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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]

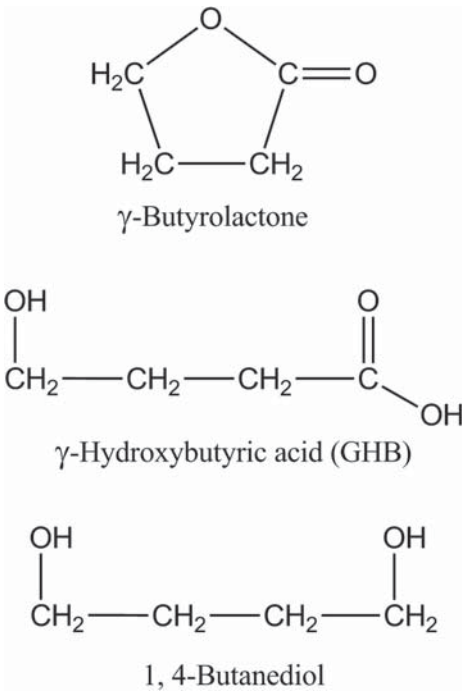

Fig. 1. The chemical structures of gamma-butyrolactone, gamma-hydroxybutyric acid and 1, 4-butanediol.

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

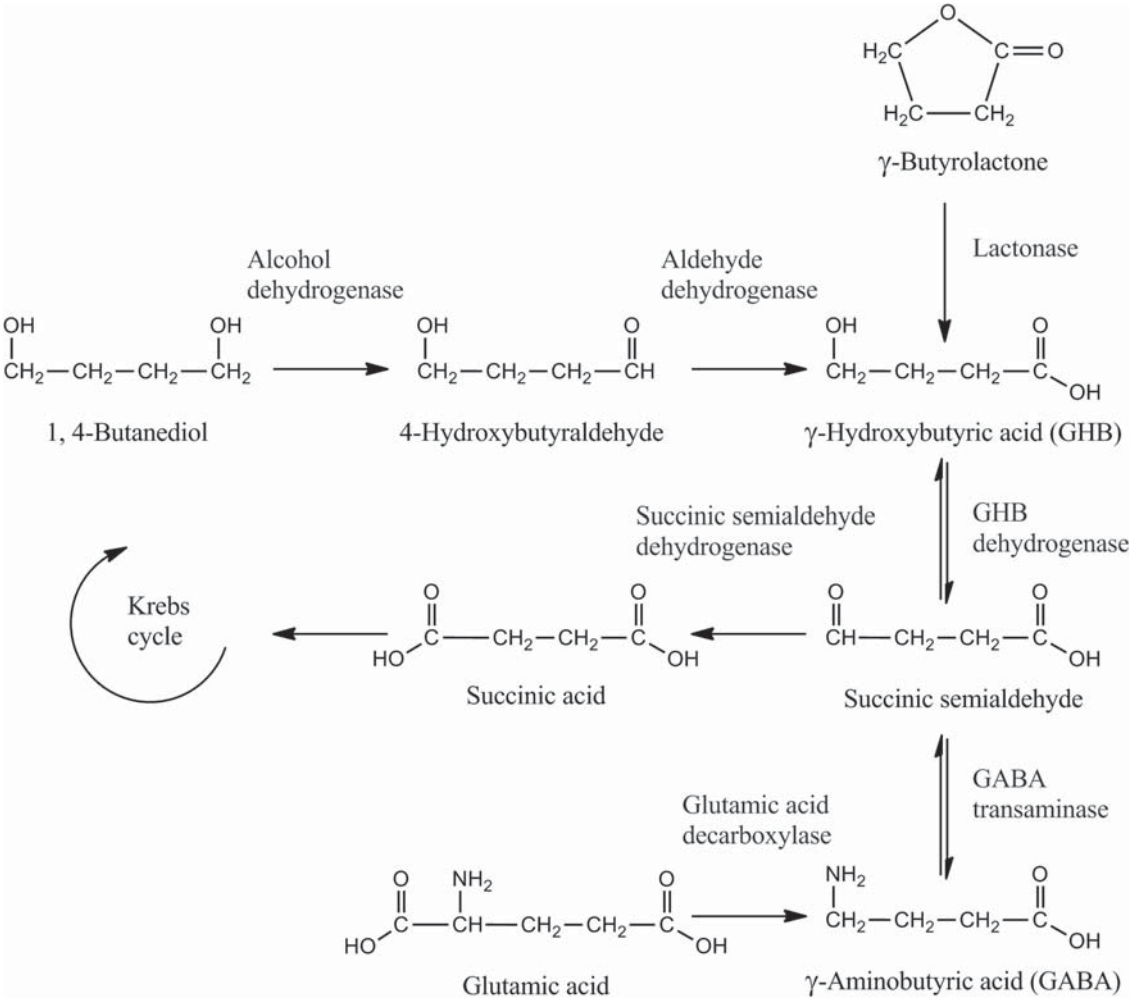

Fig. 2. A summary of the metabolic pathway of gamma-hydroxybutyrate.

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

when taken with coingestants.[20,32] Conversely, tachycardia and hypertension have also been reported.[35,36,45,119,120,122,124,136,140,147,149,152,153]ECG abnormalities occur occasionally[36] and include U waves,[31] transient P-wave inversion,[154] elevation of the ST segments,[143] possible QRS widening,[12] QTc prolongation,[143] right bundle-branch block,[31,143] and first-degree atrioventricular block.[31] Atrial fibrillation that spontaneously converted to sinus rhythm has also been reported,[32,129] while asystole may occur in severe cases.[35] Chest tightness[38,125] or palpitations[38] may also occur.

The major respiratory effects of GHB include dose-related respiratory depression,[19,20,29,31,35,37,42,110,114,119,120,122–124,136,141] bradypnea,[12,30,33,36,38,118,120,123,129,133,134,138,141,149] periodic (Cheyne–Stokes) respirations,[6,24,155] and apnea and respiratory failure.[14,24,27,31,33,43,110,114,122,125,129,130,135,136,138,140,141,143,144,149] One case series reported 30 patients that had arterial blood gases measured; 21 of these patients (70%) had a PCO_2 of 45 mmHg (6 kPa) or greater.[32] The mean arterial pH in these 30 patients was 7.32 ± 0.04; 28 (93%) had a pH of less than 7.40 and 9 (30%) had a pH less than 7.30.