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REVIEW ARTICLE

The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol

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Introduction. Gamma-hydroxybutyrate (GHB) and its precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), are drugs of abuse which act primarily as central nervous system (CNS) depressants. In recent years, the rising recreational use of these drugs has led to an increasing burden upon health care providers. Understanding their toxicity is therefore essential for the successful management of intoxicated patients. We review the epidemiology, mechanisms of toxicity, toxicokinetics, clinical features, diagnosis, and management of poisoning due to GHB and its analogs and discuss the features and management of GHB withdrawal. *Methods.* OVID MEDLINE and ISI Web of Science databases were searched using the terms "GHB," "gamma-hydroxybutyrate," "gamma-hydroxybutyric acid," "4-hydroxybutanoic acid," "sodium oxybate," "gamma-butyrolactone," "GBL," "1,4-butanediol," and "1,4-BD" alone and in combination with the keywords "pharmacokinetics," "kinetics," "poisoning," "poison," "toxicity," "ingestion," "adverse effects," "overdose," and "intoxication." In addition, bibliographies of identified articles were screened for additional relevant studies including nonindexed reports. Non-peer-reviewed sources were also included: books, relevant newspaper reports, and applicable Internet resources. These searches produced 2059 nonduplicate citations of which 219 were considered relevant. *Epidemiology.* There is limited information regarding statistical trends on world-wide use of GHB and its analogs. European data suggests that the use of GHB is generally low; however, there is some evidence of higher use among some sub-populations, settings, and geographical areas. In the United States of America, poison control center data have shown that enquiries regarding GHB have decreased between 2002 and 2010 suggesting a decline in use over this timeframe. *Mechanisms of action.* GHB is an endogenous neurotransmitter synthesized from glutamate with a high affinity for GHB-receptors, present on both on pre- and postsynaptic neurons, thereby inhibiting GABA release. In overdose, GHB acts both directly as a partial $GABA_b$ receptor agonist and indirectly through its metabolism to form GABA. *Toxicokinetics.* GHB is rapidly absorbed by the oral route with peak blood concentrations typically occurring within 1 hour. It has a relatively small volume of distribution and is rapidly distributed across the blood–brain barrier. GHB is metabolized primarily in the liver and is eliminated rapidly with a reported 20–60 minute half-life. The majority of a dose is eliminated completely within 4–8 hours. The related chemicals, 1,4-butanediol and gamma butyrolactone, are metabolized endogenously to GHB. *Clinical features of poisoning.* GHB produces CNS and respiratory depression of relatively short duration. Other commonly reported features include gastrointestinal upset, bradycardia, myoclonus, and hypothermia. Fatalities have been reported. *Management of poisoning.* Supportive care is the mainstay of management with primary emphasis on respiratory and cardiovascular support. Airway protection, intubation, and/or assisted ventilation may be indicated for severe respiratory depression. Gastrointestinal decontamination is unlikely to be beneficial. Pharmacological intervention is rarely required for bradycardia; however, atropine administration may occasionally be warranted. *Withdrawal syndrome*. Abstinence after chronic use may result in a withdrawal syndrome, which may persist for days in severe cases. Features include auditory and visual hallucinations, tremors, tachycardia, hypertension, sweating, anxiety, agitation, paranoia, insomnia, disorientation, confusion, and aggression/combativeness. Benzodiazepine administration appears to be the treatment of choice, with barbiturates, baclofen, or propofol as second line management options. *Conclusions.* GHB poisoning can cause potentially life-threatening CNS and respiratory depression, requiring appropriate, symptom-directed supportive care to ensure complete recovery. Withdrawal from GHB may continue for up to 21 days and can be life-threatening, though treatment with benzodiazepines is usually effective.

