γ-Hydroxybutyrate (GHB) — Effects on Human Performance and Behavior

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ABSTRACT. γ-Hydroxybutyrate (GHB) is a powerful central nervous system (CNS) depressant which has had a history of limited therapeutic use and, more recently, potential for abuse. GHB is a naturally occurring compound present in mammalian CNS and peripheral tissues, and a minor metabolite and precursor of γ-amino butyric acid. GHB is also an emerging recreational drug and has limited therapeutic potential. It is now a federally controlled substance. Since the substances γ-butyrolactone and 1,4-butanediol rapidly convert to GHB in vivo, they are abused as metabolic precursor drugs for GHB and are available in a wide variety of forms.

GHB alters dopaminergic activity in the CNS, and its effects are primarily those of a CNS depressant. Following low doses, euphoria, relaxation, reduced inhibitions and sedation can be observed, while vomiting, sweating, severe respiratory depression, and unconsciousness are common with GHB intoxication. Tolerance to the effects of GHB develops with chronic use, and physical and psychological addiction can follow.

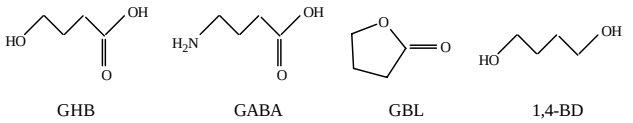
This monograph reviews the chemistry of GHB and its precursor drugs, their reported medicinal and recreational uses, pharmacology, pharmacokinetics, metabolism, analytical methodology, and interpretation issues such as postmortem endogenous concentrations and specimen storage conditions. The manuscript concludes with a discussion of the effects GHB may have on human performance. Given the ability of GHB to induce sleep and unconsciousness, recreational use of GHB and its precursor drugs GBL and 1,4-butanediol has the potential of causing impairment in psychomotor and cognitive skills.

KEY WORDS: 1,4-Butanediol, γ-butyrolactone, CNS depression, driving, γ-hydroxybutyrate, impairment, performance.

INTRODUCTION

γ-Hydroxybutyrate (GHB) is a highly efficacious central nervous system (CNS) depressant and hypnotic despite its low potency, and has had a history of limited therapeutic use and, more recently, potential for abuse.

GHB is a naturally occurring compound present in mammalian CNS and peripheral tissues, and a minor metabolite and precursor of the inhibitory neurotransmitter γ-amino butyric acid (GABA) (**Structure 1**). GHB was first synthesized in 1960 as an experimental GABA analogue for possible use in the treatment of seizure disorder [73]. Since GHB could readily cross the blood-brain barrier, the authors postulated that it could facilitate the synthesis of GABA in the brain. Although they found that GHB did not produce elevated GABA synthesis, some pharmacological properties of GHB were revealed that rendered it potentially useful as an anesthetic adjunct or induction agent. Consequently, GHB was first used clinically as an anesthetic in the 1960s. Its use was discontinued as it lacked analgesic properties, and had an unpredictable duration of action producing dramatic swings between consciousness and unconsciousness at doses consistent with anesthesia [100]. However, GHB is still currently available in several European countries as an anesthetic adjunct and hypnotic agent [70].



GHB GABA GBL 1,4-BD

Structure 1. Structures of GHB and related compounds: γ-Hydroxybutyrate (GHB), γ-aminobutyric acid (GABA), γ-butyrolactone (GBL), 1,4-butanediol (1,4-BD).

In 1966, the potential anesthetic properties of compounds that were analogs or metabolic precursors of GHB, namely γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), were also investigated (Structure 1) [129]. Both GBL, through lactonase, and 1,4-BD, through alcohol and aldehyde dehydrogenase, rapidly convert to GHB in vivo following oral administration (**Figure 1**).

In Europe, GHB is also used in the treatment of alcohol dependence [3,4,55,108], and is under investigation for the treatment of opiate withdrawal syndrome [54,55,112], narcolepsy [74,89,119,121], and fibromyalgia [118]. Within the United States there is currently no medically approved use for GHB; however, it is being evaluated for the treatment of narcolepsy.

In addition to its natural occurrence in humans and animals, GHB is now an emerging drug of abuse and is available illicitly as a powder and as a liquid. GHB is used by body builders as an alternative to anabolic steroids to enhance muscle growth, and recreationally by others for its intoxicating effects such as euphoria, reduced inhibitions, and sedation [19,55,65,82,85]. In early 1990, GHB

was sold in health food stores, gymnasiums, and via the Internet, and was classified as a food and diet supplement. Numerous emergency room reports of coma, seizures, and CNS depressive effects led the Food and Drug Administration (FDA) in November 1990 to federally ban over-the-counter sales of GHB in the United States. In 1999, the FDA issued warnings on the dangers of its metabolic and synthetic precursor drug, GBL [50,51]. On February 18, 2000, GHB was placed in Federal Schedule I of the Controlled Substances Act, with GBL cited as both a list I chemical and a controlled substance analog, and 1,4-BD falling under the controlled substance analog section [23,43]. This scheduling action included a provision for approved applications of medically formulated GHB, which will be placed in Federal Schedule III of the Controlled Substances Act.

Unfortunately, FDA warnings and scheduling have not curbed the illicit use of GHB and its precursor drugs; 1,4-BD appears to be gaining in popularity, in part due to the recent scheduling of GHB. With the increasing attention on GHB toxicity, the FDA has also requested that products containing 1,4-BD be removed from the market; however, 1,4-BD is currently still available in health food stores and via the Internet.

This manuscript is a discussion of the chemistry, legitimate and illegitimate uses, mechanism of action, therapeutic and toxic effects, pharmacokinetics, interpretation of forensic issues, and chemical analysis of GHB and its metabolic precursor drugs, GBL and 1,4-BD. The review concludes with a discussion of the effects GHB may have on human performance, namely its effects on driving behavior.

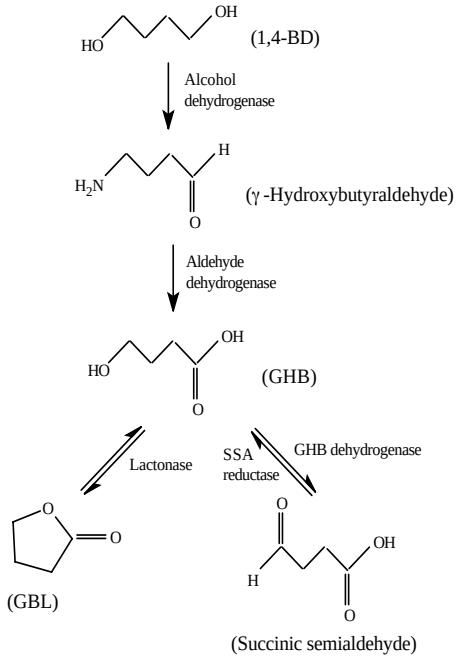


Figure 1. Metabolic pathway of GBL and 1,4-BD.

I. CHEMISTRY

A. Nomenclature

Chemical names for GHB include γ-hydroxybutyric acid, 4-hydroxybutyrate, and sodium oxybate (medically formulated GHB). Common street names and previous marketing names for GHB include Alcover, Anectamine, Degreaser + Lye, Easy Lay, Everclear, G, G-caps, Gamma-OH, Grievous Bodily Harm, Georgia Home Boy, Great Hormones at Bedtime, Liquid Ecstasy, Liquid X, Natural Sleep 500, Oxy-sleep, Salt water, Scoop, Soap, Smart drug, Somatomax-PM, Somsanit, and Vita G.

For GBL, commonly used chemical names include 2(3)-furanone dihydro, dihydro-2(3H) furanone, 4-butyrolactone, furanone, butyric acid lactone, α-butyrolactone, 4-hydroxy-γ-lactone, 4-butanolide, 4-deoxytetronic acid, γ–hydroxybutyric acid cyclic ester, and tetrahydro-2-furanone. Street names and marketing names include Beta-Tech, BLO, Blue Nitro, Eclipse 4.0, Firewater, Furan, Furomax, G3, Gamma-6480, Gamma BL, Gamma Ram, Gen X, GH Gold, Jolt, Insom-X, Invigorate, Miracle Cleaning Products, NCI-C55875, Nu-Life, ReActive, Regenerize, Remedy GH, REMForce, Renewsolvent, RenewTrient, Rest-Eze, Revitalizer, Revivarant, V3, Verve, Verve 5.0, and Wax Stripper.

Chemical names for 1,4-BD include butane-1,4-diol, butylene glycol, 1,4-dihydroxybutane, diol 14B, sucol-B, tetramethylene glycol, and tetramethylene 1,4-diol. Common street names and marketing names include Amino Flex, Biocopia PM, BlueRaine, Bomb, Borametz, BVM, Cherry/Lemon FX, Dormir, Drop, Enliven, FUBAR, FX, Growth Hormone Release Extract (GHRE), Herbal GHB, Ink Jet Printer Fluid, Inner G, Liquid Gold, Midnight, Miracle Cleaning Products, Mystik, N Force, NRG 3, Pine Needle Oil or Extract, Promusol, Rejuv@Nite, Rest-Q, Revitalize Plus, Rush, Serenity, Soma Solutions, SomatoPro, Thunder Nectar, Ultradiol, Weight Belt Cleaner, White Magic Cleaner, X-12, and Zen.

