GHB: An Important Pharmacologic and Clinical Update

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Abstract Gamma-hydroxybutyrate (GHB) intoxication is a significant cause of morbidity and mortality in patients taking the drug for recreational purposes. Due to the recent increase in emergency room visits, hospital admissions, and deaths, it has become necessary to re-examine the pharmacology, pharmacokinetics, pharmacodynamics, clinical manifestations, and potential adverse effects associated with GHB use. We present an important pharmacologic and clinical update on GHB.

INTRODUCTION

There has been a recent resurgence in the recreational use of gamma-hydroxybutyrate (GHB) in the United States. Historically, GHB was sold in health food stores until it was removed from the retail market by the Food and Drug Administration (FDA) in 1991.[1] However, the Dietary Supplement Health and Education Act of 1994 (DSHEA) made possible the legal sale of GHB precursors, gamma-butyrolactone (GBL) and 1,4-butanediol.[2] Once ingested, both GBL and 1,4 butanediol are converted enzymatically to GHB which can then exert its pharmacologic effects. Some of the medicinal uses of GHB include narcolepsy, depression, alcohol withdrawal, epilepsy, and anesthesia.[2] GHB has become a popular drug of abuse when used alone or in combination with other substances. Bodybuilders have used it for its alleged anabolic effect on muscles. Pre-clinical trials with GHB have been performed looking specifically at the interactions of brain neurotransmitters.

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Many of the problems in the United States arise from those who make GHB from recipes obtained over the Internet. GHB or its precursors are especially toxic when mixed with alcohol and other drugs to increase its euphoric effects.[3-5] This combination has led to significant morbidity and mortality.[1-8] When GHB and alcohol are consumed together the risk of respiratory depression increases substantially, exacerbating the toxicity of either drug alone.[2] This paper will review what is known about GHB and suggest appropriate emergency room management.

WHAT IS GHB?

GHB is a chemical compound structurally similar to the inhibitory brain neurotransmitter GABA. Its proposed function is as an inhibitory neuromodulator within the central nervous system, affecting the function of other neurotransmitters in the dopaminergic and gabaergic systems.[2] Physiologic and pharmacological actions are thought to be mediated through specific GHB receptors, GABA B receptors, or a combination.[9] Pre-clinical studies conducted in monkeys illustrate that GHB induces a trance-like stupor accompanied by electroencephalographic changes and hypothermia.[10] In hepatic failure and during alcohol intoxication, the rates of GHB synthesis and degradation are decreased, resulting in increased GHB serum levels and subsequent increased toxicity.[2, 11]

Many people abusing GHB frequent nightclubs and raves, while others compound GHB using recipes obtained through the Internet. Many users ingest GHB for its purported anabolic effect of enhancing body mass. Some utilize GHB to self-medicate conditions such as depression and alcoholism, although there remains a paucity of literature to support its use for

these diagnoses. Because the vehicle is often disguised as a clear, salty tasting liquid that is easily masked in alcoholic beverages, it has earned a reputation as a date rape drug.[3, 4] From August of 1995 through September of 1996, poison control centers in New York and Texas reported 69 acute poisonings and one death attributed to GHB.[12] In Minnesota during October through September 1998, an additional 34 cases of GBL toxicity were reported.[13] At Shands Hospital at the University of Florida, there were five MICU admissions requiring intubations related to GHB toxicity in a span of less than 2 years. Due to the recent resurgence of this substance as a drug of abuse, every case of unexplained sudden coma without evidence of head injury, known intake of other coma inducing drugs, or signs and symptoms of increased intracranial pressure should be considered a possible GHB overdose and treated appropriately. GHB is not included in routine toxicology screens.[14]

GABA and Proposed Mechanisms of Action

The precise pharmacological mechanism of action for GHB remains to be elucidated. However, many studies suggest the probable presence of specific GHB binding sites apart from the GABA receptor binding sites.[15, 16] It is also postulated that GHB may mimic the action of GABA acting as a neurotransmitter or neuromodulator.[17] There is compelling evidence that GHB formation may occur via a GABA independent mechanism.[15, 16] The clinically relevant question remains: How does GHB work within the GABA inhibitory neurotransmitter system?[17]

GHB is behaviorally and biochemically distinct from GABA. Studies suggest that GHB does not consistently affect GABA A or GABA B induced responses.[18] However, the data is conflicting.[2, 15-19] GHB does not appear to be a GABA prodrug or a GABA agonist. Yet the GHB precursor, Gamma-butyrolactone (GBL), may have limited GABA agonist activity.[18] One theory suggests the GABA B receptors may be stimulated by the GABA formed through GHB metabolism.[19] Another theory suggests GHB induces a G-protein-mediated decease in adenyl cyclase via a GHB-specific G protein coupled presynaptic receptor that is different from GABA B.[2, 16] Based on the data available from animal models, an indirect receptor pathway mechanism is suspected.

