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SPECIAL COMMUNICATION

Gamma-hydroxybutyric acid: an emerging recreational drug

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Summary
Gamma-hydroxybutyric acid (GHB) is no longer used as an anaesthetic induction agent because of the high incidence of myoclonic seizures and vomiting. However, it is used occasionally in Europe for the treatment of narcolepsy, alcohol dependence and opiate dependence. Since the early 1990s, GHB has become a drug of abuse in youths for its euphoric, sedative and anabolic effects. Common adverse effects include a rapid onset of drowsiness, nausea, vomiting, myoclonic seizures and coma of short duration. Clinicians should be alert for these adverse effects and consider the possibility of GHB abuse in young adults with unusual clinical presentations in the emergency department.

Keywords *Anaesthetics*, *intravenous*; gamma-hydroxybutyric acid.

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Gamma-hydroxybutyric acid (GHB) is a drug which has been a subject of investigation since 1960 and was used as an intravenous anaesthetic agent in Europe and Japan in the late 1960s [1–3]. It has become a new recreational drug among young adults and appears to have a high potential for abuse [4–7] because it produces euphoria and relaxation. An increased number of outbreaks of coma associated with seizures induced by the illicit use of GHB has been reported in the United States [4], Britain [5] and Australia. Recently, deaths due to the ingestion of GHB have been reported [6, 8]. This review aims to alert physicians to the increasing use of GHB among youths and to consider GHB poisoning in the differential diagnosis in patients presenting with coma and myoclonic seizures.

Gamma-hydroxybutyric acid ($HOOC–CH_2–CH_2–CH_2OH$) is an endogenous short-chain fatty acid found in the central nervous system (hippocampus, hypothalamus, cerebellum), kidney, heart, skeletal muscle and brown fat [9, 10]. It is thought to be derived from gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. GABA is transaminated in the brain to succinate semialdehyde, which is then reduced to GHB [10, 11]. The concentration of GHB in the kidney, heart, skeletal muscle and brown fat is 10–15 times that in the brain but the significance of this is not known.

History

GHB was first synthesised in 1960 and was shown to cross the blood–brain barrier rapidly to induce a sleep-like state with cardiovascular stability. In 1964, it was introduced as an intravenous anaesthetic induction agent [1, 2], especially for children, in Europe but was not readily accepted because of the high incidence of vomiting, petit mal (absence) and grand mal seizures [3]. In the 1970s, it was advocated for the treatment of narcolepsy as it increased slow wave sleep and reduced the symptoms of narcolepsy [12]. In 1977, Japanese investigators reported that GHB enhanced the effects of steroids and the release of growth hormone [13]. Although this finding was not validated, body builders started to use the drug to promote muscle development. Recently, GHB has been advocated in the experimental treatment of alcohol dependence [14], opiate withdrawal syndrome [15] and for neuroprotection

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in cerebral ischaemia [10]. It was also used illegally for weight control until it was withdrawn by the Food and Drug Administration (FDA) in the United States in 1989 [4].

Illicit use as a recreational drug

GHB was first reported as a drug of abuse in the United States in 1990 and the FDA acted by banning over-the-counter sales. In 1991, the Centers for Disease Control (CDC) reported 57 cases of GHB poisoning associated with seizures and coma and issued a warning about its widespread illicit use and adverse effects [4]. The severity of the signs and symptoms of poisoning caused by GHB depends on the dose and the concurrent use of alcohol and other psychoactive drugs. In 1993, rumours that the actor, River Phoenix, died from an overdose of GHB sparked street interest in the drug. Youths became more aware of its euphoric effect and the demand for the drug increased.

Since then there have been widespread reports of GHB poisoning in North America, Britain and Australia. The San Francisco Bay Regional Poison Control Center reported 17–34 cases of GHB poisoning annually between 1990 and 1995. However, in 1996, it reported 89 cases, indicating a substantial increase over the previous year [6]. Furthermore, the Poison Control Centers of New York and Texas reported 69 cases of acute poisoning and one death caused by GHB from August 1995 to September 1996 [6]. As a result of the increasing number of reports of poisoning associated with the illicit use of GHB as a recreational drug, the Drug Enforcement Agency (DEA) has recommended that GHB be classified as Schedule 1 drug [6].