B. Chemical Properties

GHB is a naturally occurring hydroxylated short-chain carboxylic acid, and GBL is its corresponding cyclic lactone. GHB is poorly soluble in lipids and organic solvents, yet freely soluble in water. The free acid of GHB has a molecular formula of $C_4H_8O_3$, a molecular weight of 104.10 a.m.u., and a pKa of 4.72. GHB is often supplied as its sodium salt ($C_4H_7NaO_3$, M.W. 126.1). The molecular formula for GBL is $C_4H_6O_2$ and its molecular weight is

86.09 a.m.u. 1,4-BD is a naturally occurring aliphatic alcohol, which has the molecular formula $C_4H_{10}O_2$, and a molecular weight of 90.12 a.m.u.

C. Source

GHB is available illicitly as a white powder, white tablets and capsules or as a clear liquid, while GBL and 1,4-butanediol are usually both liquids. They are often mixed or diluted with colored liquids to distinguish them from water, or with strong-tasting juices or alcohol to lessen their unpleasant chemical taste.

To illicitly manufacture GHB, the industrial solvent GBL can be made alkaline with lye, and heated. With addition of an acid such as vinegar to adjust the pH, the solution of GHB can be consumed. To produce GHB powder, acetone can then be added and the mixture completely dried. GBL can also be purchased via the Internet in kit form, with the necessary chemicals and instructions for the synthesis of GHB, for approximately $50. Unlike GBL, 1,4-BD is not used to illicitly manufacture GHB. This conversion is an industrial process and cannot be accomplished in a clandestine laboratory.

Illicit GHB is especially dangerous because its concentration is often unknown and potency can vary greatly from batch to batch. Illicit manufacture often introduces impurities and contaminants. Individual doses of GHB (i.e., 1 teaspoon powder, 1 capful or 1/4 ounce liquid) vary widely in price and can range from $5–40 [22].

GBL and 1,4-BD are commercially available as industrial solvents. For example, a 55-gallon drum of "Wax Stripper", containing GBL, can be purchased for $1000 [22]. These metabolic precursor drugs are also marketed as natural, non-toxic diet supplements and can be purchased from health food stores, fitness centers, and via the Internet. For example, a 32-ounce bottle of 1,4-BD typically sells for $40–70 [22]. This is similar in price to GBL-containing products.

D. Chemical Stability

GHB does not exist in a static state, even outside of the body. In solution, it co-exists in a state of equilibrium with its lactone GBL. The ratio of the two forms is dependent on the type of matrix containing the GHB and the pH of the matrix. For example, in blood, the GHB acid form predominates because blood contains the enzyme lactonase, which converts any of the lactone to the acid. Conversely, if the GHB is in a matrix that does not contain this enzyme, such as urine, stomach contents, or water, the two forms will reach equilibrium with both being present. Even if only GHB is consumed, GBL can exist in stomach contents or urine, depending on time after ingestion, temperature and pH of the matrix. In contrast, 1,4-BD does not exist in equilibrium with either GHB or GBL, and following ingestion, converts entirely to GHB over time.

As previously stated, the form that predominates depends on the pH of a matrix. GHB predominates when the pH is made >4.72, while GBL predominates when the pH is made <4.72. This is often taken advantage of when analyzing various matrices for either GHB or GBL (*see* IV. Analytical Methodology). Complete conversion to GBL is favored in dehydrating conditions at pH's below 2.0 in a concentrated acid solution. This can be achieved by the addition of a concentrated, dehydrating acid such as sulfuric acid. The rate with which the equilibrium is reached depends on the temperature and the actual pH of the matrix.

Recent investigations have examined whether products containing GBL could undergo some conversion to GHB between manufacture and sale. This is important since there is currently a wide legal distinction between the two compounds. With the recent placement of GHB in Federal Schedule I, there is more interest on the part of the illicit manufacturers in producing a GHB precursor product that will stay in the lactone form and not spontaneously convert to GHB, as penalties for GBL are perceived to be less severe. Interestingly, a seizure of solid GBL has recently been reported in California, where liquid GBL was absorbed onto silicon dioxide powder and then placed into a clear capsule [32]. In a recent study by Ciolino et al. [20], the authors found that the ratio of GHB to GBL changed depending on the pH of the matrix and storage time. At a pH of 2 at ambient storage temperature, an equilibrium between GHB and GBL was achieved after 9 days with 67% GBL to 33% GHB. At the end of 220 days of storage at ambient temperature, the proportions of GHB remaining at the following pH values were: 95% at pH 6.4, 85% at pH 5.2, and 72% at pH 4.0. In pure water, pH 7.0 and pH 12.0, GHB was stable for 202 days at ambient temperature. The GHB that was lost due to esterification was quantitatively converted to GBL. Thus, although this interconversion occurred, there was no loss in total content of GHB observed as a function of time. GBL was completely converted to GHB at pH 12.0 in a matter of minutes at ambient temperature. These conversions occur more rapidly as the temperature is increased and at a slower rate as the temperature is decreased.

II. THERAPEUTIC, RECREATIONAL, AND INDUSTRIAL USES

A. Therapeutic Use

The first clinical use of GHB was as an anesthetic adjunct and a hypnotic agent, and this application is still in use today in a number of European countries [70]. At this

time there is no medically approved use for GHB in the U.S., except for use as an FDA-approved Investigational New Drug for the treatment of narcolepsy. Evaluation of the effects of GHB on EEG tracings have revealed that the electrical patterns are closest to those observed during natural physiological sleep [88,100,133]. It is this normalization of sleep that is the basis for GHB's use in the treatment of narcolepsy. In humans, GHB enhances REM sleep and increases stages 3 and 4 of slow-wave sleep, a feature distinguishing GHB from other sedative-hypnotics such as benzodiazepines and alcohol, whose sedative and hypnotic effects do not mimic normal sleep and decrease REM sleep. If fully approved by the FDA, a pharmaceutical grade of GHB, sodium oxybate, will be marketed as Xyrem®.

For sleep induction, the recommended therapeutic dose of GHB is 1.5 to 2.25 g orally at bedtime (approximately 20–30 mg/kg for a 70-kg person), with additional doses of 1.0–1.5 g given at 3- or 4-h intervals [118]. For a prolonged deep sleep, the recommended dose is 75–100 mg/kg (approximately 5–7 g for a 70-kg person). For anesthetic induction, the dose is usually greater than 100 mg/kg (>7 g for a 70-kg person).

Another promising area for medically formulated GHB is in the treatment of alcohol withdrawal syndrome [3,4,55,108]. Exogenous administration of GHB has been shown to reduce ethanol consumption and intensity of ethanol withdrawal symptoms in rats and humans. The recommended therapeutic dose of GHB for alcohol withdrawal syndrome is 25–50 mg/kg, every 12 h (approximately 1.7–3.5 g for a 70-kg person). Adverse effects have been mild except for occasional replacement of alcohol addiction with GHB addiction, resulting in some subjects self-medicating with additional GHB to enhance its effects [2]. Treatment with GHB has also been investigated for opiate withdrawal syndrome and fibromyalgia [54,55, 112,118].

B. Recreational and Illicit Use

GHB and its analogs, GBL and 1,4-BD, are abused by body builders as an alternative to anabolic steroids to enhance muscle growth. Takahara and associates administered GHB to six healthy adult males and showed an approximately 10-fold increase in plasma growth hormone levels that peaked at 45 min post dose [132]. This effect persisted for about 15 min, after which the growth hormone levels dropped back toward the pre-treatment levels. Growth hormone levels at 120 min post dose were still above baseline but significantly below the peak level. Based upon this report, bodybuilders assumed that they could increase growth hormone levels by using GHB and thereby optimize their muscle building potential. A more recent study by Van Cauter and colleagues showed that the increase in growth hormone secretion was correlated with the enhancement of slow wave sleep induced by GHB, and that growth hormone release did not occur prior to sleep onset [133]. Another study concluded that long-term administration of GHB for the treatment of alcohol withdrawal syndrome did not affect muscle mass and the authors were unable to detect an increase in growth hormone release in the GHB treated group [1].

A follow-up study has shown that the ability of GHB to increase growth hormone, in 4-year abstinent alcoholics, does return over time [134]. The same subjects were evaluated for growth hormone release following the administration of GHB at 2–3 weeks of alcohol withdrawal and again after an abstinence period of 4 years. At 2–3 weeks of alcohol withdrawal, the alcoholic subjects showed no increase in growth hormone release, however, after 4 years of abstinence the same subjects demonstrated an increase in growth hormone level following GHB administration at nearly the same rate as non-alcoholic subjects. It is hypothesized that this is due to a reconstitution over time of the neurotransmitter pathway underlying the growth hormone-releasing activity of GHB. It has been proposed by Volpi and associates that this is a muscarinic cholinergic pathway [135]. In both studies it was not specifically mentioned whether the subjects were awake or asleep following the GHB administration. In animal studies, in both anesthetized and conscious rats and conscious dogs, various doses of GHB failed to increase growth hormone concentrations in any of the animals [111].