GHB meets many of the criteria of a neuromodulator or neurotransmitter, since it is a metabolite of GABA, and it is synthesized and stored in cerebral neurons.[20] Neuronal depolarization releases GHB into the extracellular space in a calcium dependent manner. Stimulation of receptors produces hyperpolarization in dopaminergic structures. This hyperpolarization causes a decrease in dopamine release. However, in the hippocampus and frontal cortex GHB induces a depolarization secondary to cGMP and inositol phosphate turnover.[11] After GHB is metabolized, it is not reconverted back into GABA.

Dopamine and Proposed Mechanisms of Action

GHB has a profound effect as an inhibitory neurotransmitter in the dopaminergic system. The concentration of GHB normally found in the human brain is two to three times higher in the basal ganglia than in the cerebral cortices.[21] GHB is utilized often in neurological research since it is one of only a few substances that acts primarily on dopamine release, and it acts as an inhibitor in vivo.[22, 24, 25] However, a paradoxical reaction occurs in rats anesthetized with urethane[23] or in patients with high serum concentrations of calcium.[24] In these instances, GHB stimulates dopamine rather than having the expected inhibitory response.[23]

Opiate Receptors and Proposed Mechanisms of Action

GHB and morphine have similar clinical effects, including euphoria, respiratory depression, and potential for dependence with prolonged use.[2, 26] GHB activity is reversed in part upon naloxone administration.[27, 28] The mechanism for naloxone reversing GHB effects is unknown. While it has been theorized that GHB may have central effects by acting as a direct opiate agonist, studies have shown that GHB does not bind to mu, delta, and kappa opioid receptors.[26] GHB may be an indirect agonist acting on enkephalin or dynorphin receptors, but this is not clear.[28] Therefore, reversal of GHB by naloxone probably does not involve an opioid mechanism, but may result from the reversal of GHB induced inhibition of central dopamine release.[26, 27]

Other Intracerebral Effects in Animal Models

Intraperitoneal GHB infusion causes increased dopamine in the cerebral hemispheres as well as in the hypo-

thalamus. There is a subsequent decrease in norepinephrine secretion in the hypothalamus with no change in serotonin concentrations. Low doses of GHB may selectively affect catecholaminergic neuronal activity.[29] Currently it is unclear whether this data is applicable to humans.

GHB is found in high concentrations in some peripheral tissues. It is thought that GHB may play a role in decreasing energy substrate consumption, protect tissues from anoxia, and protect tissues from excessive metabolic demand since GHB serum concentrations are known to rise under stressful circumstances. Therefore, it may be an endogenous protective agent when tissue energy supplies are low.[30, 31]

Sleep and Growth Hormone Effects

The effects of GHB on sleep have been well documented.[31-40] During the first two hours after sleep onset, there is an increase in growth hormone secretion, as well as an increase in stage IV sleep time.[32] This effect has led to the unsubstantiated use of GHB by bodybuilders. Abrupt but transient elevations in prolactin and cortisol have also been observed. Yet, thyrotropin and melatonin concentrations do not appear to be altered.[32] GHB pharmacokinetics were examined in a small cohort of adult narcoleptic patients at steady-state concentrations. Results confirmed nonlinear pharmacokinetics, and capacity-limited elimination when patients received fixed doses of 3 grams twice nightly.[33]

A small, double-blind crossover study examined the effect of GHB in patients with narcolepsy.[37] A therapeutic effect with decreased cataplexy, as well as improved nocturnal sleep quality was demonstrated.[37] GHB rapidly induced sleep without suppressing REM sleep in both normal and narcoleptic patients.[37] Another study demonstrated that cataplexy was decreased by GHB with fewer attacks and decreased subjective arousals.[38] In a placebo-controlled, double-blind, cohort study examining the efficacy of GHB on nocturnal or diurnal sleep, stage III and IV sleep was increased, whereas stage I sleep was diminished. GHB improved the REM efficiency and decreased the wake time after sleep onset.[39] GHB promoted cataplexy when administered during the day. However, it decreased daytime cataplexy when given at night.[40] Based on these studies, GHB has clearly shown benefit in treatment of narcolepsy. However, GHB is currently a schedule 1 controlled drug, and its only permitted therapeutic use is within clinical trials.[41] A new pharmaceutical formulation of GHB, known by its USAN name sodium oxybate, may become a schedule III pharmaceutical used for the treatment of narcolepsy.[41-45] GHB currently is designated as orphan drug status for the treatment of narcolepsy, and is only permitted within the scope of clinical trials.[44] The FDA will consider the safety and efficacy of NDA 21-196, Xyrem® (sodium oxybate, Orphan Medical, Inc.) in meetings scheduled for 2001.[45]

