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The γ-Hydroxybutyrate Withdrawal Syndrome

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Contents

Abstract

γ-Hydroxybutyrate (GHB) is endogenous inhibitory transmitter that, when administered in pharmacological doses, has sedative-hypnotic properties. It is used in anaesthesia for the treatment of narcolepsy/catalepsy and in alcohol/opioid detoxification treatment regimens. Based on its purported anabolic effects, GHB use became established among bodybuilders. As the euphorigenic effects of GHB became publicised, attendees at dance clubs and rave parties began to use it alone or in combination with other psychoactive drugs. Following the ban of GHB in 1990, several precursor products (e.g. γ-butyrolactone, butanediol) became widely used as replacement drugs until their ultimate proscription from lawful use in 2000. GHB and its precursors, like most sedative-hypnotic agents, can induce tolerance and produce dependence. Although many GHB users will experience a mild withdrawal syndrome upon drug discontinuation, those with chronic heavy GHB use can experience severe withdrawal. This syndrome clinically resembles the withdrawal syndrome noted from alcohol and other sedative-hypnotic drugs (e.g. benzodiazepines). Distinct clinical features of GHB withdrawal are its relatively mild and brief autonomic instability with prolonged psychotic symptoms. Patients with fulminant GHB withdrawal require aggressive treatment with cross-tolerant sedative hypnotics, such as benzodiazepines.

γ-Hydroxybutyrate (GHB) was synthesised in 1960. Although the initial use of GHB started within the bodybuilding community, its greatest public health threat has come from its use as an illicit drug. After the US FDA banned nonprescription GHB in 1990,[1] users turned to its prodrugs: γ-butyrolactone (GBL) and 1,4-butanediol (1,2-BD), which are widely available as industrial solvents. Although classified as a schedule I drug by the Drug Enforcement Administration in 2000,[1] GHB and its precursors remain popular drugs in dancing clubs and during 'rave parties' due to their euphorigenic properties. Unfortunately, GHB and its precursors also became notorious for use as 'rape drugs' because of their potent amnestic properties and simple administration (e.g. clear, colourless, relatively tasteless fluid). It is this latter use that prompted the scheduling of the GHB precursors in 2000 with the

passage of the Hillory J. Farias and Samantha Reid Date Rape Drug Prohibition Act.[2] Despite this regulatory effort, the use of GHB and its analogues (GBL, 1,2-BD) are continuing to increase.[3] It is widely assumed, as it is in this paper, that the effects of the precursor agents are identical to GHB.

Shortly after the appearance of GHB, it became apparent that chronic, heavy GHB use was capable of producing tolerance, dependence and withdrawal. This phenomenon was initially limited to bodybuilders who were using GHB and its analogues as dietary supplements because of purported 'fat-burning' and 'growth hormone-releasing' effects.[4] Studies in volunteers suggested that GHB use may in fact be associated with alterations of slow-wave sleep in normal subjects and can simultaneously enhance sleep-related growth hormone secretion.[5] Regardless of its effects on the sleep cycle, it was (and remains) common practice to administer GHB several times daily in the belief that GHB has anabolic effects.

Currently, GHB is used as an anaesthetic agent (in Europe), for the treatment of alcohol withdrawal,[6,7] and in the US and Europe for the treatment of narcolepsy (sold as sodium oxybate, or Xyrem®).[1][8] Interestingly, some patients are self-medicating with GHB to reduce alcohol intake.[9]

1. Pharmacokinetics

Exogenous GHB is very rapidly absorbed after oral administration, with peak plasma concentration between 20 and 60 minutes. Its very short half-life of 20 minutes[10] explains the need for frequent (e.g. every 3–4 hours) repetitive dosing in chronic abusers. Due to the short half-life, signs of GHB withdrawal usually occur between 1 and 6 hours after the last dose.[11] GBL is closely related to GHB and produces similar clinical effects. It is more bioavailable and lipophilic than GHB. After rapid absorption, GBL is hydrolysed to GHB by a circulating lactonase.[12] Similarly, butanediol must be oxidised to GHB by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase.[13] Although alcohol abuse does not alter the pharmacokinetics of GHB,[14] it may alter the metabolism of GHB precursors. For example, butanediol's metabolism by ADH may be inhibited by ethanol, for which ADH has a greater affinity.

2. Neuropharmacology of γ-Hydroxybutyrate (GHB) Withdrawal

GHB is a naturally occurring short-chain fatty acid that may act as a neurotransmitter in the mammalian brain.[15] It is generated through the metabolism of one of the major inhibitory neurotransmitters, γ-aminobutyric acid (GABA). This reaction occurs through the intermediate metabolite, GABA-derived succinic semialdehyde, which is converted to GHB. GHB can also be converted back to GABA via GHB dehydrogenase.[16] However, unlike other sedative hypnotics (e.g. benzodiazepines, barbiturates, ethanol), GHB does not affect $GABA_A$ receptors.[17] GHB in supraphysiological concentration may bind and agonise $GABA_B$ receptors.[18] Through $GABA_B$ receptors GHB inhibits dopamine release and probably causes up-regulation of dopamine receptors.[19] Based on several lines of evidence, including the existence of specific high-affinity binding sites for GHB in rat brain,[20] as well as the existence of specific enzyme and high-affinity uptake system for GHB,[21,22] the existence of the specific GHB receptors are postulated. However, it is important to note that the clinical effects of GHB are clinically indistinguishable from the effects of other sedative-hypnotics that act through $GABA_A$ receptors. The same holds true for the symptoms of GHB and sedative-hypnotic withdrawal. GHB withdrawal is probably mediated largely through the loss of GHB- and GABA-mediated inhibition.[11]

