases occurring in California, Georgia, and Florida.<sup>51</sup> Since that time its recreational use has grown significantly, with multiple case reports and case series in the literature. The popular underground parties known as “raves” promote the abuse of GHB as well as ketamine and methylenedioxymethamphetamine (MDMA). GHB has also been used as a means of assault, particularly in date rape.<sup>52–54</sup> The short-lived hypnotic effects, relative safety and widespread availability of the drug have made it particularly well suited to this role. The problem is compounded by the fact that routine drug screens do not detect GHB. The FDA first issued warnings regarding the use of GHB in 1990, and regulation of its possession has become

stricter over the past decade. In March 2000, GHB was added to the list of schedule I substances by the Drug Enforcement Administration (DEA). Despite the increased regulation, GHB remains widely available through the Internet where one can easily purchase the necessary reagents as well as recipes for home production.<sup>55</sup> Furthermore, GHB is still available for shipping from other countries via the Internet.

### CLINICAL FEATURES

The manifestations of GHB intoxication are primarily a result of its CNS and respiratory depression and, to a lesser extent, its effects on the cardiovascular and gastrointestinal systems. While there are multiple case series and case reports of GHB intoxication, only two series included laboratory confirmation of GHB ingestion. In one series, only eight of 20 suspected GHB intoxications were confirmed by serum mass spectrometry.<sup>49</sup> In another report, only seven of 12 suspected ingestions were confirmed using urine mass spectrometry.<sup>56</sup> One feature of GHB intoxication is the almost universal presence of cointoxicants, often multiple, that contribute to or cloud the clinical picture (Table 1). The high prevalence of coingestions and the fact that many suspected GHB overdoses lack biochemical evidence of its presence should be considered when interpreting the clinical features reported in the GHB toxidrome. Furthermore, the data regarding GHB intoxication are derived primarily from small, retrospective series, making it difficult to accurately describe the features of this entity. Historically, the typical GHB patient is a white male in the mid to late 20s with a clear history of ingestion. Most patients are transported from nightclubs, with 84% of cases presenting between midnight and 0600 hours.<sup>49,56–58</sup> Patients may also present after ingestion at gymnasiums and workout facilities. The clinical features of GHB intoxication are summarized in Table 2.

TABLE 1. Incidence of Cointoxicants in Gamma Hydroxybutyric Acid (GHB) Intoxication

Study	Ethanol	Amphetamine	Cocaine	Opiates	Marijuana	Comments
Chin et al. <sup>57</sup> (n = 88)	39%	17%	5%	3%	3%	Based on objective testing and physician report
Li et al. <sup>56</sup> (n = 7)	86%	0%	71%	0%	14%	Ethanol by patient report; others by objective testing
Garrison and Mueller <sup>58</sup> (n = 59 for ethanol; n = 57 for drugs)	63%	50%	40%	10%	60%	Objective testing in all
ElSohly and Salamone <sup>53</sup> (n = 48)	33%	13%	8%	4%	21%	Sexual assault victims, biochemical testing for all

TABLE 2. Clinical Features of Gamma Hydroxybutyric Acid (GHB) Intoxication

Study	Initial GCS*	Vomiting	Respiratory Depression	Bradycardia	Seizures	Comments
Mahon et al. <sup>49</sup> (n = 8)	Mean GCS 4.5	25%	Not reported	Not reported	0%	Prospective, confirmed GHB by serum GCMS†
Li et al. <sup>56</sup> (n = 7)	Mean GCS 6.3	14%	100%	0%	0%	Retrospective, confirmed GHB by urine GCMS
Chin et al. <sup>57</sup> (n = 88)	28% GCS 3; 61% GCS ≤8	30%	Not reported‡	36%	0%	Retrospective, no confirmation of GHB
Garrison and Mueller <sup>58</sup> (n = 78)	28% GCS 3; 56% GCS ≤8	22%	Not reported	Not reported	9%	Retrospective, no confirmation of GHB
Dyer <sup>34</sup> (n = 16)	Not reported§	44%¶	13%	13%	13%	Retrospective, no confirmation of GHB

\*GCS = Glasgow Coma Scale score.

†GCMS = gas chromatography–mass spectrometry.

‡Arterial blood gas (ABG) in 30 patients, with partial pressure of carbon dioxide (pCO<sub>2</sub>) ≥45 torr in 21.

§Four of 16 patients reported as having “coma.”

¶Forty-four percent reported as having nausea or vomiting.

Gamma hydroxybutyric acid produces a spectrum of CNS changes. Abusers ingest the substance to induce euphoria that is not associated with residual “hangover” effects. Minor effects include ataxia, nystagmus, somnolence and aggression. However, the cardinal manifestation of GHB intoxication prompting presentation to the emergency department (ED) is CNS depression, often to the point of coma. Several case series of GHB intoxication report that approximately 25% of patients present with a Glasgow Coma Scale (GCS) score of 3, and 60% with a GCS score of <9.<sup>56–58</sup> Resolution of CNS depression occurs abruptly, with patients going from unresponsive to agitated and combative over very short periods of time. There are reports of patients’ being unresponsive to painful stimuli, yet vigorously resisting intubation attempts.<sup>34,56</sup>

Respiratory depression can be a significant component of GHB intoxication and is exacerbated by ethanol and other CNS depressants. The spectrum of respiratory depression ranges from mild respiratory acidosis to apnea.<sup>34,56,57</sup> Patients have been observed to cycle between periods of apnea and agitation with hyperventilation.<sup>34,56,59</sup> This may be an exaggeration of the periodic breathing described with GHB-induced anesthesia. During therapeutic studies, GHB decreases respiratory rate, but there is usually a concurrent increase in tidal volume that maintains a near-normal minute ventilation.<sup>2,28,34,50,60,61</sup>