Treatment of Substance Abuse

GHB use in the treatment of substance abuse is commonplace in European countries.[45-50] A randomized, single-blind, controlled cohort study was conducted in Italy to compare the efficacy and safety of diazepam versus GHB in the treatment of alcohol withdrawal symptoms (AWS).[46] GHB was faster to decrease anxiety, agitation, and depression scores. The statistical significance of the differences between groups was not evaluated. Both treatment arms were determined safe and both were well tolerated in AWS management.[46]

An open label, multicenter study was conducted with GHB in the treatment of alcohol withdrawal symptoms in one hundred seventy-nine patients. The study group was treated for six months with a 50-mg/kg dose of GHB daily. The drug was well tolerated with no serious adverse effects. Complete abstinence was attained in 78% of treated patients during the study period. This was accompanied by a reduction in alcohol craving when measured by the standardized Alcohol Craving Scale. Forty-three patients remained abstinent at six months. Thirty subjects remained abstinent at one year.[47] Another study examined GHB potential to decrease alcohol withdrawal symptoms and demonstrated efficacy in reducing tremors, sweating, nausea, depression, anxiety, and restlessness. There was a noted common side effect of dizziness.[48] GHB may be useful in the treatment of alcohol dependence and accompanying withdrawal symptoms.[46-50] Larger, well controlled, long term studies need to be conducted to substantiate these observations.

GHB has also been studied for its effects on opiate withdrawal.[51-54] It had no consistent effects when used as pre-treatment for naloxone precipitated opiate withdrawal.[51, 52] Small, non-controlled studies suggested there may be a benefit in this population,[53, 54] but true efficacy has yet to be established.

ADVERSE EFFECTS

Adverse effects associated with GHB are dose-dependent. An oral dose of 10 mg/kg has been reported to cause amnesia and hypotonia. Doses of 20 to 30 mg/kg have resulted in somnolence within 15 minutes, whereas doses of greater than 50 mg/kg result in unconsciousness and coma. Small doses less than 10 mg/kg have resulted in nausea, vomiting, dizziness, confusion, drowsiness, decreased respirations and seizure-like phenomenon.[55] In addition to respiratory depression, hypotension and bradycardia may result. Dizziness may occur acutely or for several weeks after taking the last GHB dose. The synergy of GHB and alcohol or other recreational drugs is of greatest clinical concern.[2-5] The combination seems to worsen respiratory symptoms and exacerbate central nervous system effects.[2-5, 55] GHB has also been associated with a withdrawal syndrome of insomnia, anxiety, and tremor that usually resolves within three to twelve days.[20] GHB use has been correlated with hypothermia and EEG findings of spike and wave discharges that may explain the described seizure-like phenomenon in users. Studies have shown no correlation between GHB-induced absence seizures and hypothermia. They seem to occur by separate, independent mechanisms.[56] Clinicians should keep in mind that serum levels may fluctuate with circadian rhythm. One study demonstrated that daytime levels of GHB are only 61% of nighttime levels. This fact may be clinically important since most overdoses present to the emergency room at night.[57]

TREATMENT OF GHB TOXICITY

Treatment of GHB toxicity involves supportive care measures since the majority of GHB effects, even when mixed with other drugs, will wear off within hours. The most serious of these effects is the respiratory depression that can lead to hypoxia and death. The challenge in treating patients who have acquired GHB on the street is that there is no way to ascertain the dose they have consumed. Further, users often believe that they have taken a low dose but have unknowingly consumed a higher concentration contained in a small volume.

Naloxone administration in the treatment of GHB is controversial. As mentioned earlier, naloxone is an opiate antagonist that has been shown to reverse many of the central effects of GHB. It has been our experience that many patients who are using GHB also concomitantly use opiate drugs that appear in toxicology screens. It is the high association with opiate use as well as a favorable response in treated animals that we recommend use of the drug.