[32] No cases of pulmonary aspiration were recorded in this series though this has been noted in other reports.[12,14,20,27,39,122,141] Tachypnea,[36] pneumothorax,[143] and cyanosis[12,35] have also been reported. Pulmonary edema has been documented during intoxication[114,156] and a common feature at autopsy.[48,120,139,157]

Hypothermia can also occur.[19,20,29,32,36,38,41,129,133,136,141 143 144 149] One case series of 88 patients showed 48 had an initial temperature of 36°C or less and 22 patients had an initial temperature of 35°C or less.[32] Hypothermia is normally not severe.[19,32]

Metabolic features include hyperglycemia,[114,122,140] hypokalemia,[19,20,30,114] and potentially hypernatremia if large doses of the sodium salt are ingested.[112] Elevated creatine kinase activity/rhabdomyolysis may also occur.[17,19,20,24,46,147]

Nausea and vomiting are common gastrointestinal symptoms following oral or intravenous administration of GHB.[12,19,20,24,27,29,30,36,37,41,46,110,113,116,120–125,128,135,136,143,144,149,150,157] Two case series have noted vomiting in 22%[44] and 30%[32] of presentations. In the latter series, vomiting typically occurred during the final emergence from unconsciousness, although sometimes occurred during other stages of intoxication.[32] Salivation,[24,158] abdominal pain,[144] and incontinence of stool and urine may also occur.[20,120,124,125,129,136,143,147,148] Diaphoresis has also been reported.[29,31,44,119,120,136,147,149]

The majority of patients ingesting GHB recover without sequelae as long as they receive appropriate supportive care.[19,20,24,25,29,31,32,36–39,110,136,144] However, fatal outcomes have been recognized[14,15,27,39,42,48,120,139,157,159–165]; typically these occur in a prehospital setting. Death is normally due to respiratory failure.