GHB and its analogs are also used recreationally by others for their intoxicating effects such as euphoria, reduced inhibitions, and sedation [19,55,65,82,85]. They have also been marketed as natural health and diet aids, as anti-aging drugs and for weight-loss, to treat insomnia, anxiety and depression, to restore hair color and reverse balding, to enhance athletic and sexual performance, and as mood enhancers and energizers. Although GHB has gained a reputation as a date-rape drug, its most frequent use is voluntary self-administration for the aforementioned indications. Manufacturers of diet-aid type products containing GBL and 1,4-BD may mask the presence of these GHB analogs by using one of the many chemical synonyms for GBL or 1,4-BD in the list of ingredients on the product label.

Typical recreational doses administered by users are usually in excess of 1 teaspoon of GHB powder, or 1 "capful" of liquid GHB, GBL, or 1,4-BD, which is equivalent to at least 2.5 g, or 35 mg/kg of GHB for a 70-kg person [29,37,55]. Of course this would vary depending on the concentration of the particular batch of drug.

Administration of up to 4 tablespoons of GHB has been previously reported [37]. Chronic users of either GHB or its precursors have been known to administer the drug every few hours around-the-clock for periods of months to years, with estimated doses of up to 100 g of GHB ingested in one day being reported [12,29,39,60,136].

The number of emergency department (ED) mentions for GHB in the United States has risen dramatically over the last decade [36]. In 1994, there were 55 known ED mentions involving GHB. This grew to 638 mentions in 1996 and to 1282 mentions in 1998. This figure more than doubled in 1999 to 2973 ED mentions for GHB. Of these 2973 mentions, 2114 (71%) involved multiple-drug episodes while 859 (29%) involved only GHB. The typical GHB patient was a white male between 18 and 34 years of age. In 2000, the number of ED mentions for GHB almost doubled again to 4969.

By far the most common drug taken in combination with GHB is ethanol. This combination is especially dangerous as ethanol potentiates the CNS-depressant effects of GHB. Other commonly cited drugs used in combination with GHB include Ecstasy (MDMA), marijuana, methamphetamine, amphetamine, and cocaine [19,28,36].

C. Industrial Use

The most common uses of GBL and 1,4-BD are as industrial solvents. Domestic production of GBL in the United States is approximately 80,000 tons per year. In industry, GBL is widely used and would be difficult to replace based on its properties as a safe, effective, and biodegradable degreaser. The projected usage of 1,4-BD in 2001 is 750 million pounds [104]. GBL and 1,4-BD are involved extensively in the manufacturing of other chemicals, and are constituents in various cleaners, solvents, paint removers, engine degreasers, drilling oils, nail polish removers, and cyanoacrylate glue. There appears to be no legitimate use for GHB as an industrial chemical.

Illicit distributors of solutions containing GBL and 1,4-BD take advantage of the fact that these are legitimate industrial solvents. To avoid the provision in the analog law, which states that the intent of the product was for human consumption, illicit distributors mask the intent of their products by having products labeled as organic or natural cleaners, with scents and flavorings added. If it cannot be proven that the intended use is for human consumption, the distribution of GBL and 1,4-BD cannot be prosecuted under the controlled substance analog provision in the Federal Statutes. Some of these products include: an all-natural, pina-colada scented organic household solvent called Rejoov, which upon analysis contained 1,4-BD; a solvent for high-technology applications called Miracle Clean which upon analysis contained GBL and GHB; and an organic cleaning solution with citrus essence called Somax, which upon analysis contained 1,4-BD [72].

III. PHARMACOLOGY OF GHB

A. Pharmacodynamics

1. Mechanism of Action

The complete mechanism of action of GHB is still unresolved. GHB readily crosses the blood-brain barrier and is the pharmacologically active form of both GBL and 1,4-BD. In fact, it was determined as early as 1966 that GBL does not possess any CNS-depressant activity itself [115]. Researchers have postulated that GHB has some capacity as a neurotransmitter and/or neuromodulator, and investigation continues in this area.

GHB has weak agonist activity at $GABA_B$ receptors and produces an alteration in dopamine transmission. Several researchers have also demonstrated that GHB appears to have a distinct GHB-receptor site in the brain with both high- and low-affinity components. Current research suggests that this receptor appears to be a G protein-coupled presynaptic receptor that is distinct from the $GABA_B$ receptor [126].

GHB dose-dependently alters dopaminergic activity. At sub-anesthetic doses, GHB causes an initial excitation of dopaminergic neurons producing elevated levels of synaptic dopamine, which may play a part in the reinforcing effect of GHB [34,116]. At anesthetic doses, GHB blocks the impulse flow from central dopaminergic neurons resulting in a build-up of dopamine levels in the nerve terminals [16,102,113,114]. Dopamine accumulates in the nerve terminals because the synthesis of new dopamine continues while the blocking of the nerve impulse prevents its release. It has also been determined that anesthetic doses of GHB might have a similar effect on brain levels of acetylcholine, increasing acetylcholine levels by decreasing impulse flow in cholinergic neurons [124].

It has also been postulated that GHB affects cerebral glucose metabolism, temperature regulation, blood flow, and sleep patterns [87]. GHB additionally causes a detectable increase in plasma growth hormone and prolactin concentrations in humans with doses as small as 2.5 g [132].

Beyond the CNS effects, GHB has significant cardiovascular pharmacology, causing bradycardia and dysregulation of blood pressure. This may be related to an excessive parasympathetic activation by GHB, as suggested by the classic cholinergic effects of increased

salivation, urinary and fecal incontinence, and cramping [86]. There is also the potential of hypernatraemia associated with large ingestion of the sodium salt.

2. Drug Interactions

Laboratory data with rats supports the theory that ethanol has significant synergistic effects on the sedative, behavioral, and toxic properties of GHB, GBL, and 1,4-BD [92,109,110]. Due to the fact that 1,4-BD and ethanol have a similar affinity for the enzyme alcohol dehydrogenase, ethanol delays the conversion of 1,4-BD to GHB and increases its tissue concentrations [109]. There are also potential additive CNS-depressant effects between GHB and other CNS depressants such as benzodiazepines and barbiturates.

B. Effects of GHB

1. Clinical and Adverse Effects

The pharmacological effects of both GBL and 1,4-BD are ultimately those of GHB, and the primary effects of GHB are those of a CNS depressant. As early as 1962, Blumenfeld and associates listed nine qualities observed from their experiments with GHB used in human anesthesia [13]. The observations were that GHB mimics natural sleep, causes negligible reduction in minute respiratory volume, has cardiotonic effects, produces relaxation for ease of intubation, potentiates other CNS depressants, does not change oxygen consumption, permits easy control of respiration, provides very stable vital signs, and permits slow induction of anesthesia.

From a vast array of published case studies, reported clinical and adverse effects include relaxation and euphoria, reduced inhibitions, confusion, dizziness, drowsiness, sedation, inebriation, agitation, loss of peripheral vision, and somnolence. Toxicity of GHB is characterized by nausea and vomiting, profuse sweating, incontinence, visual disturbances, severe ataxia, random clonic muscle movements (twitching), bradycardia, hypotension, acute delirium, hypothermia, severe respiratory depression, mild acute respiratory acidosis, apnea, decreased level of consciousness, and unarousable unconsciousness [10,19,37, 55,83,105,136]. Although there have been some anecdotal reports of seizures associated with GHB intoxication, there is no evidence of true seizure activity as measured by EEG in humans [42]. GHB has a very steep dose-response curve and it is easy for a person to accidentally overdose. Several deaths have been reported following overdoses from GHB, GBL, and 1,4-BD alone, and in combination with other drugs [6,31,39,47,64,71,94,101, 136].

Despite there being a large intra- and intersubject variability for GHB, the effects of GHB appear to be dose-related. It has been reported that single doses of 10 mg/kg causes amnesia and hypotonia, 20–30 mg/kg causes drowsiness, euphoria, vertigo, and somnolence, 50 mg/kg causes loss of consciousness (patients are still arousable), and doses of 60 mg/kg or greater result in coma or unarousable unconsciousness [10]. Following a single dose of 30 mg/kg, subjects felt sluggish, sedated, fatigued, drunk, dazed, spaced, and carefree, compared to those subjects receiving a placebo [112]. Doses above approximately 50 mg/kg can result in transient unconsciousness, hypotonia, slowed pulse, and slowed respiration. Metcalf and associates observed EEG changes in 20 subjects given oral doses of 35–63 mg/kg GHB [100]. The EEG pattern was similar to that seen in natural slow-wave sleep. In subjects given oral GHB doses greater than 50 mg/kg, profound coma was observed at approximately 30 to 40 min post dose.

Although several articles list short-term amnesia or memory-loss as a clinical effect of GHB, there are no studies that document anterograde amnesia being produced by either GHB, or GHB and ethanol. Marinetti and Commissaris designed a study to determine whether intraperitoneally administered low doses of GHB (100 mg/kg), or GHB and ethanol (500 mg/kg), produced memory impairment in a rat model for anterograde amnesia, using 1-2 mg/kg scopolamine as a reference [93]. Memory was significantly impaired by scopolamine but not with GHB, nor GHB and ethanol. When higher doses of GHB were used (200 mg/kg), profound sedation of the rats was observed, and the tests could not be performed. Perhaps it is this profound sedation, coupled with the fact that a common characteristic of GHB sedation is a dramatic swing from consciousness to unconsciousness, that gives the user the perception of an amnesic effect.