In the UK, GHB has been available in the night clubs around London since 1994 [5] and anecdoctal evidence from the north-east of England suggests that the recreational use of the drug is widespread and on the increase [7]. The drug is not controlled under the Misuse of Drugs Act in the UK and the police have little power to prevent the spread of its illicit use. In 1996, the news media reported overdoses of GHB among teenagers in the Gold Coast and Sydney areas in Australia.

GHB is sold on the streets as 'Liquid Ecstasy', 'Liquid E', 'Liquid X', 'GHB', 'GBH', 'Georgia Home Boy', 'Grevious Bodily Harm', 'Soap', 'Scoop', 'Salty Water', 'Organic Quaalude', 'Easy Lay', 'Fantasy', 'G-Riffick', 'Cherry Menth' and sodium oxybate. It is available as a colourless, odourless liquid, powder or capsules. It has a mild soapy salty taste which can be easily masked by adding it to party drinks. So far, illicit use has only been reported by oral ingestion. GHB produces a state of relaxation with mild euphoria and is commonly taken orally at 'raves', youth parties with energetic dancing in a crowded environment for many hours. Furthermore, as a result of its abrupt coma-inducing effects and its ease of administration (added to drinks), it is becoming a popular agent of assault, a 'date rape' drug [6].

GHB can be prepared at home by mixing sodium hydroxide and butyrol lactate [6] and the recipe is available on the Internet. However, the improper manufacture of the drug can lead to a mixture of GHB and sodium hydroxide, which is extremely toxic because of the combined coma-inducing and emetogenic effects of GHB and the caustic effects of sodium hydroxide.

Neuropharmacology of GHB

GHB has been proposed to have a role as a neurotransmitter or a neuromodulator [9] in mammalian brain as specific high-affinity binding sites have been identified in hippocampus, ventrolateral thalamus and the frontoparietal and entorhinal cortex of the rat brain [16]. These high-affinity binding sites appear to be associated with dopaminergic structures.

Animal studies have shown that GHB readily crosses the blood–brain barrier and transiently decreases dopamine release followed by a two-fold increase in dopamine release [16–18]. This is associated with increased release of dynorphin in the brain. It increases the concentrations of acetylcholine, serotonin and GABA in the central nervous system. Although its structural similarity to GABA led to the suggestion that it might be a GABA agonist, GHB has partial agonist activity at $GABA_B$ receptors at concentrations above physiological levels [19, 20] and no direct actions on the $GABA_A$ receptor [21].

At low concentrations (300–600 μmol), *in vitro* studies using hippocampal slices suggest that GHB provokes neuronal depolarisation associated with an increase in the concentrations of cyclic guanosine monophosphate (cGMP) and inositol phosphate [22]. Systemic administration of high doses (1–5 $mmol.kg^{-1}$) of GHB to rats increases dopaminergic activity and induces absence (petit mal) seizures [23]. There is evidence that the epileptic effects are mediated by the weak agonist actions of GHB on $GABA_B$ receptors in the brain [19, 23, 24] and are associated with a dose-related decrease in cGMP and an increase in spike and wave discharges [24].

Electrophysiological studies have demonstrated that high doses of GHB activate both presynaptic and postsynaptic $GABA_B$ receptors in the hippocampus of rats resulting in depression of monosynaptic excitatory and inhibitory postsynaptic potentials [19].

Pharmacokinetics

GHB is metabolised to carbon dioxide and water by oxidation via Kreb's cycle with no active metabolites [1]. After oral administration, it is rapidly absorbed

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within 10–15 min. It has a very short elimination half-life of about 27 min [8]. Both oral absorption and elimination are capacity limited.