Seizures are another CNS manifestation of GHB intoxication, although the occurrence is variable. One case series of 78 patients reports a 9% incidence of seizures, while other series report no seizures.<sup>56–58</sup> There are data in rats and primates in-

dicating that GHB induces epileptiform EEG discharges similar to petit mal seizures.<sup>62–64</sup> However, multiple studies in humans fail to demonstrate any epileptogenic action of GHB.<sup>3–5,33,44,65,66</sup> Myoclonic movements of the face and extremities are described after induction of anesthesia with GHB and are also described in case reports of intoxication.<sup>44,49,57,62</sup> It is possible that these myoclonic jerks are misinterpreted as seizures. In the critically ill patient, respiratory depression may lead to hypoxic seizures.

Bradycardia is often documented in persons under the influence of GHB<sup>34,57</sup> and is a known feature of its therapeutic use.<sup>2,44,50,60–62,67</sup> Therapeutic use of GHB has minimal effects on blood pressure in man.<sup>2,44,60–62,67</sup> However, hypotension can occur in illicit intoxication, with one case series reporting an incidence of 11%.<sup>57</sup>

There are only sporadic reports of electrocardiographic (ECG) changes associated with both therapeutic and illicit GHB use. In one series, five of seven GHB-intoxicated patients developed U waves, and there was one case each of first-degree atrioventricular (AV) block and right bundle branch block (RBBB). However, five of the seven patients in this series concurrently used cocaine, an agent known to cause a multitude of ECG changes.<sup>56</sup> Transient inverted P waves occurred in 12 of 54 children receiving GHB for sedation during cardiac procedures.<sup>60</sup> Decreases in T-wave amplitude and T-wave inversion were observed in a series of cardiac patients receiving GHB. However, these cardiac patients were also hypokalemic, which makes these findings difficult to attribute to GHB.<sup>2</sup> One patient experienced transient atrial fibrillation under

the influence of GHB and barbiturates.<sup>57</sup> Finally, there is a report of transient RBBB in a child exposed to GHB.<sup>68</sup> Thus, there are no consistent or significant ECG changes seen with GHB intoxication.

Vomiting is seen frequently in GHB intoxication, with an incidence of 14–44%.<sup>34,49,56–58</sup> Emesis is also a common feature of the therapeutic use of GHB.<sup>44,61</sup> The highest incidence of vomiting seems to be during the periods of arousal, although it can occur at any time.

Mild hypothermia was noted in one series, with 69% of patients having temperatures less than 36.0°C and 31% less than 35.0°C.<sup>57</sup> Another series reported no hypothermia.<sup>56</sup>

### CLINICAL COURSE

Despite dramatic alterations in mental status and other physiologic parameters, the outcome in GHB overdose is typically good, provided the patient does not die prior to receiving medical care. In all reported deaths, the deceased person was found dead at the scene and there are no reports of patients dying of GHB overdose after seeking medical care.<sup>69–73</sup>

The ED course of GHB intoxication is summarized in Table 3. Based on published case series, patients typically recover respiratory and CNS function in two to six hours.<sup>49,56–58,73–77</sup> This is consistent with the duration of action of GHB when used therapeutically. Despite profound CNS and respiratory depression necessitating intubation, patients may not require hospital admission. The rapid recovery from GHB intoxication often permits extubation and discharge to home from the ED after a period of observation.<sup>49,56–58,73</sup> Patients who do not recover in six hours are atypical of GHB intoxication, and an alternative diagnosis should be sought.

### DRUG INTERACTIONS

Case reports of interactions between GHB and other substances appear in the literature. One report describes a patient having severely depressed mental status and respirations after ingesting 10 mg/kg of GHB, a dose which he had exceeded

many times in the past. The patient had recently been started on ritonavir and saquinavir, and these are thought to have exacerbated his response to GHB.<sup>78</sup> These drugs are known to inhibit the cytochrome p450 system, which may decrease first-pass hepatic metabolism of GHB, leading to potentiation of its effects.<sup>27</sup>

Studies in rats demonstrate that GHB and 1,4-butanediol (a prodrug of GHB) have a synergistic effect with ethanol.<sup>79,80</sup> Cross-tolerance between GHB and ethanol has also been demonstrated and gamma-butyrolactone, a GHB congener, reduces voluntary consumption of ethanol in rats.<sup>13,81</sup> Animal and human data have shown that GHB is efficacious in the treatment of ethanol dependence and withdrawal.<sup>9–12,25,82</sup> These data suggest that there is some biochemical similarity between the actions of GHB and ethanol. However, research into the nature of these interactions is incomplete and often contradictory.

### MANAGEMENT

Despite the dramatic alterations in mental status and respiratory function, most GHB patients do well with supportive measures. Beyond supportive care, the most important endeavor of the treating physician is to thoroughly search for the presence of cointoxicants and occult trauma that may require intervention.