Keywords CNS/Psychological; Organ/tissue specific; Complications of poisoning; Pharmaceuticals; Gamma hydroxybutyrate; Gamma-butyrolactone; 1,4-butanediol

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Introduction

Gamma-hydroxybutyrate (GHB) and its precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), are drugs of abuse which act primarily as central nervous system (CNS) depressants (Fig. 1). Since the initial investigations into gamma butyrolactone (GBL) in 1947[1,2] and GHB in 1960,[3] their biological, pharmacological, and toxicological properties have been studied extensively. 1,4-butanediol (1,4-BD) is an important industrial solvent and was discovered in 1890.[4]

GHB, commonly known as "Liquid ecstasy," "Gamma-O," "G," "Georgia Home Boy," "Mils," "Liquid X," and "Liquid G," is a short-chain carboxylic acid neurochemical messenger that occurs within the mammalian CNS. GHB is both a metabolite and a precursor of the inhibitory neurotransmitter gamma-hydroxybutyrate (GABA) and acts as a neuromodulator in the GABA system (see below).[5] While endogenous concentrations of GHB function as a neuromodulator in various neurobiochemical pathways, supratherapeutic doses of GHB can readily cross the blood–brain barrier leading to profound CNS and respiratory depression.

All three chemicals were shown to possess anesthetic properties and in the early-mid 1960's, GHB was first trialed as clinical anesthetic agent.[6,7] However, many of the early studies demonstrated that it lacked analgesic and muscle relaxant properties and produced a number of adverse effects; it never became established as a general anesthetic agent.[8] Other research involving a single study with six subjects suggested that GHB administration was associated with an increased release of growth hormone and an increase in REM sleep.[9] Subsequently, GHB became popular at training gyms and fitness centers as bodybuilders began to use it as a supplement, anticipating an increase in lean muscle mass due to increased growth hormone concentrations. It was also promoted in health stores for weight control and sedation.[10] However, as reports of adverse effects became more frequent, GHB was prohibited in 1990 in the United States of America.[11] The related chemicals GBL and 1,4-BD were substituted for GHB leading to predictable consequences and toxicity.[11,12]

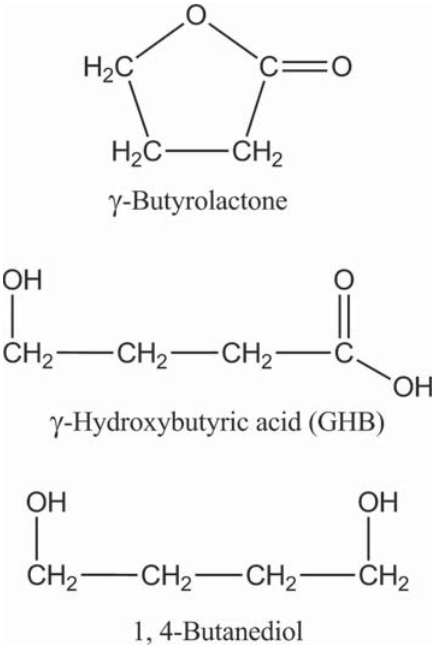

Fig. 1. The chemical structures of gamma-butyrolactone, gamma-hydroxybutyric acid and 1, 4-butanediol.

The intoxicating properties of GHB (and GBL and 1,4-BD) led to them becoming popular as substances of abuse, mostly in some parts of Europe, the United States, and Australasia.[10,13–28] When taken recreationally, users may co-ingest GHB with other drugs of abuse including ethanol,[15,19,24,29–43] cannabis,[15,19,20,24,29–34,36,39,44–46] amfetamines,[15,19,20,24,29,32–34,36–39,44,47] cocaine,[15,19,20,29,31,32,34,36–39,41,44,47] opioids,[15,19,20,25,32,36,48] benzodiazepines,[15,19,39,41,44,47] and other sedative or anesthetic drugs,[19,20,31,36,37,39] which may lead to a myriad of adverse clinical effects and social problems.

Although GHB has also been implicated in sexual assaults as a "date rape" drug,[39,47,49–53] a recent review of the literature suggested that GHB is rarely present in cases of drug-facilitated sexual assault.[54] The sodium salt of GHB, sodium oxybate, was also investigated for the treatment of cataplexy in patients with narcolepsy; an oral solution was approved in 2002 in the United States and in 2005 in Europe.[8,55] It has also been considered in Europe, particularly Italy, for the treatment of alcoholism.[56]

The aim of this paper is to review the epidemiology, mechanisms of toxicity, toxicokinetics, clinical features, diagnosis, and management of poisoning due to GHB and its precursors, GBL and 1,4-BD, and to review the features and management of the GHB withdrawal syndrome.