GHB use alongside other CNS depressant drugs may increase toxicity by producing synergistic CNS depression.[15,166] and coingestants may also contribute to fatalities involving GHB.[15,39,48,164,165]

Diagnosis

A diagnosis of GHB intoxication is typically made on the basis of the patient's history and presentation. However, as such symptoms are not specific, it may be difficult to differentiate GHB poisoning from other sedative-hypnotic intoxications, especially if no history of GHB use is available to the clinician.[29]

A number of analytical methods to detect GHB, both in urine and serum, have been utilized; including gas or liquid chromatography coupled with electron capture and flame ionization, mass spectrometric detection, liquid chromatography-mass spectrometry (LCMS), and ultraviolet-visible spectrophotometry.[29,47,115,146,149,167–174] However, serum or urine concentrations cannot be readily assayed in most hospital laboratories. Interpretation of serum or urine concentrations may also be difficult due to confounding factors such as the rapid metabolism and elimination of GHB, the presence of endogenous GHB, spontaneous GHB-to-GBL interconversion, and possible erroneous results from collection and storage of samples.[172,175–179] Interpretation is also complicated by the poor correlation between plasma/urine concentrations and clinical effects.[29] Analytical assessment should not therefore be considered a routine component of diagnosis.

Management

Decontamination

The efficacy of activated charcoal or gastric lavage following GHB ingestion has not been assessed formally. Decontamination is unlikely to be beneficial in the majority of cases because of the drug's rapid absorption, particularly when consumed in a liquid form. Additionally, as patients typically do well with supportive care, the risk of adverse effects from decontamination likely outweighs any benefit. Gastric lavage and activated charcoal are therefore not indicated for sole GHB ingestions. However, activated charcoal may have a role in patients who have taken coingestants for which activated charcoal is an appropriate treatment. Activated charcoal (50–100 g) should only be considered in patients who are alert, stable, and cooperative, or have a protected airway. It must be administered cautiously, because of the risk of coma and/or loss of airway protective reflexes and pulmonary aspiration.[40,180]

Supportive care

Supportive care is the mainstay of management, with primary emphasis on respiratory and cardiovascular support. Initial treatment includes securing intravenous access and continuous cardiac and blood pressure monitoring along with pulse oximetry and arterial blood gas monitoring.

Airway protection including rapid sequence induction with endotracheal intubation and/or assisted ventilation is indicated in patients unable to maintain an airway or in the situation of hypercarbia or hypoxia unresponsive to oxygen administration. GHB is commonly associated with vomiting[32] and,

in the presence of loss of protective airway reflexes, this may increase the risk of pulmonary aspiration, therefore intubation would be additionally recommended in this situation.[181] Occasionally some patients may become agitated or combative when intubation is attempted, even in the state of deep coma[31,119]; sedation in incremental doses or paralysis may be required to assist intubation.[119] The risk of apnea or aspiration may be increased if there is coingestion of other CNS depressants[40]; careful airway management is vital for a successful patient outcome.[32]

The majority of patients with bradycardia are hemodynamically stable; pharmacological intervention is rarely required, though atropine may be useful when the patient suffers hemodynamically-unstable bradycardia.[24,31,32,40,154,182] Intravenous fluids should be administered for mild hypotension. Although GHB-induced hypotension requiring pressor therapy has not been reported, lack of response to intravenous fluids may require administration of agents with vasopressor and/or inotropic properties along with admission to an intensive care unit. Central hemodynamic monitoring may be indicated in the case of refractory hypotension or shock.

Myoclonic movements typically do not require any specific treatment but benzodiazepine administration may be useful.[128] If generalized seizures do occur, managing the airway and providing adequate oxygenation and ventilation may be all the treatment required. If seizures persist in well-ventilated patients, they should be treated with a benzodiazepine: lorazepam 2–4 mg by slow intravenous injection into a large vein in an adult (in a child under 12 years 100 μg/kg; max. 4 mg), repeated once after 10 minutes if necessary. Alternatively, diazepam 10 mg may be given intravenously in an adult at a rate of 5 mg/min (in a child under 12 years, 300–400 μg/kg), repeated once after 10 minutes if necessary.[183] If, however, seizures are refractory, phenobarbital (10 mg/kg, infused at a rate of not more than 100 mg/min) may be necessary as second-line therapy.[184]

Laboratory monitoring including blood glucose and serum electrolytes is recommended in symptomatic patients.[185] Dextrose should be given if indicated.[175]

Potential antidotes

There are no specific antidotes for GHB poisoning. However, some pharmaceuticals have been investigated as potential antidotes.