Because GHB has been used in the study of epilepsy, there is a question regarding the necessity, benefits, and risks associated with the use of anticonvulsants in the treatment of GHB-induced seizures. EEG changes induced by GHB were normalized with Phenobarbital administration.[58] In addition, myoclonic jerking was abolished with ethosuximide, decreased with diazepam, and increased with clonazepam.[58] Anticonvulsants experimentally decreased the frequency of myoclonic jerking when administered prior to GHB.[58] Stupor was decreased with ethosuximide.[58] Valproate and ethosuximide are thought to decrease the GABA-like effect at the GABA B receptor by inhibition of GHB dehydrogenase.[59] The question for the clinician to ponder is whether the use of anticonvulsants will alter the respiratory depression and CNS side effects of GHB in humans. There is no clear answer at this time. Theoretically, benzodiazepines may worsen respiratory depression, whereas, intravenous valproic acid merits further study in humans and consideration as a potential treatment for GHB induced seizures. Diazepam has been used in humans to treat GHB and GBL withdrawal syndrome with success. Reported regimens have utilized diazepam for 6 to 11 days.[60-62]

Another therapeutic option for the treatment of GHB toxicity is physostigmine.[1, 63-65] Historically, GHB was used in Europe for anaesthesia. Its use was curtailed because of side effects including long recovery times due to difficulty in arousal after surgical procedures. Henderson and Holmes demonstrated that 2mg of intravenous physostigmine provided a rapid, safe, and sustained awakening in GHB anesthetized-patients within a 2 to 10 minute window.[64] The mechanism of GHB reversal involves the cholinergic system with

direct or indirect effects on dopamine and GABA. Physostigmine can cause cholinergic crisis and caution should be exercised when administering the drug. Side effects of physostigmine include nausea, vomiting, salivation and bradycardia. Atropine should be at the bedside, especially since GHB also causes bradycardia.[63] Despite its proven benefit, the side effects of physostigmine may present more of a risk than a benefit in treating GHB overdose.[65] At our hospital, routine use is not recommended. Physostigmine is considered if there is an acute need to wake the patient for neurological or physical examination in cases of emergent surgery after a traumatic accident.

The final note on treatment is that many patients with GHB overdose awaken from a comatose state suddenly and may display aggressive behavior. Therefore, patients with suspected overdose should be restrained with soft wrist and ankle restraints as well as a posey-vest. This precaution will eliminate difficulty in securing the patient's airway during a sudden awakening and decrease the risk for aspiration pneumonia and self-extubation. Patients may awaken and attempt to self-extubate before they are adequately exchanging oxygen. Extubate patients who are aggressive and violent with caution. Patients may not oxygenate well without ventilation despite normal movement of all extremities and the ability to communicate with staff.

Mechanism for the Sudden Awakening in GHB

The one truly distinguishing feature of GHB toxicity is the sudden awakening of the patient from a comatose state to a normal or hyperactivated state of arousal. A similar awakening is seen in patients who have strokes involving the paramedian vessels that supply medial thalamus and areas of the reticular activating system. Similarly, patients with paramedian infarctions arouse suddenly from a comatose state and have continuous fluctuations in their level of consciousness. Clinically these arousal syndromes can be treated by dopamine agonists or amphetamines. It is known that extrastriatal sources[66,67] of dopamine exist and they are currently being mapped. The dopamine pathways involving medial thalamic areas remain unpublished at this time. One potential mechanism for coma followed by sudden awakening in GHB toxicity may involve transient inhibition of medial thalamic dopamine release by GHB that may have a strong inhibitory effect on the dopamine neurotransmitter system. The paramedian infarction of the thalamus may provide a useful model for the study of the sudden awakening phenomenon. This mechanism remains to be elucidated.

Clinical Presentation

Eight cases of GHB overdose presented to the University of Florida for acute management between August 1997 and April 1998. Previously we described the six common presentations of GHB toxicity[1] (Table 1).

Table 1: Clinical Presentations of GHB Toxicity

1.	Abrupt Awakening
2.	Self Extubation with the Possibility of Aspiration Pneumonia
3.	Mixed with Other Drugs
4.	Bradycardia or Atrial Fibrillation
5.	Mixed with Ecstasy
6.	Observation of a patient without intubation

Since most cases present post-ingestion of multiple drugs of abuse, it is important to understand the potential central nervous system (Table 2), cardiovascular (Table 3), respiratory (Table 4), and other adverse effects of GHB and popular drugs of abuse (Table 5).