Clinical effects

The clinical effects of GHB have been well studied. An oral dose of 10 mg.kg^{-1} in humans produces short-term amnesia and hypotonia. Sleep and drowsiness are induced at doses of 20–30 mg.kg^{-1} [7, 25, 26]. It induces rapid eye movement (REM) sleep in patients with narcolepsy and promotes non-REM sleep in normal people [12]. An intravenous dose of 50–60 mg.kg^{-1} produces general anaesthesia with little analgesia in humans within 5 min lasting for 1–2 h [3] and is associated with mild hypotonia, bradycardia, vomiting, bradypnoea and Cheyne–Stokes respiration. At higher doses, severe cardiorespiratory depression, coma and myoclonic seizures occur. The lethal dose (LD_{50}) has been estimated to be 5–15 times the dose required to induce unconsciousness [2].

Tolerance and physical dependence have been reported recently [27] with prolonged use of high doses of GHB, resulting in withdrawal symptoms which include insomnia, muscle cramps, tremors and anxiety.

Toxic effects and treatment

The signs and symptoms of GHB poisoning have been reported at doses [25, 28] from ≈ 2.5 g (one teaspoon) to 30 g (four tablespoons). The adverse effects include dizziness, nausea, vomiting, myoclonic muscle movements (jerks), agitation, confusion, hallucinations, loss of peripheral vision, emergence delirium, bradycardia, Cheyne–Stokes breathing and coma [4–7, 25–28]. As a result of the high incidence of vomiting (greater than 50%) there is a risk of pulmonary aspiration. Therefore, treatment is aimed at protecting the airway and mechanical ventilatory support may be required. These adverse effects are seen within 15 min of oral ingestion of the drug. As gastrointestinal absorption is very rapid, gastric lavage and activated charcoal are of limited value. Spontaneous recovery usually occurs within about 7 h because of the short elimination half-life of the drug. Anticonvulsants such as sodium valproate have been shown to antagonise the epileptogenic effects of GHB in laboratory animal models [29] but the clinical value of these drugs in humans is not known. Management is therefore largely supportive.

Almost total amnesia occurs and this makes counselling and follow-up treatment difficult as it does not deter the patients who cannot remember their near-fatal experience. The adverse effects of GHB are potentiated by alcohol and other psychoactive drugs that may be used at the rave parties.

As the drug is not detectable by routine toxicological tests, diagnosis depends on the history at the scene. Emergency medicine physicians and anaesthetists should have a high index of suspicion of the toxic effects of GHB when attending to patients presenting with coma and myoclonic seizures at the emergency department. Public education efforts should be focused on the adverse effects of the drug, the potential for physical dependence and the dangers of using the drug with other psychoactive agents.

References

1 Laborit H. Sodium 4 hydroxybutyrate. *International Journal of Neuropharmacology* 1964; **43:** 433–52.
2 Vickers MD. Gamma hydroxybutyric acid. *Proceedings of Royal Society of Medicine* 1968; **61:** 821–3.
3 Hunter AS, Long WJ, Ryrie CC. An evaluation of gamma hydroxybutyric acid in paediatric practice. *British Journal of Anaesthesia* 1971; **43:** 620–7.
4 Centers for Disease Control. Multistate outbreak of poisonings associated with the illicit use of gamma hydroxybutyrate. *Journal of the American Medical Association* 1991; **265:** 447–8.
5 Steel IM, Ryan JM. γ-Hydroxybutyrate is a new recreational drug that may lead to loss of consciousness. *British Medical Journal* 1996; **313:** 424.
6 Centers for Disease Control. Gamma hydroxybutyrate use in New York and Texas, 1995–1996. *Journal of the American Medical Association* 1997; **277:** 1511.
7 Thomas G, Bonner S, Gascoigne A. Coma induced by abuse of γ-hydroxybutyrate (GBH or Liquid ecstasy): a case report. *British Medical Journal* 1997; **314:** 35–6.
8 Ferrara SD, Tedeschi L, Frison G, Rossi A. Fatality due to Gamma Hydroxy butyric acid (GHB) and Heroin intoxication. *Journal of Forensic Sciences* 1995; **40:** 501–4.
9 Vayer P, Mandel P, Maitre M. Gamma Hydroxybutyrate, a possible neurotransmitter. *Life Sciences* 1987; **41:** 1547–57.
10 Mamelak M. Gamma hydroxybutyrate; an endogenous regulator of energy metabolism. *Neuroscience and Biobehavioral Reviews* 1989; **13:** 187–98.
11 Roth RH, Giarman NJ. Conversion of in vivo gamma aminobutyric acid to gamma butyric acid in the rat. *Biochemical Pharmacology* 1969; **18:** 247–50.
12 Mamelak M, Scharf MB, Woods M. Treatment of narcolepsy with Gamma Hydroxybutyrate; a review of clinical and sleep laboratory findings. *Sleep* 1986; **9:** 285–9.
13 Takahara J, Younuki S, Yakushiji W. Stimulatory effects of gamma hydroxybutyric acid on growth hormone and prolactin release in humans. *Journal of Clinical Endocrinology and Metabolism* 1977; **44:** 1014–6.
14 Gallimberti L, Canton G, Gentile N, *et al*. Gamma hydroxybutyrric acid for the treatment of alcohol withdrawal syndrome. *Lancet* 1989; **2:** 787–9.
15 Gallimberti L, Cibin M, Pagnin P, *et al*. Gamma hydroxybutyric acid for the treatment of opiate withdrawal syndrome. *Neuropsychopharmacology* 1993; **9:** 77–81.