2. Duration of Effects

Clinical and adverse effects are rapidly observed following ingestion of GHB. Onset of effects occurs within 10–30 min, and peak plasma concentrations are achieved within 20–45 min. Effects generally last 2–5 h and complete recovery from GHB overdose occurs within 3–6 h, although this is dose dependent.

While investigating the potential anesthetic properties of GBL and 1,4-BD, Sprince and associates observed that sleep induction time was the shortest with GBL and longest with 1,4-BD as compared to GHB [129]. This would be due in part to GBL being more lipophilic than GHB and therefore is absorbed faster, and 1,4-BD metabolizes more slowly to GHB than does GBL and hence there is a delay in its effects.

3. Tolerance and Withdrawal Effects

Tolerance to the CNS effects of GHB develops with chronic treatment or use, and the most likely negative outcome of chronic GHB use is physical and psychological addiction. GBL has also been shown to produce cellular tolerance in mice [56,57]. Severe GHB withdrawal has been documented with chronic use of GHB, GBL, or 1,4-BD. The clinical presentation of GHB withdrawal ranges from mild clinical anxiety, confusion, agitation, tremors, diaphoresis, and insomnia to combativeness and hostility, muscular cramps, profound disorientation, delirium, delusions, increasing paranoia with auditory, tactile and visual hallucinations, tachycardia, hypertension, extraocular motor impairment, and in some cases a temporary schizophrenic-like state [29,39,60,120]. Symptoms, which can be severe, generally resolve without sequelae after various withdrawal periods, usually in the order of several days to one or two weeks. Treatment with benzodiazepines, phenobarbital, and haloperidol has been successful for symptoms of a withdrawal syndrome.

However, in the treatment of narcolepsy with chronic GHB administration in humans, no tolerance developed to the enhanced sleep and decreased episodes of cataplexy observed in the subjects [14,89]. It is not unusual for a drug to produce tolerance to some but not all of its effects, especially if that tolerance is cellular in nature. It has also been demonstrated that a cross-tolerance exists between GHB and ethanol. In a study by Columbo and associates, rats were chronically treated with either GHB or ethanol [21]. Once the rats became tolerant to the motor-impairing effects of GHB or ethanol, the ethanol-tolerant rats were challenged with GHB and the GHB-tolerant rats were challenged with ethanol. A tolerance to the motor-impairing effects was still evident even though the drug challenge was not the same drug that the rat had become tolerant to. Since this study did not measure GHB or ethanol concentration, the type of tolerance (cellular or dispositional) was not determined. This indicates the possibility for those individuals that chronically use either ethanol or GHB to withstand a larger dose of either drug and achieve a higher concentration of either drug before they exhibit impairment, as compared to an individual with no tolerance to either GHB or ethanol.

4. Treatment of GHB Overdose

Clinical management of an acute GHB intoxication is largely supportive, and centers on stabilizing and maintaining vitals and symptoms. Airway management, endotracheal intubation for airway protection, ventilation, and prevention of aspiration are often necessary. Extubation following 2–6 h of mechanical ventilation is common. There are no widely accepted antidotes to GHB, although physostigmine, a cholinesterase inhibitor, has proven useful to counter the sedative effects of GHB. Spontaneous and full recovery from GHB following acute overdose is common within a few hours and usually is without long-term effects. A possible complication in GHB overdose cases is the concurrent use of other drugs.

C. Pharmacokinetics

1. Absorption and Distribution

Oral doses of GHB are rapidly absorbed from the gastrointestinal tract. GHB exhibits first-pass metabolism when administered orally with approximately 65% bioavailability when compared to an equivalent IV dose [79]. Absorption of GHB has been shown to be a capacity-limited process with increases in dose resulting in increases in time to peak concentration [48]. In humans it has been documented that there is an increased rate of absorption if GHB is administered on an empty stomach, resulting in a reduced time to reach maximum plasma concentrations of GHB [15]. An increase in maximum plasma GHB concentration is also observed.

The concentration of GHB in brain equilibrates with other tissues after approximately 30 min. GHB crosses the placental barrier at a similar rate to that in the blood-brain barrier. The distribution of GHB into the cerebrospinal fluid (CSF) appears to lag behind that in blood or brain. After a 500 mg/kg IV dose of GHB was administered to dogs, plasma levels peaked within 5 min, brain levels peaked within 10 min, but it was 170 min before CSF levels reached their maximum. This suggests a passive diffusion of GHB from serum or brain into the CSF [125]. In alcohol-dependent patients, GHB did not accumulate in the body upon repeated doses nor did it exhibit any protein binding [105].

The absorption of GBL has been shown to occur faster than GHB, since GBL is much more lipophilic or nonpolar and can therefore cross cell membranes more readily than GHB [81]. It has also been proposed that in addition to the better absorption of GBL, it may also distribute differently than GHB. An early study comparing the distribution of equimolar doses of GHB and GBL in rats found that although peak plasma levels were higher with GHB, they remained elevated longer with GBL [117]. In addition, levels of GBL in the lean muscle mass of the rat were always elevated compared to levels of GHB, suggesting sequestration of GBL into lean muscle prior to its conversion to GHB. Since lean muscle does not contain the lactonase enzyme, it is conceivable that this could occur. The GBL could then redistribute into the blood to be converted to GHB. This could explain the prolonged elevated levels of GHB in blood that occur when GBL is given. Neither GHB nor GBL is sequestered in fat.

The absorption and distribution of 1,4-BD is quite similar to GHB. It is a lipophobic or polar compound so it does not absorb faster then GHB. After its absorption, it requires a two-step enzymatic conversion to GHB, which results in a slightly longer time to peak GHB concentration and also a longer time of elevated GHB level. The conversion of 1,4-BD to GHB can be slowed or inhibited by ethanol, pyrazole, or disulfiram [91].

2. Concentrations

a. Endogenous GHB Concentrations

Anderson and Kuwahara analyzed 50 antemortem blood specimens from individuals with no evidence of GHB use [5]. No detectable amounts of GHB were observed in any of the blood specimens, using a limit of detection of 0.5 mg/L. Similarly, endogenous GHB concentrations were measured in 192 blood specimens from living subjects thought to be non-GHB users [24]. All measurable blood GHB concentrations were below 1 mg/L, using a detection limit of 0.5 mg/L.

LeBeau and co-workers investigated urinary GHB levels to differentiate between endogenous and exogenous concentrations [75]. Every urine void produced by eight non-GHB-using subjects (five males, three females) over a one-week period was individually collected and analyzed for the presence of endogenous GHB, using a limit of detection of 0.19 mg/L. Overall, the mean endogenous GHB concentration detected was 1.01±1.24 mg/L (range 0.00–6.63 mg/L). Individual mean concentrations were as low as 0.28 mg/L and as high as 3.02 mg/L. The data also suggested significant differences in the median endogenous urinary GHB concentrations between male (1.07 mg/L) and female (0.23 mg/L) subjects. While there were significant intra- and inter-individual variations in the urinary levels of endogenous GHB, the concentrations did not fluctuate to levels that were higher than the laboratory's reporting level for urinary GHB of 10 mg/L.

Normal endogenous levels of GHB in CSF in humans are dependent upon age and the presence of seizure disorder [127]. Infants had higher levels of GHB (0.26–0.27 mg/L) in the CSF than older children (0.11–0.13 mg/L) who in turn had higher levels than adults (0.02–0.03 mg/L). Children with myoclonic-type seizures had the highest levels of GHB in the CSF (0.78–0.97 mg/L), whereas children with other types of seizures had the next highest levels (0.37–0.48 mg/L). Along with the analysis of the CSF for GHB, the serum of all subjects was also analyzed. Of the 130 subjects analyzed, none had any measurable amount of GHB in the serum, with a limit of detection of the assay of 0.002 mg/L.

In rats, GHB concentrations in brown fat, kidney, muscle, and heart specimens have been shown to be greater than 1 μg/g, while liver, lung, blood, brain, and white fat had GHB concentrations lower than 0.25 μg/g [103].

b. Exogenous GHB Concentrations

Peak blood and plasma concentrations are observed within 20 to 45 min and are detectable for 6–10 h, depending on dose. Peak urine concentrations are observed within 4 h of drug administration and are detectable for up to 10–12 h. Subsequently, any delay in obtaining clinical specimens could result in a significant decrease in blood, plasma, or urine concentrations.

Therapeutic GHB. Single oral doses of 12.5, 25, and 50 mg/kg in eight healthy male subjects produced mean plasma concentrations of 23 (±9), 46 (±22), and 80 (±28) mg/L, at 25, 30, and 45 min, respectively [105]. Following a single oral dose of 25 mg/kg GHB, peak serum concentrations in 10 alcohol-dependent patients ranged from 24 to 88 mg/L (mean 54±19 mg/L) [48]. When the same subjects were given repeated oral doses of 25 mg/kg every 12 h, peak serum concentrations ranged from 32 to 85 mg/L (mean 55±19 mg/L) when measured following the 13th dose.