Methods

OVID MEDLINE (January 1950–July 2011) and ISI Web of Science (1900–July 2011) databases were searched using the terms "GHB," "gamma hydroxybutyrate," "gamma-hydroxybutyric acid," "4-hydroxybutanoic acid," "sodium oxybate," "gamma-butyrolactone," "GBL," "1,4-butanediol," and "1,4-BD" alone and in combination with the keywords "pharmacokinetics," "kinetics," "poisoning," "poison," "toxicity," "ingestion," "adverse effects," "overdose," and "intoxication." In addition, bibliographies of identified articles were screened for additional relevant studies including nonindexed reports. Non-peer-reviewed sources were also included: books, relevant newspaper reports, and applicable Internet resources. These searches produced 2059 nonduplicate citations, which were then screened via their title or abstract (if available) for those referring specifically to the mechanisms of action, toxicokinetics, clinical features, and management of GHB toxicity and withdrawal in humans; 219 were considered relevant.

Epidemiology

There are limited data regarding statistical trends on world-wide use of GHB and it analogs; nevertheless some

tentative conclusion can be inferred from data, typically obtained from government and nongovernment organizations, and poison center statistics. In Europe, there has been a fourfold increase in drug seizures by authorities over the 2005–2009 period that, according to the UN Office on Drugs and Crime,[57] account for almost 80% of the world total; in kilogram equivalents, seizures have increased from 156 in 2005 to 675 in 2009. Nevertheless, when compared to seizures of other types of synthetic drugs, such as amfetamines and MDMA, the total number is still comparatively low.[58] A recent publication from the European Monitoring Centre for Drugs and Drug Addiction investigating trends in GHB use in Europe, found there was limited information on the prevalence of use of GHB and its analogs but suggested its use is generally low; however, there is evidence of higher use among some sub-populations, settings, and geographical areas.[58] Another UN report suggests there is a growing concern in Europe, with an increasing number of people seeking treatment for addiction to GHB and GBL.[59]

Detection and seizures of both ketamine and GHB/GBL by the Australian Customs and Border Protection Service have steadily increased between 2002 and 2011.[60] The Australian National Drug Strategy Household Survey for 2010 showed 0.8% of people aged 14 years or older had used GHB at some stage in their life. This was an increase from 0.5% in 2004.[61] In contrast, rates of use in the United States, based on the American Association of Poison Control Centers summary of GHB poison center enquiries, have declined from 1386 in 2002[62] to 546 for the year 2010.[63]

Mechanisms of action

GHB is an endogenous neurotransmitter that is predominantly distributed within discrete regions of the mammalian brain,[64] though it is also present in the blood, urine, and other peripheral tissues.[65] GHB is both a metabolite and a precursor of the inhibitory neurotransmitter gamma-hydroxybutyrate (GABA),[66] and acts as a neuromodulator in the GABA system. An overview of its biochemical pathway is presented in Fig. 2 with a detailed description in the *Toxicokinetics* section.

GHB is synthesized from glutamate, typically within GABA-releasing neurons, that are predominantly located in the hippocampus, cortex, thalamus, and amygdala.[67–69] Upon depolarization, endogenously released GHB has a high affinity for GHB-receptors, present both on pre- and