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16 Snead OC, Liu C. Gamma hydroxybutyric acid binding sites in rat and human brain synaptosomal membranes. *Biochemical Pharmacology* 1984; **33:** 2587–90.
17 Roth R, Doherty J, Walters J. Gammahydroxybutyrate: a role in the regulation ofcentral dopamine neurons? *Brain Research* 1980; **189:** 556–60.
18 Snead OC. Gamma Hydroxybutyric acid: a mini review. *Life Sciences* 1977; **20:** 1935–44.
19 Xie XM, Smart TG. γ-Hydroxybutyric acid depresses monosynaptic excitatory and inhibitiory post-synaptic potentials in rat hippocampal slices. *European Journal of Pharmacology* 1992; **212:** 193–6.
20 Xie XM, Smart TG. Gamma hydroxybutyric acid hyperpolarizes hippocampal neurons by activating $GABA_B$ receptors. *European Journal of Pharmacology* 1992; **212:** 291–4.
21 Serra M, Sanna E, Foddi C, Congas A, Biggio G. Failure of Gamma hydroxybutyrate to alter the function of GABAA receptor complex in rat cerebral cortex. *Psychopharmacology* 1991; **104:** 351–5.
22 Vayer P, Maitre M. γ-Hydroxybutyrate stimulation of the formation of cyclic GMP and Inositol phosphates in rat hippocampal slices. *Journal of Neurochemistry* 1989; **52:** 1382–7.
23 Snead OC. Basic mechanisms of generalised absence seizures. *Annals of Neurology* 1995; **37:** 146–57.
24 Bernasconi R, Lsuber J, Marescaux C, *et al*. Experimental absence seizures: potential role of γ-hydroxybutyric acid and $GABA_B$ receptors. *Journal of Neural Transmission* 1992; **35** (Suppl.): 155–77.
25 Chin M-Y, Kreutzer RA, Dyer JE. Acute poisonings from γ-Hydroxybutyrate in California. *Western Journal of Medicine* 1995; **92:** 380–4.
26 Steele MT, Watson WA. Acute poisoning from Gamma Hydroxybutyrate (GHB). *Missouri Medicine* 1995; **92:** 354–7.
27 Galloway GP, Frederick SL, Staggers FE, Gonzales M, Stalcup SA, Smith DE. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction* 1997; **92:** 89–96.
28 Dyer JE. Gammahydroxybutyrate – a health food product producing coma and seizures. *American Journal of Emergency Medicine* 1991; **9:** 321–4.
29 Cash CD. Gammahydroxybutyrate: an overview of the pros and cons for it being a neurotransmitter and/or a useful therapeutic agent. *Neuroscience and Biobehavioral Reviews* 1994; **18:** 291–304.

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