Respiratory effort is often preserved in GHB overdose despite coma or marked depression of mental status. However, severe respiratory depression and apnea may occur and are indications for endotracheal intubation. Reports of complete loss of airway reflexes and aspiration pneumonia further emphasize the importance of proper airway management.<sup>2,68,69,75,83</sup>

The need for pharmacologic aids to intubate the severely intoxicated GHB patient may vary depending on the clinical circumstances. Deeply comatose patients can be intubated using only a paralytic agent, allowing GHB to serve as its own induction agent.<sup>59,78,83</sup> However, the addition of a short-acting induction agent, such as etomidate,

**TABLE 3. Emergency Department (ED) Course of Gamma Hydroxybutyric Acid (GHB) Intoxication**

Study	Admitted	Intubated	Mean Duration of Intubation	Average Time in ED if Not Admitted
Chin et al. <sup>57</sup> (n = 88)	11%	13%	179 minutes	Not reported
Mahon et al. <sup>49</sup> (n = 8)	0%	50%	80 minutes	Not reported
Li et al. <sup>56</sup> (n = 7)	43%	57%	3.5 hours	6 hours
Garrison and Mueller <sup>58</sup> (n = 78)	4%	10%	Not reported	3 hours

may be useful to prevent the agitation frequently observed during the intubation of GHB patients.<sup>44,56,59</sup>

Post-intubation sedation in GHB overdose is useful to allow for smooth recovery and controlled extubation. However, excessive sedation may necessitate mechanical ventilation even after the effects of GHB have ceased. A reasonable approach is to administer a single dose of a short acting sedative/hypnotic agent (e.g., midazolam). The need for continued mechanical ventilation can be reassessed after the effects of the sedative/hypnotic agent have passed.

Cardiovascular effects related to GHB are unlikely to require aggressive therapy. GHB-induced bradycardia responds to atropine.<sup>44,61,67</sup> There are no reports of GHB-induced hypotension requiring pressor therapy. The presence of a significant conduction delay or other ECG abnormalities is not typical of GHB intoxication and, if present, should prompt a search for another cardiotoxic substance.

The role of gastrointestinal (GI) decontamination in cases of GHB intoxication is unclear. The rapid absorption of the drug argues against the routine use of activated charcoal. Furthermore, the incidence of vomiting may be increased by the administration of charcoal, placing the patient at higher risk for aspiration pneumonitis. One could argue that decontamination may be useful to decrease the absorption of coingestants that frequently accompany GHB. However, activated charcoal is not efficacious for the most common coingestants such as ethanol, marijuana or inhaled cocaine. Additionally, the mortality of GHB intoxication is low, even in the presence of coingestants, once the patient reaches the hospital. These arguments make a strong case against GI decontamination in cases of GHB overdose. If the patient requires intubation for airway protection or respiratory depression, the risk of aspiration is lessened and the use of charcoal may be appropriate.

Some pharmacokinetic properties of GHB, specifically the low  $V_D$ , minimal protein binding, and small size (MW 104) make it well suited to elimination by dialysis. However, the short duration of clinical effects make extracorporeal drug elimination unnecessary. There are no reported cases of GHB intoxication requiring hemodialysis.

While not included on standard drug screens, GHB can be detected in urine and serum by mass spectrometry/gas chromatography.<sup>52,53,70,84-86</sup> The rapid elimination of GHB makes detection difficult, with the majority of patients having no measurable plasma level six hours after receiving therapeutic doses.<sup>26,29,30,32</sup> There is evidence that GHB is a product of postmortem decomposition, as significant

levels can be detected in blood, but not urine, from deceased patients not known to have ingested GHB.<sup>72</sup>

## ANTIDOTES

While multiple drugs have been studied, there is no specific antidote for GHB in clinical use today. Anticonvulsant drugs such as clonazepam, phenytoin, phenobarbital, and diazepam do not reverse GHB-induced coma.<sup>87,88</sup> Ethosuximide and dextroamphetamine reverse GHB-induced CNS depression in monkeys, although their clinical use for this purpose has not been reported.<sup>87-89</sup>

Flumazenil has been shown to antagonize GHB-induced anxiolysis and growth hormone secretion in animals but does not reverse CNS depression.<sup>90,91</sup>

Naloxone reverses behavioral, physiologic, and biochemical effects of GHB in animals<sup>5,46-48,92</sup>, but does not reverse CNS or respiratory depression in humans.<sup>56,68,75,76,83,93</sup>

Physostigmine has been used as an analeptic agent in GHB intoxication.<sup>93,94</sup> While studies demonstrate the safety and effectiveness of physostigmine as a reversal agent for GHB-induced anesthesia,<sup>95,96</sup> safety in the controlled setting of anesthesia cannot be extrapolated to safety in the setting of overdose. In GHB overdose there is a high incidence of coingestants, including sympathomimetics, that may lower seizure threshold and alter cardiac conduction. The administration of physostigmine to patients under these conditions may precipitate seizures or cardiac arrhythmias, unwanted complications of its use. Furthermore, patients with severe effects from GHB overdose typically have favorable outcomes with supportive therapy. Reversal of GHB-induced coma with physostigmine does not improve outcome or shorten ED stays when compared with supportive care.<sup>93,94</sup> Therefore, the use of physostigmine as a reversal agent for GHB intoxication is not recommended at this time.

A specific GHB antagonist, NCS-382, is used in basic science research. However, to the best of our knowledge, this agent has not been used in the clinical setting.

## PRODRUGS OF GHB

As the regulation of GHB has tightened, users have turned to its prodrugs to circumvent the law. GBL and 1,4-butanediol are congeners of GHB with legitimate industrial uses that have now become drugs of abuse.

Gamma-butyrolactone is a compound that, when ingested, produces a clinical picture very similar to

that of GHB.<sup>74,75,77,97-99</sup> It is used widely as an industrial solvent and is marketed as a dietary supplement under the names Blue Nitro, Firewater, Renewtrient, and Revivarant, among many others. The oral bioavailability of GBL in rats is 85%, higher than that of GHB.<sup>31</sup> There is no evidence that GBL can bind the GHB receptor; its effects are seen only after metabolism to GHB.<sup>100-102</sup> This conversion is catalyzed by a peripheral lactonase with a half-time of less than 1 minute.<sup>100,101,103</sup> In scientific studies, GBL has a longer duration of action than GHB, possibly due to differences in drug distribution.<sup>5,31,100,102</sup> However, there is no evidence of a longer duration of action of GBL in the setting of illicit use.