In another study, two separate doses of 3 g GHB (equivalent to 26–52 mg/kg) were administered to six narcoleptic patients 4 h apart [119]. These patients were chronic nightly users of GHB. The mean peak plasma GHB concentrations observed were 62.8 mg/L (range 30–102 mg/L) and 91.2 mg/L (range 47.5–125 mg/L), following the first and second dose, respectively. An intravenous dose of 50 mg/kg in an adult produced a peak blood GHB level of approximately 170 mg/L within 15 min [59]. A 75 mg/kg oral dose given to 4 adults prior to bedtime produced peak plasma GHB concentrations averaging 90 mg/L at 2 h, with a decline to 9 mg/L by 6 h [61].

GHB blood levels were measured in 16 adults anesthetized with doses of 50, 75, 100, and 165 mg/kg GHB [59]. The smallest dose given, 50 mg/kg, produced peak blood levels up to 182 mg/L and the largest dose given, 165 mg/kg, produced peak blood levels greater than 416 mg/L. Fourteen patients received doses of 100 mg/kg with resulting peak blood levels ranging from 234 to 520 mg/L. Twelve of the 16 patients required intubation, not necessarily those who received the highest doses of GHB.

GHB-Related Intoxications. GHB concentrations were measured in 54 suspected GHB intoxicated patients presenting to an emergency department [28]. Patients were aged between 17 and 59 years (median 28 years) and 83%

were male. GHB concentrations ranged from 29 to 490 mg/L (mean 137 mg/L; median 103 mg/L). Ethanol and/or other drugs such as MDMA and marijuana were detected in two-thirds of the patients. Clinical symptoms on admission included disorientation, copious vomiting, ataxia, decreased heart rate and blood pressure, sinus bradycardia, respiratory depression, apnea, and sudden altered states of consciousness. Several patients became combative, necessitating restraints, and many required intubation. It was unknown whether the subjects had administered GHB or one of its precursor drugs, GBL, or 1,4-BD.

Three patients arrived simultaneously at an emergency department 1 h after ingesting GHB [38]. Each had a Glascow Coma Score (GCS) of 3, and all regained consciousness within 3.5 h of drug ingestion. On admission, GHB concentrations in urine were 521, 1857, and 141,000 mg/L in the three patients; however, GHB was detected in only one of the patient's serum at a concentration of 101 mg/L. On discharge, which was 5 h after drug ingestion, GHB concentrations in urine were 286, 571, and 857 mg/L, respectively.

An unconscious 23-year-old female was admitted to an emergency department after suddenly losing consciousness at a house party [84]. She had consumed ethanol, smoked a few "joints", and drunk a small amount of GHB. In the hospital, the female had a GCS of 6, and showed signs of bradycardia and respiratory depression. Following 45 min of unaltered consciousness, the patient awoke suddenly. A serum specimen was positive for 125 mg/L GHB and 0.13 g/100 mL ethanol.

Zvosec and associates detail several cases of 1,4-BD intoxication [136]. Following a 4.5-g dose of Inner G, a 37-year-old female was found disoriented, incontinent of urine, and yelling and thrashing on the ground. In the hospital, the patient showed signs of aggression, agitation, ataxia, a labile level of unconsciousness and a GCS of 11. GHB was detected in the patient's serum and urine at concentrations of 317 mg/L and 716 mg/L, respectively. In a separate incident, the same patient ingested an unknown amount of Zen, and was again hospitalized. The patient was intubated and received mechanical ventilation for 3 days, during which she had severe symptoms of GHB-related withdrawal. Her urine was positive for GHB at a concentration of 5140 mg/L. This patient admitted to using 1,4-BD and GBL containing supplements for one year to treat insomnia and depression. During this time, she had numerous other GHB-related intoxications requiring treatment. In another case, a 22-year-old male had consumed between 6.3–8.4 g Serenity. He was found unconscious by friends 1 h after drug ingestion. When paramedics arrived, the patient was vomiting and was unresponsive to painful stimuli. He also had bradycardia, hypotension, respiratory depression, and urinary incontinence, and a GCS of 3. The patient was intubated and received mechanical ventilation, and then extubated after 4 h. GHB was detected in the patient's urine at a concentration of 415 mg/L.

An individual was taken to an emergency room after becoming unconscious following the ingestion of FUBAR, a 1,4-BD-containing product [107]. The GHB concentration measured in a blood and urine specimen, collected approximately 9 h after hospitalization, was 13 mg/L and 272 mg/L, respectively.

GHB-Related Fatalities. Ferrara and associates first reported a GHB-related fatality in 1995 [47]. A 42-year-old male was a known heroin addict, and had been in treatment with GHB for several months. The man was subsequently found dead. Following autopsy, GHB concentrations detected were: blood 11.5 mg/L, urine 258.3 mg/L, bile 57 mg/L, vitreous 84.3 mg/L, brain 40 mg/kg, liver 43 mg/kg, and kidney 47 mg/kg. Morphine and 6-monoacetylmorphine were also detected in the decedent.

A similar distribution study was performed on another fatal GHB intoxication case [6]. Postmortem fluid and tissue concentrations were as follows: heart blood 1473 mg/L, femoral blood 761 mg/L, urine 407 mg/L, vitreous 771 mg/L, bile 1440 mg/L, liver 1578 mg/kg, and gastric 0.78 g total.

A 15-year-old female was with friends at a party when she became violently ill after consuming a drink suspected of containing both GHB and GBL [94]. She fell into a coma and subsequently died in the hospital. Antemortem blood and urine specimens were collected in the hospital 6 h after drug ingestion, and were positive for GHB at concentrations of 510 mg/L and 2300 mg/L, respectively. Postmortem blood and urine were also collected, and GHB was detected in heart blood at 15 mg/L and in urine at 150 mg/L. The deceased had a 14-h survival time prior to death, which explains the lower postmortem GHB blood and urine concentrations. The same authors describe another case in which a regular GHB user was found dead in bed. GHB was detected in heart blood at 66 mg/L, femoral blood 77 mg/L, vitreous 85 mg/L, and urine 1260 mg/L.

GHB was detected in blood, brain, and hair root bulbs from a suspected fatal GHB overdose case [64]. Heart blood contained 648 mg/L GHB, peripheral blood contained 330 mg/L, while 221 ng/mg was detected in a frontal cortex brain specimen. Exposed head hair contained no detectable amounts of GHB; however, plucked and washed root bulbs with the outer root sheath removed contained 47.4 ng/mg GHB. Plucked and unwashed root

bulbs with the outer root still attached contained 2221 ng/mg GHB. This is the only paper to date to report exogenous hair root bulb concentrations of GHB.

While at a bar with friends, an individual took large swigs from a "Gatorade" bottle that was being passed around [107]. The subject passed out, lost bladder and bowel control, and subsequently died. Postmortem blood was positive for 400 mg/L GHB and 0.22 g/100 mL ethanol. A vitreous humor specimen collected one week after embalming was positive for 211 mg/L GHB and 0.12 g/100 mL ethanol.

Two fatal 1,4-BD intoxications have also been reported [136]. In the first case, a 42-year-old female was found dead after ingesting between 5.4–10.8 g of NRG3 to treat insomnia. This dose was equivalent to 95–189 mg/kg of body weight. A postmortem blood specimen was positive for 220 mg/L 1,4-BD and 837 mg/L GHB. Postmortem urine was positive for 1756 mg/L 1,4-BD and 1161 mg/L GHB. The stomach contents were also positive for 1,4-BD and GHB, at concentrations of 579 mg/kg and 201 mg/kg, respectively. In the second case, a 32-year-old male had taken a 20-g dose of Thunder Nectar for its purported ability to increase libido. This dose was equivalent to approximately 300 mg/kg of body weight. The subject and his wife had received a "dietary supplement" from a friend who told them it was non-toxic. The bottle was received unlabeled and without dosage instruction. The wife had consumed an 11–14 g dose and subsequently fell asleep or unconscious. When she awoke some 7 h later, she found her husband dead on the floor covered in vomitus, with signs of fecal incontinence. Postmortem blood was positive for GHB at a concentration of 432 mg/L, while 1,4-BD and GHB were detected in urine at 845 mg/L and 5430 mg/L, respectively. GHB was also detected in bile (670 mg/L) and vitreous (330 mg/L) specimens.

A 40-year-old female was found unresponsive on a couch with foam around her nose and mouth [71]. The subject was known to regularly consume a product containing 1,4-BD, and a bottle found near her body was identified as 1,4-BD. The following postmortem 1,4-BD and GHB concentrations were detected: blood 7.6 and 280 mg/L, vitreous 12.3 and 324 mg/L, urine 146 and 6171 mg/L, respectively. GHB was also detected in bile at a concentration of 218 mg/L. In another fatal 1,4-BD intoxication, 26 g of the drug was ingested [95]; 1,4-BD and GHB were detected in postmortem heart blood at concentrations of 78 mg/L and 416 mg/L, respectively, while urine 1,4-BD and GHB concentrations were 870 mg/L and 1810 mg/L, respectively.