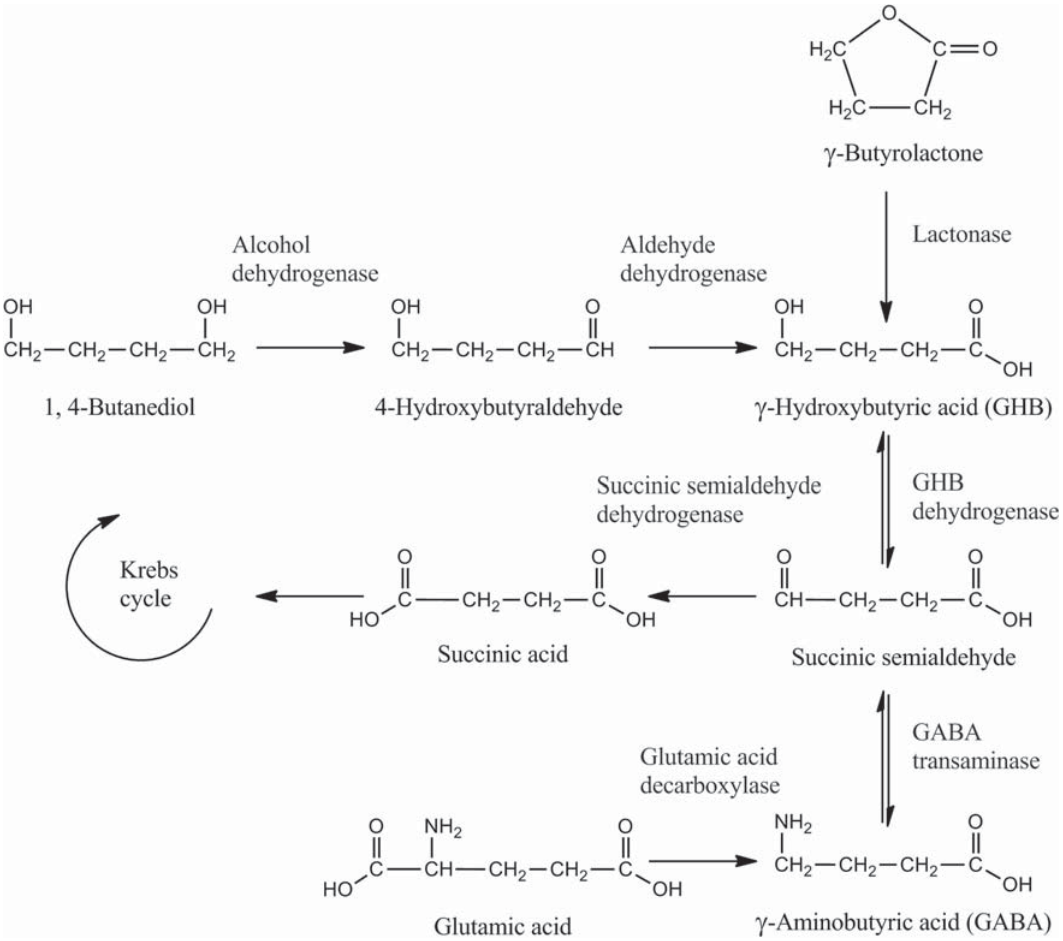

Fig. 2. A summary of the metabolic pathway of gamma-hydroxybutyrate.

postsynaptic neurons.[70,71]. It acts principally upon G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release.[70,71] GHB also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions,[72,73] and it modulates the serotonin[74] and opioid[75] systems. Additionally, GHB also modulates the release of growth hormone,[76] but lacks any anabolic effects.[77]

Endogenous concentrations of GHB, derived from postmortem samples, can range from 2 to 20 nmol/g,[64] though evidence with animal tissues suggests values may increase twofold over 6 hours following death.[64] In contrast to endogenous concentrations, exogenous sources of GHB, typically elevated to an excess of 1000 nmol/g tissue, can act directly as partial $GABA_b$-receptor agonist and indirectly through its metabolism to form GABA[78] (see Fig. 2), both resulting in membrane hyperpolarization and subsequent CNS depression.[79]

Toxicokinetics

GHB pharmacokinetics have been studied in healthy volunteers,[80–84] narcoleptics,[85,86] alcoholics,[87] and patients with liver impairment.[88] A further study monitored GHB kinetics following 1,4-butanediol administration to healthy volunteers.[89] The pharmacokinetics do not appear to vary significantly among healthy human volunteers, narcoleptic patients, or alcohol-dependent patients. However, when healthy adult volunteers and patients with biopsy-proven liver cirrhosis were compared, there was a marked reduction in clearance following oral administration and significant prolongation of elimination half-life.[88] A summary of kinetic parameters reported from these studies are presented in Table 1.

Absorption

GHB is well absorbed orally. Peak blood concentrations occur 25–60 minutes post-ingestion.[80–82,84–88,90] The onset of clinical and electroencephalographic (EEG) effects typically occur 15–20 minutes postexposure with peak effects at 30–60 minutes postingestion.[80,83,91] Studies suggested that oral absorption of GHB is nonlinear with limited capacity at higher doses leading to an increased interval of time to achieve Tmax and a decrease in the normalized Cmax.[80] One study, for example, demonstrated that the average time to achieve peak concentration increased from 25 minutes at a dose of 12.5 mg/kg to 45 minutes at a dose of 50 mg/kg.[80] Bioavailability was determined as 26% in one human study,[92] though animal investigations suggested 50–94% values.[93,94] Reduced bioavailability in humans is thought to be mainly due to more extensive first pass metabolism.[92,94] The ingestion of food with oral GHB has been shown to reduce mean peak plasma concentrations, increase median time to peak concentration, and decrease the area under the plasma concentration-time curve.[81]