An animal model of GHB tolerance and withdrawal has been developed, which demonstrated that these effects can develop very rapidly (i.e. several days).[23] It was proposed that tolerance to GHB is result of two mechanisms: induction of GHB metabolism and decrease in CNS sensitivity to GHB.[24]

3. Withdrawal Following GHB Overuse

Because of the different regimens by which the drug is administered, withdrawal is more common among bodybuilders who use the drug in a several-times-daily dosing schedule for weeks than among club users who generally use GHB on weekends only. However, there are reports of clinically significant withdrawal syndromes in patients who used GHB and its analogues as sleep aids.[25] The estimated daily dose of GHB, used by the patients who experienced severe withdrawal, ranged between 43 and 144 g/day.[11]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

4. Withdrawal Following Therapeutic Use of Sodium Oxybate

The abrupt cessation of sodium oxybate, the pharmaceutical form of GHB, in the treatment of narcolepsy did not produce an identifiable withdrawal syndrome.[8] Narcolepsy patients who were receiving sodium oxybate in the range of 3–9g nightly for up to 44 months experienced minimal symptoms upon discontinuation of therapy.[8] This information supports that GHB withdrawal is unlikely in once-daily users, but can be expected in the subpopulation that is using GHB more frequently (e.g. every 3–4 hours).

The anxiolytic and myorelaxant dose of GHB is approximately 10 mg/kg, while a dose between 20–30 mg/kg is hypnotic. Coma is usually induced at dosages of 50 mg/kg.[26] More than 50% of recreational GHB users reported using GHB not more than once a week, with an average of 1–3 capfuls at 2–3 times per day/night.[27] The 'capful' concentration of a street dose may vary from 500mg to 5g per dose.[27]

5. Signs and Symptoms of GHB Withdrawal

Clinically, withdrawal from GHB and its precursors is nearly identical to the alcohol or sedative-hypnotic withdrawal syndrome with which clinicians are more familiar. One of the early signs reported in patients with GHB withdrawal is disabling insomnia with the patient commonly complaining that he/she "had not slept in a week".[28] Some patients experience severe anxiety or a sense of impending doom, which may last for a week.[29] As with alcohol withdrawal, tremulousness is common and seizures may occur. With increasingly severe withdrawal, delirium with auditory and visual hallucinations, disorientation and severe agitation may occur. A distinct feature of GHB withdrawal, which differentiates it from alcohol withdrawal, is the relative paucity of significant autonomic instability (e.g. diaphoresis, tachycardia, hypertension). Unlike the alcohol withdrawal syndrome, seizures are uncommon in patients with GHB withdrawal.

The time course of the GHB withdrawal syndrome also varies considerably from that of alcohol withdrawal. While the alcohol withdrawal syndrome does not typically become significant for 12–24 hours after the last intake of ethanol, GHB withdrawal, as noted, often manifests 1–6 hours after last use. Despite its abrupt onset, the delirium of GHB withdrawal may last up to 2 weeks, whereas the alcohol withdrawal syndrome is generally complete by 7 days. The prolonged delirium and psychosis associated with GHB withdrawal may relate to $GABA_B$ associated up-regulation of dopamine receptors.

As noted, the majority of patients with GHB withdrawal are fitness enthusiasts. However, even recreational GHB users may experience very mild and nonspecific symptoms including anxiety and tremors that serves to reinforce their addictive behaviour.[29] The diagnosis of GHB withdrawal should therefore be suspected in any patient who is known to be a user of GHB or one of its precursors. Similarly, this diagnosis should be considered in patients who by history or physical examination are serious weight trainers who present with delirium or agitation. If history of sedative-hypnotic abuse is lacking, it is possible that these patients are misdiagnosed and transferred to a psychiatric unit.

6. γ-Butyrolactone Withdrawal

Multiple case reports describe a similar syndrome as with GHB withdrawal, including: mild tachycardia and hypertension, paranoid delusions, hallucinations and rapid fluctuations in sensorium.[30-32] As with GHB, the majority of the cases involved bodybuilders who were using GBL for several months on a daily, around-the-clock regimen. Severe GBL withdrawal requires intensive care unit admission and aggressive treatment with sedative hypnotics.[11]

7. Laboratory Testing

GHB levels, although able to be obtained from reference laboratories, are not helpful for establishing the diagnosis of GHB or precursor withdrawal. This is reminiscent of alcohol withdrawal, where even having the blood alcohol concentration readily available is not helpful in the diagnosis due to the large degree of tolerance some users experience. The patient's urine generally remains positive for GHB for 12 hours after the last use.[33] As GHB testing is not available in a clinically relevant manner, its use should be reserved for forensic purposes.