3. Metabolism

The predominant metabolic pathway for GHB is oxidation to succinic semialdehyde by a cytosolic $NADP^+$ dependent enzyme called GHB dehydrogenase (**Figure 2**) [66,68,69]. This enzyme has been demonstrated in brain, liver, heart, spleen, testis, brown fat, and kidney, with liver, kidney, and brown fat having the greatest activity. A second enzyme capable of oxidizing GHB to succinic semialdehyde has also been identified [67]. This enzyme, GHB transhydrogenase, is located in the microsomal fraction and requires no co-factor; however, it is completely dependent on α-ketoglutarate in a coupled reaction. The enzyme can also catalyze the reverse reaction.

Several drugs have been demonstrated to inhibit GHB dehydrogenase; these include valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram, and cyanide. It is not clear if therapeutic levels of these drugs would significantly inhibit GHB metabolism if administered concurrently. Several naturally found metabolic products, formed in excess in natural disease states, have also been shown to inhibit GHB dehydrogenase. Such compounds include α-keto isovalerate, α-keto isocarproate, and α-keto β-methyl *n*-valerate (elevated in a condition called maple sugar urine disease), phenylacetate (elevated in persons with phenylketonuria or PKU) and the ketone bodies β-hydrobutyrate and acetoacetate (elevated in persons with untreated diabetes and in a starvation state) [69]. In these abnormal conditions, the elevated levels of these naturally occurring metabolites could significantly inhibit the metabolism of GHB.

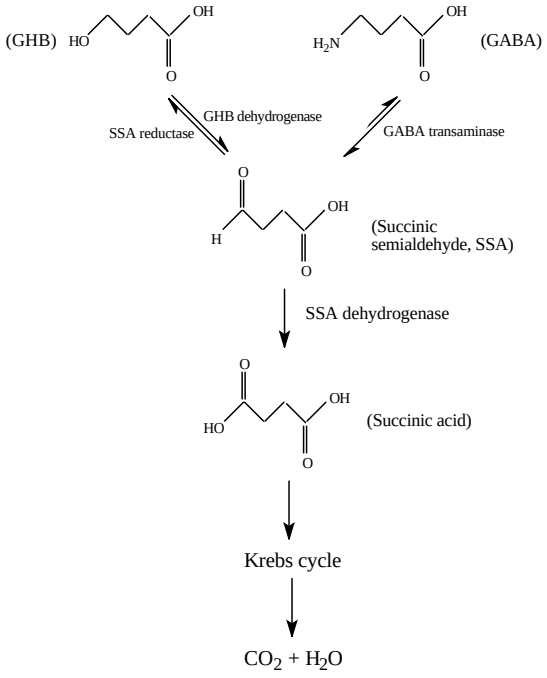


Figure 2. Metabolic pathway of GHB and GABA.

The second step in the metabolism of GHB is the oxidation of succinic semialdehyde to succinic acid via an NAD^+ dependent enzyme called succinic semialdehyde dehydrogenase [18]. The succinic acid then becomes a substrate in the Krebs Cycle and is ultimately metabolized to CO_2 and H_2O, hence there are no active metabolites of GHB.

GBL is rapidly hydrolyzed to GHB, in vivo, with a half-life of less than 1 min [117]. The enzyme lactonase, present in blood and liver, catalyzes this reaction (Figure 1). 1,4-BD is converted to GHB by a two-step process [62]; however the conversion is not as rapid as the hydrolysis of GBL. The first step of 1,4-BD to GHB metabolism is catalyzed by the NAD^+ dependent alcohol dehydrogenase yielding γ-hydroxybutyraldehyde. The activity of alcohol dehydrogenase towards 1,4-BD is similar to its activity towards ethanol, hence ethanol is a competitive inhibitor of 1,4-BD metabolism to GHB. The second step is the conversion of γ-hydroxybutyraldehyde to GHB via a reaction catalyzed by aldehyde dehydrogenase. This aldehyde dehydrogenase-mediated conversion can be inhibited by disulfiram. The liver, brain, kidney, and heart are able to convert 1,4-BD to GHB, with liver showing the greatest conversion capacity per gram of tissue [62].

A rare genetic disorder has been identified in which a deficiency in succinic semialdehyde (SSA) dehydrogenase causes an accumulation of GHB and SSA. Also known as GHB aciduria, persons with this disorder have elevated levels of GHB in their blood, spinal fluid, and urine because excess succinic semialdehyde is reduced to GHB via succinic semialdehyde reductase (Figure 2). Due to the increased levels of GHB, this disorder can cause symptoms ranging from mild oculomotor problems, ataxia, hyperkinesis and convulsions, to severe psychomotor retardation and psychosis [58,63]. It is commonly characterized by mental, motor, and language delays accompanied by hypotonia. Accumulated GHB has been shown to reach concentrations as high as 260 mg/L in urine, 105 mg/L in serum, and 62 mg/L in CSF [63].

GHB can also be a metabolite of other ingested compounds. The pro-drug Ftorafur, an anticancer drug commonly used to treat colon cancer, is metabolized first to the active drug 5-fluorouracil and then to GBL/GHB in vivo, in both humans and rabbits. In rabbits, as much as 20 to 40% of the administered Ftorafur dose is metabolized to GBL/GHB. After a single dose of Ftorafur, human subjects showed GHB plasma concentrations of between 1 and 2 mg/L [8]. These levels are 2 to 4 times greater than the endogenous GHB plasma and blood levels described in this monograph (*see* Section III.C.2.a.). A recent paper, which describes a case of tetrahydrofuran poisoning in a 55-year-old woman, documented elevated GHB concentrations in serum and urine. The woman was admitted to the hospital in a deep, hypotonous, and unreactive coma with bilateral mydriasis. Tetrahydrofuran concentrations in serum and urine specimens collected upon admission were 813 and 850 mg/L, and GHB concentrations were 239 and 2977 mg/L, respectively. The woman was discharged from the hospital after eight days without sequelae [17].

4. Elimination

Following an intravenous dose, GHB exhibits zero order or capacity-limited elimination kinetics. As such, GHB has no true half-life, and the time required to eliminate half of a given dose increases as the dose increases. A daily therapeutic dose of 25 mg/kg had a half-life of 27±5 min in humans as determined in alcohol-dependent patients under GHB treatment [48]. In subjects treated with 26 to 52 mg/kg GHB, the mean elimination half-life was 53 min (range 27–71 min) [119]. Similar elimination half-lives were determined in 24 healthy subjects given 4.5 and 9 g GHB, in two equally divided doses 4 h apart [14]. The resulting elimination half-lives were 35 and 50 min, respectively. Disposition kinetics of GHB can change under conditions of moderate or severe liver dysfunction. Mean area under the curve (AUC) values for GHB were double or greater in cirrhotic patients as compared to healthy individuals. Patients with ascites showed an increased apparent half-life for GHB, probably due to an increased volume of distribution, as compared to healthy subjects [46].

Overall, GHB is rapidly eliminated. Even following a relatively large oral dose of 75-100 mg/kg, GHB can be undetectable in plasma after 8 h and in urine after 12 h [61]. Typically, an average of less than 1 % of an ingested dose is recovered as unchanged drug in the urine, suggesting extensive hepatic metabolism [48].

IV. ANALYTICAL METHODOLOGY

Gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) methods have been frequently reported for the analysis of GHB and GBL in biological fluids or tissues. GHB and GBL can be extracted from biological specimens using liquid-liquid, solid phase (SPE), and solid phase micro-extraction (SPME) techniques, with subsequent detection by GC using flame ionization detection (GC-FID), and by GC-MS using electron impact (EI) or positive or negative chemical ionization (CI).

GHB is a small polar molecule, which is not easily isolated from biological matrices and interferences, is thermally instable, and displays poor chromatographic

properties. Consequently, many methods target GBL following its conversion from GHB. This is accomplished by heating the specimen in the presence of a strong acid (e.g., trichloroacetic or sulfuric acid), followed by extraction of GBL with benzene, chloroform, or methylene chloride [45,78,80,101,105,106,130]. Characteristic mass spectral ions for GBL are *m/z* 86, 56, and 42.

LeBeau and co-workers describe a method that employs two aliquots of specimen [78]. The first aliquot was converted to GBL with concentrated sulfuric acid while the second was extracted without conversion. A simple liquid-liquid methylene chloride extraction was employed, and the aliquots were screened by headspace GC-FID without derivatization. Specimens that screened positive by this method were then re-aliquoted, subjected to the same extraction with the addition of the deuterated analogs of GHB and GBL as internal standards, and analyzed by EI GC-MS in full scan mode. This method displayed linearity in both blood and urine from 5 to 1000 mg/L, with recoveries that averaged between 75 and 87%.

In other procedures, GHB has been extracted from biological specimens using a variety of extraction techniques, prior to derivatization and subsequent analysis by GC-MS. Due to its thermal instability and polar nature, derivatization is necessary prior to direct chromatographic analysis of GHB. Silylation of the hydroxyl and carboxylate moieties using BSTFA is most frequently used.