1,4-Butanediol is an industrial solvent which is sold on the street under many names, including Pine Needle Extract, Pine Needle Oil, Thunder Nectar and Serenity. Following ingestion, individuals develop a clinical toxidrome similar to that of GHB and GBL.<sup>73,75,104</sup> Like GBL, 1,4-butanediol is unable to bind the GHB receptor and must be metabolized to GHB in order to exert its effects.<sup>105-107</sup> This pathway has not been clearly delineated but likely involves an alcohol dehydrogenase in the liver and an unknown pathway in the CNS.<sup>106,108</sup> Ethanol may delay the onset of toxic effects of 1,4-butanediol through competitive inhibition of alcohol dehydrogenase.<sup>107,109</sup> Additionally, the combination of ethanol and 1,4-butanediol may increase mortality above that seen with either agent alone.<sup>79</sup>

## GHB WITHDRAWAL

As abuse of GHB and its prodrugs has increased, there has emerged a withdrawal syndrome similar to that seen with ethanol and sedative-hypnotic drugs. Clinical characteristics of the syndrome include tremors, agitation, auditory and visual hallucinations, tachycardia, and hypertension.<sup>82,110-124</sup> Wernicke-Korsakoff syndrome has also been associated with GHB withdrawal.<sup>111</sup> As with abuse of ethanol and benzodiazepines, the binge user does not seem to be at risk for significant withdrawal symptoms. Rather, long-term use of GHB or its congeners with round-the-clock dosing at short intervals seems to be a prerequisite for development of the withdrawal syndrome.<sup>82,110-124</sup>

Benzodiazepines are the mainstay of therapy, although neuroleptics, beta-blockers, chloral hydrate, and barbiturates have also been used.<sup>82,110,111,113-115,117-124</sup>

While withdrawal from GHB, GBL, or 1,4-butanediol is similar to withdrawal from ethanol and sedative/hypnotics in its symptoms and treatment, some significant differences exist. The GHB withdrawal syndrome often requires extremely large

doses of benzodiazepines. Chin reports a case of withdrawal requiring 1,138 mg of lorazepam over 4 days, and Craig et al. describe a case of severe GHB withdrawal requiring 507 mg of lorazepam over a period of 90 hours.<sup>113,122</sup> Dyer et al. report one patient requiring 129 mg of lorazepam during the first day of withdrawal, with other patients requiring between 9 and 20 mg per day.<sup>112</sup> Onset of withdrawal symptoms typically occurs within a few hours after cessation of GHB or its prodrugs.<sup>112,114,115,118,120,123,124</sup> Patients with significant withdrawal symptoms may remain symptomatic and/or require treatment for 5 to 15 days.<sup>82,110-115,117,121-124</sup> One death was reported in association with GHB withdrawal, although at necropsy the exact cause was not clear.<sup>112</sup>

## CONCLUSIONS

Gamma hydroxybutyric acid (GHB) and its congeners, GBL and 1,4-butanediol, are popular drugs of abuse at nightclubs and rave parties. Their primary clinical effects are CNS and respiratory depression which may constitute life threatening emergencies. With supportive care, including intubation in some cases, patients typically have a full recovery in six hours or less. Abrupt cessation of these drugs may lead to a withdrawal syndrome requiring large quantities of benzodiazepines to control. Physicians practicing in the acute care setting should be aware of the GHB toxidrome and its withdrawal syndrome.

## References

1. Bessman SP, Fishbein WN. Gamma-hydroxybutyrate, a normal brain metabolite. *Nature*. 1963; 200:1207-8.
2. Laborit H. Sodium 4-hydroxybutyrate. *Int J Neuropharmacol*. 1964; 3:433-52.
3. Metcalf DR, Emde RN, Stripe JT. An EEG-behavioral study of sodium hydroxybutyrate in humans. *Electroencephalogr Clin Neurophysiol*. 1966; 20:506-12.
4. Snead OC.  $\gamma$ -Hydroxybutyrate model of generalized absence seizures: further characterization and comparison with other absence models. *Epilepsia*. 1988; 29:361-8.
5. Cash CD. Gammahydroxybutyrate: an overview of the pros and cons for it being a neurotransmitter and/or a useful therapeutic agent. *Neurosci Biobehav Rev*. 1994; 18:291-304.
6. Mamelak M. Gammahydroxybutyrate: an endogenous regulator of energy metabolism. *Neurosci Biobehav Rev*. 1989; 13:187-98.
7. Godschalk M, Dzoljic MR, Bonta IL. Slow wave sleep and a state resembling absence epilepsy induced in the rat by  $\gamma$ -hydroxybutyrate. *Eur J Pharmacol*. 1977; 44: 105-11.
8. Winters WD, Spooner CE. Various seizure activities following gamma-hydroxybutyrate. *Int J Neuropharmacol*. 1965; 4:197-200.
9. Addolorato G, Balducci G, Capristo E, et al. Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol withdrawal syndrome: a randomized comparative study