Like GHB, 1,4-BD is rapidly absorbed and promptly metabolized to GHB. Following the oral administration of 25 mg/kg of 1,4-BD in healthy adult volunteers, the mean 1,4-BD Cmax was reached at 24 ± 12 minutes, with measurable plasma GHB concentrations within 5 minutes postingestion and the mean Cmax at 39.4 ± 11.2 minutes.[89]

Distribution

Animal studies have shown that distribution occurs rapidly and appears to follow a two-compartment model.[93] Mean volumes of distribution have been reported to range from 192 to 741 mL/kg when given to healthy volunteers[81,82,89] and from 225.9[86] to 307 mL/kg[85], when administered to narcoleptic patients. The volume of distribution was reduced from 225.9 to 196.7 mL/kg after 8 weeks of GHB therapeutic administration.[86] Volumes of distribution do not appear to be significantly affected by gender or food.[81] Studies have shown that GHB crosses the placenta in animals[95] and humans,[96,97] and

Table 1. A summary of the mean key pharmacokinetic parameters of GHB.

Mean time to peak plasma concentration (min)	Mean residence time (min)	Mean apparent volume of distribution [Vz/F] (mL/kg)	Mean clearance [CL/F](mL/min/kg)	Mean elimination rate constant (h-1)	Mean half-life (min)	Reference
25*	45	–	14	–	20	80
30*	53	–	9	–	22	80
45*	70	–	7	–	23	80
41.3	73.2	741	15.8	–	30	82
60*	–	202	3.8	–	39	82
60*	–	218	4.2	–	37	82
45*	–	192	3.7	–	34	82
120*	–	384	6.2	–	41	82
42	–	–	–	0.98	44	84
36	–	–	–	1.01	43	84
36	–	–	–	1.06	40	84
54	–	–	–	1.23	34	84
43	–	225.9	4	–	43	86
45*	77	198	4.5	–	32	88
45*	110	285	4.1	–	56	88
30*	68	–	7.9	–	27	87
45*	96	–	5.3	–	35	87

*Median value.

also passes across the blood–brain barrier.[78,98–101] *In-vitro* studies indicate that GHB shows limited plasma protein binding.[80]

Metabolism

GHB is primarily metabolized hepatically to succinic semialdehyde by means of NAD(P) + -linked oxidation by GHB dehydrogenase (Fig. 2). Succinic semialdehyde is metabolized primarily to succinic acid by succinic semialdehyde dehydrogenase[102]; alternatively, it can also be metabolized to GABA by GABA transaminase.[103] Succinic acid enters the citric acid cycle and is ultimately metabolized to water and carbon dioxide.[40]

The related chemicals, 1,4-BD and GBL, are metabolized endogenously to GHB. 1,4-BD is metabolized by alcohol dehydrogenases to gamma-hydroxybutyraldehyde and then by aldehyde dehydrogenase to form GHB; ethanol can inhibit this metabolism as it acts as a competitive substrate to alcohol dehydrogenase, whereas fomepizole will also stop its metabolism by inhibiting alcohol dehydrogenase.[43,104–106] GBL is converted to GHB by serum lactonase; this enzyme is not present in brain tissue.[107,108]

Elimination

Exogenous GHB demonstrates rapid nonlinear elimination kinetics in both animals[93,95,98,100,109] and humans.[80,92] This is thought to be most likely due to saturatable metabolic pathways.[80] GHB is predominantly eliminated following the biotransformation pathway, as outlined in Fig. 2, to form GABA and ultimately enter the Krebs cycle; less than 2% of the parent drug is eliminated unchanged in the urine.[83,84,87] The reported half-life of GHB in kinetic studies in humans is generally consistent with mean values between 20 and 53 minutes,[80–82,84–89] with the majority of a dose being completely eliminated within 4–8 hours postingestion.[87,90] Mean clearance (CL/F) values range from 3.7 to 15.8 mL/min/kg in either fed or fasted healthy volunteers.[80–82]