An extraction procedure using Toxi-tube® A and Toxi-tube® B extraction tubes (Toxi-Lab, Inc.) was reported for the separate analysis of GBL and GHB, respectively [53]. In this procedure, the Toxi-tube® B extract required derivatization with BSTFA prior to the analysis of GHB by GC-MS. A simple liquid-liquid extraction procedure using ethyl acetate has been described for the direct analysis of GHB in blood and urine [25]. Following derivatization to its di-TMS derivative by BSTFA/1% TMCS, GHB was detected using GC-MS in EI mode, with selected ion monitoring of m/z 233, 204, and 117 for di-TMS GHB and *m/z* 235, 103, and 117 for the internal standard di-TMS diethylene glycol. The method gave a 55% extraction recovery in blood, a limit of detection in blood and urine of 0.5 mg/L, and a linear response of 1–100 mg/L in blood and 1–200 mg/L in urine. A procedure similar to this was described for the analysis of GHB in urine using d_6-GHB as the internal standard [41]. Extraction recovery ranged from 80–85%, with a linear response from 2–50 mg/L.

Several SPE techniques have been described using either Chem-Elute® SPE columns [7], United Chemical Technologies Clean Screen® ZSGHB020 columns [64,97], or Multi-Prep® Anion Exchange GVSA-200 Gravity Flow columns [11]. These methods all detect GHB by GC-MS in EI mode, following extraction from blood and urine and derivatization using BSTFA/1% TMCS. De Vriendt and associates describe a high-performance liquid chromatography procedure following SPE using Bond Elute®-SAX (strong anion exchange) cartridges [33]. Extraction recoveries of GHB from plasma averaged 79%, with a limit of quantitation of 10 mg/L, and a linearity of 10–750 mg/L.

Using only 0.1 mL blood and d_6-GHB as the internal standard, Pearson and Blackburn extracted GHB from blood using methanol:ammonium hydroxide (99:1) [107]. A clean-up step was implemented using hexane-saturated *N*,*N*-dimethylformamide, and GHB was derivatized using BSTFA/1% TMCS. A linearity of 1–500 mg/L was obtained. For urine, samples were run through Clean Screen® ZSGHB020 SPE columns, prior to the above liquid extraction, to filter out the excess interferon urea. Another method utilizing the same SPE columns has been modified to include GHB and 1,4-BD analysis in blood, vitreous, and tissue homogenate samples [30,71]. Sample size is only 200 μL and the procedure requires a sample preparation step of extraction with acetone prior to elution on the SPE column using methanol:ammonium hydroxide (99:1). The eluent is then taken to dryness and derivatized with BSTFA/1% TMCS. The ions monitored were 233, 234, and 235 for di-TMS GHB; 239, 240, and 241 for di-TMS GHB-d_6; 219, 220, and 221 for di-TMS 1,4-BD; and 223, 224, and 225 for di-TMS 1,4-BD-d_4.

Most recently, SPME has been used successfully to analyze for GHB and GBL. GHB was derivatized in urine specimens with hexyl-chloroformate and then extracted directly from the sample using SPME [12]. Separation and detection were performed using quadrupole ion trap GC-MS, with a limit of detection of 2 mg/L and a linearity of 5-100 mg/L. Frison and associates describe a SPME method in plasma and urine, which converts GHB to GBL and uses d_6-GBL as internal standard [52]. Detection was by GC-MS with spectra from both CI and EI ionization modes, with a limit of detection of 0.05 mg/L and 0.1 mg/L, for plasma and urine, respectively.

Unchanged 1,4-BD may be detected in a biological specimen if enough is ingested and/or the interval since ingestion is short. McCutcheon and associates utilize a simple one-step extraction at physiological pH into n-butyl chloride for the extraction of 1,4-BD [98]. The solvent is dried down to about 75 μL and subjected to GC-MS analysis. The 1,4-BD elutes prior to GBL with a detection limit between 50 and 100 mg/L. Research by the authors is currently underway to improve this method. A method specific for the detection of 1,4-BD in liver and brain tissue is described by Barker and associates [9]. This method involves a complicated extraction scheme, which

utilizes different extraction protocols for the aqueous and lipid fractions of the tissues. Both fractions are then lyophilized to dryness, extracted again, and subsequently derivatized with heptafluorobutyric anhydride. Deuterated 1,4-BD was used as an internal standard, with identification and quantitation by EI GC-MS in the SIM mode. The method demonstrated a mean recovery of 74% for the aqueous fraction and 88% for the lipid fraction. The linearity range was 0–1.0 μg/g wet weight of tissue with a limit of detection of 0.01 μg/g wet weight of tissue.

V. INTERPRETATION ISSUES

A. Endogenous Postmortem Production

Extreme caution must be exercised when interpreting potential GHB-related fatalities, as GHB can be endogenously produced postmortem. Often laboratories will set their own cut-off concentration for reporting a positive postmortem GHB blood result. However, this can be difficult in certain postmortem specimens, particularly if there is any survival time between ingestion and death, as the blood levels of GHB can easily fall into the range of postmortem production. It is therefore the authors' recommendation that in a suspected fatal GHB-related overdose case, specimens such as urine, vitreous, and CSF be collected and analyzed to verify blood results. In addition to the analysis of multiple specimens, the circumstances surrounding the death can help in the interpretation of potentially fatal GHB overdoses.

In a study of 96 postmortem cases assumed to be non-GHB users, mean GHB concentrations detected in heart blood specimens were 12 mg/L (range 1.6 to 36 mg/L), femoral blood 11 mg/L (range 1.7 to 48 mg/L), and urine 4.6 mg/L (range 0 to 14 mg/L) [5]. In a study of 17 non-GHB-related deaths, a median GHB concentration of 9.8 mg/L was detected in femoral blood specimens (range 3.0 to 107 mg/L) [24]. Urine and vitreous from the same cases, where available, were also analyzed for GHB. Ten of the 12 urine specimens were positive for GHB, with concentrations ranging from 1 to 7 mg/L and a median concentration of 5 mg/L. Three of the eight vitreous specimens were positive for GHB, with concentrations ranging from 1 to 6 mg/L and a median concentration of 1.5 mg/L. Similarly, in a study of 20 non-GHB-related postmortem cases, 15 of the blood specimens were positive for GHB with an average concentration of 25 mg/L (range 3.2–168 mg/L) [49]. Eight corresponding urine specimens were also analyzed; however, no GHB was detected (detection limit: 1 mg/L). It can be seen from these three studies that endogenous postmortem blood concentrations overlap with those reported following therapeutic administration of GHB (*see* Section III.C.2.b.).

Animal studies have also demonstrated that endogenous GHB levels can rise postmortem. It was discovered that if the animals were killed using microwave irradiation, postmortem GHB accumulation was blocked [40]. This suggests some type of enzymatic conversion from a GHB precursor. Succinic semialdehyde has been proposed as a possible source. This could occur by two pathways. Shortly after death, a cessation of Krebs cycle activity occurs due to a lack of oxygen, which would result in an increase in substrates that would normally utilize this pathway, succinic acid being one. The buildup of succinic acid would drive the reaction toward succinic semi-aldehyde, and then succinic semialdehyde reductase would convert the succinic semialdehyde to GHB (Figure 2). The second pathway involves the metabolism of previously sequestered GABA that is being released from storage vesicles as the natural decomposition process proceeds. Excess GABA would be exposed to the GABA transaminase enzyme, which would convert it to succinic semialdehyde, which could in turn be converted to GHB in addition to proceeding on to succinic acid. These theories are consistent with the observation that microwave irradiation prevents postmortem accumulation of GHB since the exposure to the microwaves would denature the enzymes. This is also supported by the fact that GHB production is not seen in blood specimens that have an enzyme inhibitor added. As the decomposition process continues, the drop in pH that occurs would eventually denature all of these enzymes.

Consequently, the most likely source of postmortem GHB production is putrescine (1,4-butanediamine), a biogenic polyamine initially detected in decaying animal tissues, but now known to be present in all eukaryotic and prokaryotic cells where it is important for cell proliferation and differentiation [99]. Research on polyamine metabolism by Seiler demonstrated the formation of GABA from putrescine both in visceral organs and in the CNS of vertebrates [122]. This is a two-step enzymatic process in the polyamine metabolic pathway that involves diamine oxidase and aldehyde dehydrogenase to form GABA. In organs that do not contain high activity of diamine oxidase, such as brain, an alternative pathway is available for the conversion of putrescine to GABA. This pathway involves the conversion of putrescine to monoacetylputrescine by the enzymatic addition via polyamine aminotranferase of acetylcholine. Monoacetylputrescine is a substrate for monoamine oxidase. The subsequent action of monoamine oxidase, followed by aldehyde dehydrogenase and acetylpolyamine deacetylase, results in the formation of GABA [123]. In addition, Snead and associates observed an 80–100% increase in GHB concentrations in rat brain after intracerebroventricular administration of putrescine [128].