- versus benzodiazepine. *Alcohol Clin Exp Res.* 1999; 23: 1596–1604.
10. Gallimberti L, Gentile N, Cibir M, et al. Gamma-hydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet.* 1989; 2:787–9.
  11. Fadda F, Colombo G, Mosca E, Gessa GL. Suppression by gamma hydroxybutyric acid of ethanol withdrawal syndrome of rats. *Alcohol Alcohol.* 1989; 24:447–51.
  12. Gallimberti L, Ferri M, Ferrara SD, Fadda F, Gessa GL. Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double blind study. *Alcohol Clin Exp Res.* 1992; 16:673–6.
  13. Fadda F, Argiolas A, Melis MR, De Montis G, Gessa GL. Suppression of voluntary ethanol consumption in rats by gamma-butyrolactone. *Life Sci.* 1989; 32:1471–7.
  14. Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. *Can J Neurol Sci.* 1979; 6:1–6.
  15. Scharf MB, Brown D, Woods M, Brown L, Hirschowitz J. The effects and effectiveness of  $\gamma$ -hydroxybutyrate in patients with narcolepsy. *J Clin Psychiatry.* 1985; 46: 222–5.
  16. Mamelak M, Scharf MB, Woods M. Treatment of narcolepsy with  $\gamma$ -hydroxybutyrate. a review of clinical and sleep laboratory findings. *Sleep.* 1986; 9:285–9.
  17. Lammers GJ, Arends J, Declerck AC, Ferrari MD, Schouwink G, Troost J. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep.* 1993; 16:216–20.
  18. Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of  $\gamma$ -hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. *Sleep.* 1990; 13:479–90.
  19. Scrima L, Hartman PG, Johnson FH, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. *Biol Psychiatry.* 1989; 26:331–43.
  20. Maitre M. The  $\gamma$ -hydroxybutyrate signaling system in brain: organization and functional implications. *Prog Neurobiol.* 1997; 51:337–61.
  21. Kaufman EE, Nelson T, Goochee C, Sokoloff L. Purification and characterization of an NADP<sup>+</sup>-linked alcohol oxidoreductase which catalyzes the interconversion of  $\gamma$ -hydroxybutyrate and succinic semialdehyde. *J Neurochem.* 1979; 32:699–712.
  22. Tunnicliff G. Sites of action of gamma-hydroxybutyrate (GHB)—a neuroactive drug with abuse potential. *Clin Toxicol.* 1997; 35:581–90.
  23. Vayer P, Mandel P, Maitre M. Gamma-hydroxybutyrate, a possible neurotransmitter. *Life Sci.* 1987; 41:1547–57.
  24. Roth RH, Giarman NJ. Conversion *in vivo* of  $\gamma$ -aminobutyric acid to  $\gamma$ -hydroxybutyric acid in the rat. *Biochem Pharmacol.* 1969; 18:247–50.
  25. Poldrugo F, Addolorato G. The role of  $\gamma$ -hydroxybutyric acid in the treatment of alcoholism: from animal to clinical studies. *Alcohol Alcohol.* 1999; 34:15–24.
  26. 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; 45:353–6.
  27. Lettieri J, Fung H. Absorption and first-pass metabolism of <sup>12</sup>C-gamma-hydroxybutyric acid. *Res Commun Chem Pathol Pharmacol.* 1976; 13:425–37.
  28. Helrich M, McAslan TC, Skolnik S, Bessman SP. Correlation of blood levels of 4-hydroxybutyrate with state of consciousness. *Anesthesiology.* 1964; 25:771–5.
  29. Ferrara SD, Zotti S, Tedeschi L, et al. Pharmacokinetics of  $\gamma$ -hydroxybutyric acid in alcohol dependent patients after single and repeated oral doses. *Br J Clin Pharmacol.* 1992; 34:231–5.
  30. Ferrara SD, Tedeschi L, Frison G, et al. Effect of moderate or severe liver dysfunction on the pharmacokinetics of  $\gamma$ -hydroxybutyric acid. *Eur J Clin Pharmacol.* 1996; 5: 305–10.