Physostigmine. Physostigmine has been investigated as a potential antidote. It had been used with claimed success as a reversal agent in patients under GHB-induced anesthesia.[186] The use of physostigmine following emergency department presentations has also been reported in a limited number of cases. One article reported the apparent reversal of sedative effects in two patients[133] while another case series described reversal of GHB toxicity in three patients but lack of response in a further patient.[129] It is not possible to determine if the improvement in level of consciousness was directly associated with the administration of physostigmine in these cases. The apparent reversal may have reflected the normal clinical course and resolution of GHB poisoning. Additionally, limitations of these studies included the lack of control groups, the studies not being blinded, and concurrent use of other sedatives such as diazepam being administered in a large number of the patients.[187] A more recent case series of five patients did not demonstrate response to physostigmine.[188] Pharmacological studies in rats did not show a significant relationship between GHB and central acetylcholine-mediated neurotransmission[189] or show an increase in acetylcholine concentrations in the central nervous system[190] suggesting there is no plausible pharmacological mechanism for physostigmine in reversing GHB toxicity. Additional animal studies have shown that physostigmine does not produce arousal and leads to physostigmine toxicity when administered to GHB-intoxicated rats.[191]

Additional risks of using physostigmine for GHB poisoning are the potential dangers of cholinergic syndrome, seizures, bradycardia, atrial fibrillation, and/or asystole, especially in the situation of recreational polydrug use.[188,192,193] High level evidence that would demonstrate efficacy, safety, or improved outcomes such as randomized, placebo-controlled trials of physostigmine versus supportive care have not been performed to date. Reviews of the available literature investigating physostigmine as a potential antidote suggest that there is not sufficient scientific evidence to support the use of physostigmine in acute GHB overdose.[187,188] Physostigmine cannot be recommended.

Naloxone. Naloxone has been studied in animal experiments as a reversal agent, though with mixed results. In two rat studies, it was shown to reverse behavioral, EEG, and dopaminergic effects.[98,194] whereas in a further study in mice it did not reverse GHB-induced narcosis.[195] One report in humans investigating the effects of GHB on growth hormone release reported that naloxone pre-treatment did not antagonize GHB-induced growth hormone release.[40] Naloxone has been used in the following poisoning in humans, though with limited effect on reversing toxicity[31,40,119,121,123,134,142,143,196]; its use is therefore not recommended.

Flumazenil. Flumazenil, a selective benzodiazepine receptor antagonist, has also been investigated in the treatment of GHB intoxication. An investigation in mice reported that pretreatment with flumazenil delayed intoxication; however, when administered after GHB, it did not alter intoxication.[197] Another study in rats reported flumazenil antagonized the anxiolytic effects of GHB.[198] In humans, it has been shown to reduce GHB-induced growth hormone release.[40] However, flumazenil has not shown any effect when used in humans to reverse clinical effects following poisoning[119,196] and thus, its use is not recommended.

$GABA_B$ antagonist, SCH 5091. A selective $GABA_B$ antagonist, SCH 5091, has been investigated in experimental animal studies as a potential antidote. It was found to significantly reduce mortality in mice when administered after the mice had been given a lethal intragastric dose of GHB

or 1,4-BD.[199,200] However, SCH 50911 has not been studied in human GHB poisoning and, therefore, there is limited information on its efficacy.

Enhanced elimination

There are limited data on the usefulness of hemodialysis, hemoperfusion, hemodiafiltration, or hemofiltration to enhance elimination of GHB. Given GHB has a low molecular weight along with minimal protein binding[80] and a relatively small volume of distribution,[82,88,89] it should be amenable to extracorporeal elimination. However, it would only be expected to be helpful in those very severely poisoned.[35] Due to rapid GHB clearance and the short duration of features, extracorporeal techniques would not be anticipated to be of clinical benefit in most patients.