Every patient with severe signs of GHB withdrawal should have electrolytes, creatine phosphokinase and urine examined to rule out rhabdomyolysis and consequent renal failure and dysrhythmia in patients with severe agitation. Obtaining a urine toxicology screen for drugs of abuse may be helpful from a long-term psychiatric management perspective, but generally has little impact on the management of the acute episode.

Patients who present with GHB or precursor withdrawal-related delirium, psychosis or agitation, or without a clear history of abuse, should have an appropriate medical work-up to exclude other causes before the diagnosis of withdrawal is established. This often includes obtaining a head computed tomography scan and performing a lumbar puncture to eliminate the possibility of

CNS processes such as encephalitis, meningitis or trauma. Note that given the aforementioned use of GHB to temper the use of alcohol, alcohol withdrawal and GHB withdrawal can coexist, complicating the clinical diagnosis and management.[9]

8. Treatment

The majority of patients with mild symptoms of GHB withdrawal can be treated as outpatients with the use of long-acting benzodiazepines. Those with more severe signs and symptoms require aggressive inpatient care to prevent injury, hyperthermia and rhabdomyolysis, as well as to control the symptoms of psychosis. GHB users are commonly polysubstance abusers, and they may experience concurrent ethanol or benzodiazepine withdrawal. Also, other comorbidities should be sought and appropriately managed (e.g. hypoglycaemia, seizures, thiamine deficiency).

8.1 Benzodiazepines

Conceptually, the preferred therapy for any substance withdrawal syndrome would be reintroduction of the implicated substance, in this case GHB. Of course this is problematic given the drug's legal status and difficulty obtaining the medicinal preparation. Sodium oxybate is a schedule III agent (oxybate is a unique drug that is dual scheduled) and release of the drug requires that the patient be entered into a registry and the drug must be obtained directly from the supplier.

Therefore, the mainstay of the therapy for GHB withdrawal is sedation with benzodiazepines. Benzodiazepines are $GABA_A$ agonists and, as such, do not function in a truly equivalent pharmacological manner as GHB. However, the clinical effects are comparable and they moderate the withdrawal syndrome allowing time for clinical recovery. The specific benzodiazepine and dosage chosen is relatively unimportant providing an appropriate dosage regimen is followed. As during therapy of the alcohol withdrawal syndrome, symptom-triggered therapy is preferred[34] rather than dosing on a strict schedule. The drug should be administered initially in rapidly escalating doses until control of agitation or delirium is achieved while observing closely for the signs of respiratory depression. Some patients will not respond to the treatment with standard doses of benzodiazepines and will require unusually high doses; up to 2655mg of diazepam over 90 hours is reported.[35] This is readily explained by the fact that cross-tolerance is not complete; that is, the $GABA_A$ receptor is not solely responsible for the clinical effects of GHB nor for its withdrawal syndrome. One possibility, as in ethanol withdrawal, may be that tonic inhibition by GHB of the glutamatergic excitatory neurotransmitter system results in its up-regulation.[36] Upon withdrawal of the inhibitory agent (i.e. GHB) hyperexcitability results, and since this is mediated by the NMDA-glutamate receptor complex it is insensitive to benzodiazepines. Correspondingly, although GHB may moderate the alcohol withdrawal syndrome,[6,7] ethanol may not be sufficiently cross-tolerant to treat GHB withdrawal.[25]

8.2 Phenothiazines

Patients who lack the history of the GHB addiction and abuse and who present with hallucination and/or frank psychosis may be admitted directly to psychiatry and treated with antipsychotic medication. The use of these agents in the treatment of GHB withdrawal is generally considered inappropriate due to their presumed lack of efficacy and significant adverse effects, e.g. anticholinergic effects, dystonic reactions and prolongation of the corrected QT interval with the risk of cardiac dysrhythmias and the possibility of lowering the patient's seizure threshold.[37] It is very important to elicit the history of GHB abuse in any patients that presents with psychotic features, especially if the patient is lacking previous history of psychiatric disorder.

8.3 Pentobarbital/Propofol

It is prudent that in patients with 'benzodiazepine-resistant' GHB withdrawal the clinician consider the addition of other pharmacotherapy with barbiturates and propofol. Because of its capability to directly open both $GABA_A$ and voltage-gated chloride channels, these drugs should be successful at sedating even the most benzodiazepine-resistant GHB/GBL withdrawal patient.[30] It is important to observe patients for signs and symptoms of respiratory depression and intervene earlier to protect the airway and to maintain adequate ventilation/oxygenation.

9. Conclusion

GHB withdrawal remains a relatively rare phenomenon. Although therapeutic use of prescription GHB (sodium oxybate) is not associated with withdrawal upon cessation, mild, clinically insignificant symptoms of withdrawal may occur in recreational users. Most cases of severe withdrawal occur in bodybuilders and others who use exceedingly high doses, several times daily, for prolonged periods of time. Aggressive therapy with cross-tolerant sedative agents such as benzodiazepines or propofol must be utilised to control the patient's behaviour and to avoid complications (e.g. rhabdomyolysis, hyperthermia, death).

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