  31. Lettieri J, Fung H. Improved pharmacological activity via pro-drug modification: comparative pharmacokinetics of sodium  $\gamma$ -hydroxybutyrate and  $\gamma$ -butyrolactone. *Res Commun Chem Path Pharmacol.* 1978; 22:107–18.
  32. Scharf MB, Lai AA, Branigan B, Stover R, Berkowitz DB. Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep.* 1998; 21:507–14.
  33. Mamelak M, Escriu JM, Stokan O. The effects of  $\gamma$ -hydroxybutyrate on sleep. *Biol Psychiatry.* 1977; 12:273–88.
  34. Dyer JE.  $\gamma$ -Hydroxybutyrate: a health-food product producing coma and seizurelike activity. *Am J Emerg Med.* 1991; 9:321–4.
  35. Snead OC, Liu C. Gamma-hydroxybutyric acid binding sites in rat and human brain synaptosomal membranes. *Biochem Pharmacol.* 1984; 33:2587–90.
  36. Tunnicliff G. Significance of  $\gamma$ -hydroxybutyric acid in the brain. *Gen Pharmacol.* 1992; 23:1027–34.
  37. Williams SR, Turner JP, Crunelli V. Gamma-hydroxybutyrate promotes oscillatory activity of rat and cat thalamocortical neurons by a tonic GABA<sub>B</sub> receptor-mediated hyperpolarization. *Neuroscience.* 1995; 66:133–41.
  38. Xie X, Smart TG.  $\gamma$ -Hydroxybutyrate hyperpolarizes hippocampal neurons by activating GABA<sub>B</sub> receptors. *Eur J Pharmacol.* 1992; 212:291–4.
  39. Mathivet P, Bernasconi R, De Barry J, Marescaux C, Bittinger H. Binding characteristics of  $\gamma$ -hydroxybutyric acid as a weak but selective GABA<sub>B</sub> receptor agonist. *Eur J Pharmacol.* 1997; 321:67–75.
  40. Vayer P, Mandel P, Maitre M. Conversion of  $\gamma$ -hydroxybutyrate to  $\gamma$ -aminobutyrate *in vitro*. *J Neurochem.* 1985; 45:810–14.
  41. Doherty JD, Stout RW, Roth RH. Metabolism of [<sup>12</sup>C]  $\gamma$ -hydroxybutyric acid by rat brain after intraventricular injection. *Biochem Pharmacol.* 1975; 24:469–74.
  42. Margolis RK. The effect of  $\gamma$ -hydroxybutyric acid on amino-acid levels in brain. *Biochem Pharmacol.* 1969; 18:1243–6.
  43. Giarman NJ, Schmidt KF. Some neurochemical aspects of the depressant action of  $\gamma$ -butyrolactone on the central nervous system. *Br J Pharmacol.* 1963; 20:563–8.
  44. Vickers MD. Gammahydroxybutyric acid. *Int Anesthiol Clin.* 1969; 7:75–89.
  45. Waldmeier PC, Fehr B. Effects of baclofen and  $\gamma$ -hydroxybutyrate on rat striatal and mesolimbic 5-HT metabolism. *Eur J Pharmacol.* 1978; 49:177–84.
  46. Crosby G, Ito M, Kaufman E, Nelson T, Sokoloff L. Naloxone pretreatment alters the local cerebral metabolic effect of  $\gamma$ -hydroxybutyrate in rats. *Brain Res.* 1983; 275: 194–7.
  47. Feigenbaum JJ, Howard SG. Naloxone reverses the inhibitory effect of  $\gamma$ -hydroxybutyrate on central DA release *in vivo* in awake animals: a microdialysis study. *Neurosci Lett.* 1997; 224:71–4.
  48. Snead OC, Bearden LJ. Naloxone overcomes the dopaminergic, EEG and behavioral effects of gamma hydroxybutyrate. *Neurology.* 1980; 30:832–8.
  49. Mahon KD, Tomaszewski CA, Tayal VS. Emergency department presentation of serum confirmed GHB ingestions [abstract]. *Acad Emerg Med.* 1999; 6:395–6.
  50. Lund LO, Humphries JH, Virtue RW. Sodium gamma hydroxybutyrate: laboratory and clinical studies. *Can Anaes Soc J.* 1965; 12:379–85.
  51. Centers for Disease Control. Epidemiologic notes and reports: multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *MMWR.* 1990; 39:861–3.