Following the oral administration of 1,4-BD 25 mg/kg, the mean elimination half- life was reported to be 39.3 ± 11 minutes in healthy adult volunteers.[89]

Clinical features

The majority of information regarding the features of GHB poisoning is obtained from case reports and case series; many of these did not have the diagnosis confirmed analytically, instead relying on self-reporting which thereby limits their accuracy. Nevertheless, the majority of these papers did provide a relatively consistent toxidrome for GHB toxicity in humans. Mild clinical effects, such as short-term anterograde amnesia, hypotonia, and euphoria, are anticipated following the ingestion of GHB doses below 10 mg/kg.[40,110] At doses of 20–30 mg/kg, drowsiness, sleep, and myoclonus can occur,[40,111] whereas doses of 50 mg/kg may cause coma.[110,112,113] Doses in excess of 50 mg/kg may lead to the onset of coma, bradycardia, and/or respiratory depression.[40,110–113] Thus, patients may present with CNS Symptoms ranging from sudden drowsiness through to unresponsive and profound coma, depending on the dose ingested.[12,14,19,20,24,25,27,29–33,35–43,45–47,106,110,114–149] symptoms typically occur within 15–45 minutes,[12,30,41] and resolve within a relatively short interval of time; CNS depression usually persists for 1–3 hours with patients making a complete recovery typically within 4–8 hours.[12,32,43,111,116–119,121,122,124,147,149]

In one case series of 88 patients who took GHB, the reported presenting Glasgow Coma Scale (GCS) scores were 3 in 25 patients (28%), 4–8 in 28 patients (33%), whereas 17 patients (19%) had a GCS score of 14 or 15.[32] Other common neurological effects include ataxia,[29,45,115,119–121,131,149] disorientation,[30,38,136,144,149] dizziness,[20,120,123–125,132,144] confusion,[20,45,124,125,136] hallucinations,[124,125,131,149] somnolence,[117,121,136,147] slurred speech,[115,131,149] dysarthria,[38,120] confusion,[12,20,149] headache,[38,46] incoordination,[115,124] euphoria,[113,136] amnesia,[120,136] hypotonia,[12,24,41,45,110] hyporeflexia[118,133,139,143] tremor,[110,115] and myoclonus.[19,110,117,120,150] Seizures or seizure-like activity have also been reported,[19,20,24,32,33,35–37,41,106,110,116,122,124,125,128,136,142,148] although, the majority of studies have shown seizures are uncommon. Some cases where seizures have been reported may have resulted from a misdiagnosis of myoclonus that was attributed to generalized seizures.[31] Nevertheless, seizures may still occur secondary to hypoxia or due to coingested intoxicants.

Agitation, bizarre behavior, and combativeness has been noted in some patients, either at presentation or upon wakening[12,19,20,24,29,31,36,38,42,46,115,119,120,122,124,127,129,136,142,144,145,147,149,150]; this may also occur when intubation is attempted, or may also occur when the patient is in a deep coma.[31,119] Patients can also alternate between agitation and somnolence.[136,145]

Other less common neurological effects may include bruxism,[129] vertigo,[110] disinhibition,[38] increased sexual arousal,[132] delusions,[144] extrapyramidal side effects,[131] dystonias,[131] and athetoid posturing.[129] Miosis is common[12,20,38,40,43,46,114,119,122,123,125,134,136,140,142] while mydriasis[20,35,38,46,47,115,117,123,124] and horizontal and vertical gaze nystagmus[45,46,115,131,149] may also occur. Pupils may also be sluggish or nonreactive.[12,35,124,125,141]

Common cardiovascular effects include bradycardia,[19,20,24,30,35,37,38,43,110,115,116,120,122–124,126,127,129,130,133,135,136,140–143,147,149,150] and hypotension.[20,36,38,41,110,116,120,129,134,135,141,149] Mild bradycardia without hemodynamic compromise is the most common cardiovascular effect; this is evident both following its use in anesthesia[151] and in recreational use.[32] One case series of 88 overdose patients showed that 32 (36%) developed bradycardia but only one case was deemed severe enough to require atropine.[32] In this case series, bradycardia was associated with decreased levels of consciousness; those with bradycardia had a mean GCS of 4 whereas those without bradycardia had a mean initial GCS score of 9.[32] Hypotension is rare when GHB is the sole ingestant,[38] though it is reported more commonly

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