Patients often arrive in the emergency room with low Glasgow Coma Scale (GCS) scores and respiratory depression. They are often hypothermic with no focal neurological deficits aside from their severely depressed level of consciousness. A warming blanket should be employed if needed. Alcohol levels may be low despite their comatose state. They are often taking other recreational drugs including opiates, warranting the use of naloxone. Coma is typically self-limiting whether intubated or not they will wake up in a few hours. As stated above, sudden awakening is often accompanied by agitation and violence and warrants prophylactic use of restraints to prevent self-extubation, aspiration pneumonia, and injury to the patient or staff. Patients may be awake and intubated, but still not adequately breathing on their own. Patients should be monitored prior to extubation to ensure the return of normal respirations. GHB- induced bradycardia may be masked by concomitant use of amphetamines, cocaine, or by

dehydration. It is unclear at this time whether or not GHB can precipitate abnormal heart rhythms, but atrial fibrillation has been reported.[1,68, 69]

The implementation of an effective emergency department protocol can prevent morbidity and mortality as well as decrease hospital admissions associated with this drug of abuse.[1] Due to the resurgence of GHB as a drug of abuse, health care providers must take an active role in the identification and treatment of patients with GHB associated toxicity.

Table 2: CNS Effects of GHB Toxicity Compared to Other Drugs of Abuse*

GHB	Amnesia, coma, seizure-like phenomenon, unconsciousness
Cocaine[70]	Confusion, anxiety, dizziness, delerium, headache, mydriasis, exopthalmus, hyperresponsive reflexes, convulsions, unconciousness
Ecstasy (MDMA[a]) *,[71]	Agitation, coma, convulsions, mydriasis, panic, paranoia
Ethanol[b,72]	CNS depression, decreased or absent deep tendon reflexes, coma
Heroin/Opiate[73]	Glasgow Coma Scale Score of <12, miotic pupils
Methamphetamine*,c, [74]	Agitation, anxiety, hallucinations, delerium, toxic psychosis, siezures

**Features may be variable. MDMA = 3,4-methylenedioxymethylamphetamine*

a. Also known as "E", "XTC", "X", and "ADAM"

b. Presentation may vary

c. Also known as "Speed", "Crank", "Go", "Crystal", and "Crystal-meth"

Table 3: Cardiovascular Effects of GHB Toxicity Compared to Other Drugs of Abuse*

GHB	Bradycardia, hypotension
Cocaine[70]	Paroxysmal atrial tachycardia, hypertension, Immediate death due to direct cardiotoxicity without the appearance of CNS effects
Ecstasy (MDMA[a,b])*,[71]	Hypertension followed by hypotension, spontaneous bleeding, tachycardia, ventricular arrhthmias
Ethanol[a,72]	Cardiac dysfunction (profound bradycardia)
Heroin/Opiate[73]	Sinus bradycardia, sinus tachycardia, hypertension, hypotension, palpitations, syncope
Methamphetamine*,[74]	Atrial & ventricular arrhythmias, chest pain, hypertension, myocardial ischemia, palpitations

**Features may be variable. MDMA = 3,4-methylenedioxymethylamphetamine*

a. Also known as "E", "XTC", "X", and "ADAM"

b. Presentation may vary

c. Also known as "Speed", "Crank", "Go", "Crystal", and "Crystal-meth"

Table 4: Respiratory Effects of GHB Toxicity Compared to Other Drugs of Abuse*

GHB	Respiratory depression
Cocaine[70]	Death from respiratory arrest, irregular (Cheyne-Stokes) respiration
Ecstasy (MDMA[a,b]) *,[71]	Respiratory depression
Ethanol[a,72]	Respiratory depression
Heroin/Opiate[73]	Respiratory depression <12 breaths/min
Methamphetamine*, [74]	Dyspnea

**Features may be variable. MDMA = 3,4-methylenedioxymethylamphetamine*

a. Also known as "E", "XTC", "X", and "ADAM"

b. Presentation may vary

c. Also known as "Speed", "Crank", "Go", "Crystal", and "Crystal-meth"

Table 5: Miscellaneous Effects of GHB Toxicity Compared to Other Drugs of Abuse*

GHB	Hypotonia
Cocaine[70]	Chills, diaphoresis, hyperthermia, nausea, pallor, vomiting
Ecstasy (MDMA[a]) *,[71]	Diaphoresis, elevated serum creatinine, creatine phosphokinase, & LFTs, hypoglycemia, hyperthermia, metabolic acidosis, muscle rigidity
Ethanol[a,72]	BAL 150 to >300 mg%, flushed skin progressing to cyanosis, hypoglycemia, hypothermia, peripheral vasodilation, shock
Heroin/Opiate[73]	Circumstantial evidence or history of heroin, response to naloxone
Methamphetamine[c,74]	Hyperthermia, rhabdomyolosis

**Features may be variable. MDMA = 3,4-methylenedioxymethamphetamine*

a. Also known as "E", "XTC", "X", and "ADAM"

b. Presentation may vary

c. Also known as "speed", "crank", "go", "crystal", and "crystal-meth"

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