52. Schwartz RH, Milteer R, LeBeau MA. Drug facilitated sexual assault ('date rape'). *South Med J*. 2000; 93: 558-61.
53. ElSohly MA, Salamone SJ. Prevalence of drugs used in cases of alleged sexual assault. *J Anal Toxicol*. 1999; 23: 141-6.
54. Mullins ME. Laboratory confirmation of flunitrazepam in alleged case of date rape. *Acad Emerg Med*. 1999; 6: 966-8.
55. Henretig F, Vassalluzo C, Osterhoudt K, et al. "Rave by net": Gamma-hydroxybutyrate (GHB) toxicity from kits sold to minors via the Internet [abstract]. *J Toxicol Clin Toxicol*. 1998; 36:503.
56. Li J, Stokes SA, Woeckener A. A tale of novel intoxication: seven cases of  $\gamma$ -hydroxybutyric acid overdose. *Ann Emerg Med*. 1998; 31:723-8.
57. Chin RL, Sporer KA, Cullison B, Dyer JE, Wu TD. Clinical course of  $\gamma$ -hydroxybutyrate overdose. *Ann Emerg Med*. 1998; 31:716-22.
58. Garrison G, Mueller P. Clinical features and outcomes after unintentional gamma hydroxybutyrate (GHB) overdose [abstract]. *J Toxicol Clin Toxicol*. 1998; 36: 503-4.
59. Li J, Stokes SA, Woeckener A. A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. *Ann Emerg Med*. 1998; 31:729-36.
60. Hunter AS, Long WJ, Rylie CG. An evaluation of gamma-hydroxybutyric acid in paediatric practice. *Br J Anaesth*. 1971; 43:620-7.
61. Appleton PJ, Burn JMB. A neuroinhibitory substance: gamma hydroxybutyric acid. *Anesth Analg*. 1968; 47: 164-70.
62. Vickers MD. Gamma hydroxybutyric acid. *Proc R Soc Med*. 1968; 61:821-4.
63. Snead OC. Gamma hydroxybutyrate in the monkey I. Electroencephalographic, behavioral and pharmacokinetic studies. *Neurology*. 1978; 28:636-42.
64. Snead OC, Yu RK, Huttenlocher PR. Gamma hydroxybutyrate: correlation of serum and cerebrospinal fluid levels with electroencephalographic and behavioral effects. *Neurology*. 1976; 26:51-6.
65. Lapiere O, Montplaisir J, Lamarre M, Bedard MA. The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep triggering mechanisms. *Sleep*. 1990; 13: 24-30.
66. Entholzner E, Mielke L, Pichlmeier R, Weber F, Schneck H. EEG changes during sedation with gamma-hydroxybutyric acid. *Anaesthetist*. 1995; 44:345-50.
67. Virtue RW, Lund LO, Beckwith HJ, Vogel JHK. Cardiovascular reactions to gamma hydroxybutyrate in man. *Can Anaesth Soc J*. 1966; 13:119-23.
68. Suner S, Szlatenyi CS, Wang RY. Pediatric gamma hydroxybutyrate intoxication. *Acad Emerg Med*. 1997; 4: 1041-5.
69. Centers for Disease Control and Prevention. Gamma hydroxy butyrate use—New York and Texas, 1995-1996. *MMWR*. 1997; 46:281-3.
70. Ferrara SD, Tedeschi L, Frison G, Rossi A. Fatality due to gamma-hydroxybutyric acid (GHB) and heroin intoxication. *J Forens Sci*. 1995; 40:501-4.
71. Timby N, Eriksson A, Bostrom K. Gamma-hydroxybutyrate associated deaths [letter]. *Am J Med*. 2000; 108: 518-9.
72. Fieler EL, Coleman DE, Baselt RC.  $\gamma$ -Hydroxybutyrate concentrations in pre- and postmortem blood and urine [letter]. *Clin Chem*. 1998; 44:692.
73. Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, Peacock EA. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med*. 2001; 344:87-94.
74. Rambourg-Schepens M, Buffet M, Durak C, Mathieu-Nolf M. Gamma butyrolactone poisoning and its similarities to gamma hydroxybutyric acid: two case reports. *Vet Hum Toxicol*. 1997; 39:234-5.
75. Ingels M, Rangan C, Bellezzo J, Clark RF. Coma and respiratory depression following the ingestion of GHB and its precursors: three cases. *J Emerg Med*. 2000; 19: 47-50.
76. Viera AJ, Yates SW. Toxic ingestion of gamma-hydroxybutyric acid. *South Med J*. 1999; 92:404-5.
77. Higgins TF, Borron SW. Coma and respiratory arrest after exposure to butyrolactone. *J Emerg Med*. 1996; 14: 435-7.
78. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and  $\gamma$ -hydroxybutyrate. *Arch Intern Med*. 1999; 159:2221-4.
79. Poldrugo F, Barker S, Basa M, Mallardi F, Snead OC. Ethanol potentiates the toxic effects of 1,4-butanediol. *Alcohol Clin Exp Res*. 1985; 9:493-7.
80. McCabe ER, Layne EC, Saylor DF, Slusher N, Bessman SP. Synergy of ethanol and a natural soporific—gamma hydroxybutyrate. *Science*. 1971; 171:404-6.
81. Colombo G, Agabio R, Lobina C, Reali R, Fadda F, Gessa GL. Cross-tolerance to ethanol and  $\gamma$ -hydroxybutyric acid. *Eur J Pharmacol*. 1995; 273:235-8.
82. Bowles TM, Sommi RW, Amiri M. Successful management of prolonged  $\gamma$ -hydroxybutyrate and alcohol withdrawal. *Pharmacotherapy*. 2001; 21:254-7.
83. Thomas G, Bonner S, Gascoigne A. Coma induced by abuse of gamma-hydroxybutyrate (GHB or liquid ecstasy): a case report. *BMJ*. 1997; 314:35-6.
84. 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; 11:483-7.
85. Elian AA. A novel method for GHB detection in urine and its application in drug-facilitated sexual assaults. *Forens Sci Int*. 2000; 109:183-7.
86. Lettieri JT, Fung H. Evaluation and development of gas chromatographic procedures for the determination of  $\gamma$ -hydroxybutyric acid and  $\gamma$ -butyrolactone in plasma. *Biochem Med*. 1978; 20:70-80.
87. Snead OC. Gamma hydroxybutyrate in the monkey III. Effect of intravenous anticonvulsant drugs. *Neurology*. 1978; 28:1173-8.
88. Snead OC. Gamma hydroxybutyrate in the monkey II. Effect of chronic anticonvulsant drugs. *Neurology*. 1978; 28:643-8.
89. Snead OC. Gamma hydroxybutyrate in the monkey IV. Dopaminergic mechanisms. *Neurology*. 1978; 28: 1179-82.
90. Schmidt-Mutter C, Pain L, Sandner G, Gobaille S, Maitre M. The anxiolytic effect of  $\gamma$ -hydroxybutyrate in the elevated plus maze is reversed by the benzodiazepine receptor antagonist, flumazenil. *Eur J Pharmacol*. 1998; 342:21-7.
91. Gerra G, Caccavari R, Fontanesi B, et al. Flumazenil effects on growth hormone response to gamma-hydroxybutyric acid. *Int Clin Psychopharmacol*. 1994; 9:211-5.
92. Vayer P, Gobaille S, Mandel P, Maitre M. 3'-5' Cyclic-guanosine monophosphate increase in rat brain hippocampus after gamma-hydroxybutyrate administration. Prevention by valproate and naloxone. *Life Sci*. 1987; 41: 605-10.
93. Yates SW, Viera AJ. Physostigmine in the treatment of