GHB withdrawal syndrome

Clinical features

Dependence and tolerance are additional risks following regular use of GHB or its analogs; tolerant users can be exposed to higher doses in comparison to naive participants.[113] Following an interval of abstinence, users can suffer a withdrawal syndrome. The GHB-related syndrome seems consistent with other hypnotic/sedative withdrawal syndromes,[201] and has been well documented in the peer-reviewed literature[181,201–204] Commonly reported symptoms include auditory and visual hallucinations,[98,201,203,205–221] tremors,[34,98,113,201,205–208,212,214–216,218–227] tachycardia,[34,98,201,203,205–208,211,214–218,223,224] hypertension,[98,201,205,208,211,214,216–218,224] sweating,[98,201,205,207,208,211–218,220,223,225,226] agitation,[34,201,203,211,213,215,217,219,227,228] anxiety,[113,201,205,208,214,216,222–224,226,229] paranoia,[201,208,209,211–214,216,218,221,226] insomnia,[98,113,205,207,211,214,216,217,221,222,225] disorientation,[201,203,205,206,208,211,214,221] confusion,[201,205,208,211,214,219,227] and aggression/combativeness.[201,206,210,218,226] Patients may also suffer depression,[214,216,225] miosis,[211] nystagmus,[208,215,221,224] cardiac palpitations,[219,224,225] dyspnea,[219] tachypnea,[212] nausea and vomiting,[201,223] diarrhea,[201,229] and abdominal pain,[224] though this is less common.

Withdrawal can occur rapidly following the last dose taken by the user; in one case series, it developed within 1–12 hours.[113,201,205] The duration of these clinical effects may continue for 3–21 days.[113,201–203,205] In severe cases, delirium,[34,98,203,215–217,219,222,227] psychosis,[14,207,211,214,218–220] rhabdomyolysis,[203,205,220] and seizures,[201,203,211,226,227] are observed which may become life-threatening.[201,220] One anorexic female patient with a history of GHB use and alcoholism developed Wernicke–Korsakoff syndrome following abstinence from GHB.[221] This case was likely due to alcohol withdrawal along with malnutrition/thiamine deficiency.

Management

Benzodiazepine administration is typically employed to treat this syndrome.[201,205,208,211,212,217,223,229] Benzodiazepines have sometimes been reported to be ineffective; in these cases, patients have then been treated with a variety of alternate pharmaceutical agents either in combination with or substituted for benzodiazepines. These agents include barbiturates,[113,215,216,218,220] valproic acid,[214] carbamazepine,[214] gabapentin,[214] chloral hydrate,[207,214] baclofen,[214,222,227] clonidine,[214,225] paroxetine,[225] beta blockers,[225,230] bromocriptine,[203] trazadone,[206,214,216] fentanyl,[98] propofol,[98,120,220] or antipyschotics.[201,206–208,211,213,218–221,228] To date, there have been no rigorous prospective clinical trials investigating GHB withdrawal treatments; benzodiazepine administration appears to be the treatment of choice and, if necessary, barbiturates, baclofen, or propofol as second line management options.[40,181,201,203,204,216] Although there is limited experience in GHB withdrawal, dexmedetomidine has been used for other withdrawal syndromes and may also offer an interesting option.[231] Thiamine is not required unless there is a history of ethanol excess and/or malnutrition.[181] Monitoring in an intensive care unit is also recommended.

Conclusions

GHB is a relatively commonly abused drug. It is absorbed rapidly, extensively metabolized, and has a short half-life. Synthesized from glutamate, it is an endogenous neurotransmitter which has a high affinity for specific GHB-receptors, present both on pre- and postsynaptic neurons. Additionally, when ingested, GHB can act as a partial $GABA_b$ receptor agonist, leading to detrimental neurological, psychological, cardiovascular, and other systemic effects which may be potentially life-threatening. Patients typically present with CNS depression; respiratory depression, hypoventilation, myoclonus, and bradycardia may also be evident. Treatment consists of symptom-directed supportive care with emphasis on respiratory support. Patients invariably make a full recovery provided they are hospitalized and receive appropriate supportive care.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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