B. Specimen Storage

Several studies have demonstrated that clinical and postmortem GHB concentrations can rise under inappropriate specimen storage conditions. Storage time and temperature, and the use of preservatives, can impact the GHB concentration in biological specimens. Doherty and associates observed an increase in brain GHB concentrations after 6 h, with a further increase when the specimens were left at room temperature [35]. Increases in CSF GHB concentrations have also been observed after 12 h of storage at room temperature [127]. Urine specimens from two non-GHB-using subjects were periodically analyzed for GHB over a six-month period, following storage at either room temperature, 5 °C or –10 °C [76]. The specimens maintained in a frozen state showed the smallest increases in endogenous GHB concentration (up to 116%), while the specimens stored at room temperature showed relatively large increases (up to 404%). However, none of the specimens ever increased more than 1 mg/L above the original concentration, and none of the specimens demonstrated increases that would be consistent with exogenous GHB ingestion (≥ 10 mg/L).

Frozen clinical blood specimens from non-GHB-related cases, showed artificial production of up to 13 mg/L GHB when preserved with trisodium citrate-citric acid buffer (yellow-top tubes) over time [77]. Other tubes containing sodium citrate and citric acid, such as light blue-top tubes, may have a similar effect. Absence of the preservative sodium fluoride and storage at room temperature has also been shown to increase endogenous postmortem GHB concentrations [131]. GHB concentrations increased by 50% in non-preserved specimens, even when refrigerated at 4 °C, when compared to preserved blood specimens. When non-preserved specimens were stored at room temperature, the concentration almost doubled. The addition of sodium fluoride did not affect the concentration of GHB in urine specimens that were compared.

VI. EFFECT ON HUMAN PERFORMANCE

The effects of GHB on actual driving performance, using driving simulator or open/closed driving circuits, have not yet been scientifically investigated. However, empirical and epidemiological data suggests that, at sufficient doses, the sedative and hypnotic effects of the drug would impair cognitive and psychomotor function. At such doses, GHB and its precursor drugs can cause dizziness, drowsiness, agitation, visual disturbances, somnolence, severe respiratory depression, and unarousable unconsciousness. These classical clinical symptoms are clearly contraindicated for the safe operation of a motor vehicle. Interestingly, several labels taken from products containing GHB, GBL, or 1,4-BD warn consumers of such possible adverse effects. For example, on a bottle of "ReActive" found in the possession of a driver arrested for impaired driving, the label stated " … a dose will induce stage 3 and 4 (deep) sleep in most people within 30 minutes … if ingested, do not operate machinery" [26].

Elimination of GHB from the body is relatively quick, and the onset of withdrawal symptoms can occur within 1 to 6 h following the dose. Withdrawal symptoms can include severe agitation, anxiety, tremor, combativeness, mild tachycardia, hypertension, psychosis, and prolonged delirium with auditory and visual hallucinations [39]. In addition to the use of GHB or its metabolic precursors, it is clear that driving skills may also be severely impaired while a person is suffering withdrawal from GHB.

A review of the literature provides clear evidence of a dose or concentration-dependent increase in cognitive and psychomotor impairment. For example, Helrich and associates correlated blood levels of GHB with state of consciousness in 16 adult human patients (**Table 1**) [59]. This study revealed that GHB blood levels as high as 99 mg/L could be achieved with the patient still displaying an "awake" state. A light sleep state was characterized by the subject spontaneously coming in and out of consciousness (63–265 mg/L GHB). Subjects in the medium sleep state were clearly asleep but were able to be aroused (151–293 mg/L GHB). At the highest concentrations, GHB produced a deep sleep characterized by response to stimuli with a reflex movement only (244–395 mg/L GHB). There was an overlap in concentrations across the four states of consciousness described due to inter-individual differences.

A. Laboratory/Performance Studies

Two published reports investigating the effects of GHB on psychomotor performance failed to demonstrate gross impairment. Ferrara and associates concluded that oral doses of 12.5 and 25 mg/kg of GHB, (equivalent to 0.88 g and 1.75 g in a 70-kg person) had no effect on attention, vigilance, alertness, short-term memory or psychomotor co-ordination in 12 healthy adults [44]. Tests measured critical flicker fusion, critical tracking, choice reaction time (visual), letter recognition, vigilance (vi-

Table 1. Blood GHB concentration (mg/L[a]) and state of consciousness

Awake	Light sleep	Medium sleep	Deep sleep
0–99	63–265	151–293	244–395

[a] Values were converted from micromoles/L.

sual), and sedation self-rating, and were conducted at 15, 60, 120, and 180 min post-dose. Unfortunately, no corresponding GHB concentrations were obtained. The authors did report however, that 66% and 50% of the subjects experienced either dizziness or dullness following dosages of 25 and 12.5 mg/kg, respectively. Mattila and associates concluded that oral doses of 1 and 2 g of GHB, neither deteriorates driving skills (reactive and coordination skills, and attention) nor increases the effects of low doses of alcohol [96]. There was only a slight increase in the number of reaction mistakes following the 2-g dose.

Typical doses administered by GHB users, however, often exceed 1 teaspoon, which is equivalent to at least 2.5 g, or 35 mg/kg for a 70-kg person. Further studies on psychomotor performance using higher and more relevant doses of GHB would be valuable.

B. Epidemiology Studies

Stephens and Baselt first reported an account of an individual potentially driving under the influence of GHB in 1994 [130]. A 42-year-old man was discovered asleep behind the steering wheel of his automobile, which was at a standstill in a traffic lane with the engine running. The man admitted ingesting a white powder given to him by an acquaintance at a gymnasium about 1 h earlier. Police observed him to have horizontal and vertical gaze nystagmus, muscle flaccidity, severe ataxia, and he was unable to stand unassisted. A urine specimen collected approximately 2 h post-ingestion contained 1975 mg/L GHB and 26 ng/mL of 11-nor-9-carboxy-tetrahydrocannabinol. The urine GHB concentration measured was consistent with a dose of at least 100 mg/kg.

Marinetti reported several cases of GHB-impaired driving [90]. In one incident, a driver was observed driving slowly from curb to curb and was followed by police for several miles. When contact was made, the driver had vomited inside his truck, had no sense of his location, name, or destination, was incoherent and could only repeat questions asked of him by the police. The GHB concentration measured in a blood specimen was 135 mg/L, and the driver admitted ingesting RenewTrient. The same driver was stopped 10 months later. The driver was sweating, had a delayed pupil response, was unable to track a pen, and exhibited horizontal and vertical gaze nystagmus. A urine specimen was collected and the GHB concentration was measured at 1900 mg/L. In another case, the driver was found passed out along the roadside, outside his vehicle. The subject was hospitalized and a blood GHB concentration of 361 mg/L was detected.

Thirteen cases of suspected impaired driving, in which GHB was identified, were encountered over a 20-month period [26]. Concentrations in blood specimens collected between 1–3.5 h of the arrest ranged from 26 to 155 mg/L (mean 87 mg/L, median 95 mg/L). In eight cases, GHB was the only drug detected, and symptoms reported were generally those of a CNS depressant. The subjects were typically stopped because of erratic driving, such as weaving, ignoring road signs, and near-collisions. Common signs of impairment included confusion and disorientation, incoherent speech, short-term memory loss, dilated pupils, lack of balance and unsteady gait, poor coordination, poor performance of field sobriety tests, copious vomiting, unresponsiveness, somnolence, and loss of consciousness.

In 11 cases of driving under the influence of GHB, concentrations of GHB in blood and urine specimens ranged from 81–360 mg/L and 780–2380 mg/L, respectively [107]. Circumstances of their arrest, observed driving behavior and signs of impairment were similar to the above case reports.

A 38-year-old male was arrested seven times over an 8-month period for driving under the influence of GHB [27]. A blood specimen was drawn between 1.5–2.5 h after first police contact in each incident, and GHB concentrations ranged from 44 to 184 mg/L (mean 100 mg/L; median 73 mg/L). Signs of impairment generally included erratic driving (severe lane travel, collisions, and near-collisions), slurred speech, disorientation, slow to react, shaking, agitation, unable to focus, poor coordination and balance, poor performance in field sobriety tests, somnolence, and unconsciousness. During several police interviews, the subject stated he was addicted to GHB and GBL, and admitted having taken RenewTrient, Dream On, V35, “fitness supplements”, and GBL. During the same period, the subject had been admitted numerous times to several hospitals for acute GHB/GBL intoxications.

C. Drug Recognition Evaluation (DRE) Profile

In many North American states and provinces, trained DRE officers can reach informed conclusions concerning the kind of drug(s) causing the impairment observed in the subject. Such informed conclusions are based on a preliminary breath test to determine blood alcohol concentration; preliminary assessment of the subject’s speech, breath, appearance, demeanor, behavior etc; examinations of the subject’s eyes; psychophysical evaluations of the subject based on divided attention tests (standardized field sobriety tests); and examination of the subject’s vital signs.

The DRE profile for GHB closely resembles that of the profile of other CNS depressants such as ethanol. The

DRE indicators for GHB use include: presence of horizontal gaze nystagmus; presence of vertical gaze nystagmus (in high doses); lack of convergence; dilated pupils; slow reaction to light; decreased pulse rate; decreased blood pressure; and normal to decreased body temperature. Other common signs that DRE officers may look for include normal to flaccid muscle tone, evidence of vomiting, profuse sweating, subject slow to respond, slurred speech, unsteady gait, lack of coordination, poor performance on standardized field sobriety tests, somnolence, and loss of consciousness.

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