- $\gamma$ -hydroxybutyric acid overdose. *Mayo Clin Proc.* 2000; 75:401–2.
94. Caldicott DGE, Kuhn M. Gamma-hydroxybutyrate overdose and physostigmine: teaching new tricks to an old drug? *Ann Emerg Med.* 2001; 37:99–102.
  95. Henderson RS, Holmes CM. Reversal of the anaesthetic action of sodium gamma-hydroxybutyrate. *Anaesth Intensive Care.* 1976; 4:351–4.
  96. Holmes CM, Henderson RS. The elimination of pollution by a non-inhalational technique. *Anaesth Intensive Care.* 1978; 6:120–4.
  97. LoVecchio F, Curry SC, Bagnasco T. Butyrolactone-induced central nervous system depression after ingestion of RenewTrient, a “dietary supplement” [letter]. *N Engl J Med.* 1998; 339:847–8.
  98. Centers for Disease Control and Prevention. Adverse events associated with the ingestion of gamma-butyrolactone. Minnesota, New Mexico and Texas, 1998–1999. *MMWR.* 1999; 48:137–40.
  99. Hardy CJ, Slifman NR, Klontz KC, Dyer JE, Coody GL, Love LA. Adverse events reported with the use of gamma butyrolactone products marketed as dietary supplements [abstract]. *J Toxicol Clin Toxicol.* 1999; 37: 649.
  100. Giarman NJ, Roth RH. Differential estimation of gamma-butyrolactone and gamma-hydroxybutyric acid in rat blood and brain. *Science.* 1964; 145:583–4.
  101. Roth RH, Giarman NJ.  $\gamma$ -Butyrolactone and  $\gamma$ -hydroxybutyric acid—I. Distribution and metabolism. *Biochem Pharmacol.* 1966; 15:1333–48.
  102. Roth RH, Delgado JMR, Giarman NJ.  $\gamma$ -Butyrolactone and  $\gamma$ -hydroxybutyric acid—II. The pharmacologically active form. *Int J Neuropharmacol.* 1966; 5:421–8.
  103. Roth RH, Giarman NJ. Preliminary report on the metabolism of  $\gamma$ -butyrolactone and  $\gamma$ -hydroxybutyric acid. *Biochem Pharmacol.* 1965; 14:177–8.
  104. Dyer JE, Galbo MJ, Andrews KM. 1,4-Butanediol, “Pine Needle Oil”: overdose mimics toxic profile of GHB [abstract]. *J Toxicol Clin Toxicol.* 1997; 35:554.
  105. Roth RH, Giarman NJ. Evidence that central nervous system depression by 1,4-butanediol is mediated through a metabolite, gamma-hydroxybutyrate. *Biochem Pharmacol.* 1968; 17:735–9.
  106. Bessman SP, McCabe ERB. 1,4-butanediol—a substrate for rat liver and horse liver alcohol dehydrogenases. *Biochem Pharmacol.* 1972; 21:1135–42.
  107. Poldrugo F, Snead OC. 1,4-butanediol,  $\gamma$ -hydroxybutyric acid and ethanol: relationships and interactions. *Neuropharmacology.* 1984; 33:109–13.
  108. Snead OC, Furner R, Liu CC. *In vivo* conversion of  $\gamma$ -aminobutyric acid and 1,4-butanediol to  $\gamma$ -hydroxybutyric acid in rat brain. *Biochem Pharmacol.* 1989; 38: 4375–80.
  109. Schneider T, Burkhardt K, Donovan JW. Butanediol toxicity delayed by preingestion of ethanol. *Int J Med Toxicol.* 2000; 3:1.
  110. Dyer JE, Andrews KM. Gamma hydroxybutyrate withdrawal [abstract]. *J Toxicol Clin Toxicol.* 1997; 35:553–4.
  111. Friedman J, Westlake R, Furman M. “Grievous Bodily Harm”: gamma hydroxybutyrate abuse leading to a Wernicke-Korsakoff syndrome. *Neurology.* 1996; 46: 469–71.
  112. Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med.* 2001; 37: 147–53.
  113. Craig K, Gomez HF, McManus JL, Bania TC. Severe gamma-hydroxybutyrate withdrawal: a case report and literature review. *J Emerg Med.* 2000; 18:65–70.
  114. Galloway GP, Frederick SL, Staggers F. Physical dependence on sodium oxybate [letter]. *Lancet.* 1994; 343:57.
  115. Galloway GP, Frederick SL, Staggers FE, Gonzales M, Stalcup SA, Smith DE. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction.* 1997; 92:89–96.
  116. Greene T, Dougherty T, Rodi A.  $\gamma$ -Butyrolactone (GBL) withdrawal presenting as acute psychosis [abstract]. *J Toxicol Clin Toxicol.* 1999; 37:651.
  117. Catalano MC, Glass JM, Catalano G, Burrows SL, Lynn WA, Weitzner BS. Gamma butyrolactone (GBL) withdrawal syndromes. *Psychosomatics.* 2001; 42:83–8.
  118. Addolorato G, Caputo F, Capristo E, Bernardi M, Stefanini GF, Gasbarrini G. A case of gamma-hydroxybutyric acid withdrawal syndrome during alcohol addiction treatment: utility of diazepam administration. *Clin Neuropharmacol.* 1999; 22:60–2.
  119. Hernandez M, McDaniel CH, Costanza CD, Hernandez OJ. GHB-induced delirium: a case report and review of the literature on gamma hydroxybutyric acid. *Am J Drug Alcohol Abuse.* 1998; 24:179–83.
  120. Schneir AB, Ly BT, Clark RF. A case of withdrawal from the GHB precursors gamma-butyrolactone and 1,4-butanediol. *J Emerg Med.* 2001; 21:31–3.
  121. Hutto B, Fairchild A, Bright R. [gamma]-Hydroxybutyrate withdrawal and chloral hydrate [letter]. *Am J Psychiatry.* 200; 157:1706.
  122. Chin RL. A case of severe withdrawal from gamma-hydroxybutyrate [letter]. *Ann Emerg Med.* 2001; 37:551–2.
  123. Mycyk MB, Wilemon C, Aks SE. Two cases of withdrawal from 1,4-butanediol use. *Ann Emerg Med.* 2001; 38:345.
  124. McDaniel CH, Miotto KA. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five case studies. *J Psychoactive Drugs.* 2001; 33:143–9.