SEVERE GAMMA-HYDROXYBUTYRATE WITHDRAWAL: A CASE REPORT AND LITERATURE REVIEW

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Abstract—We report a case of gamma-hydroxybutyrate (GHB) withdrawal resulting in severe agitation, mental status changes, elevated blood pressure, and tachycardia hours after stopping chronic use of GHB. The patient admitted to substantial GHB abuse on a daily basis for 2.5 years. Previous attempts at cessation reportedly resulted in diaphoresis, tremors, and agitation. The patient’s symptoms, negative polypharmacy history, and negative urine and blood toxicological analysis for alcohol, benzodiazepines, sedative-hypnotics, or other substances suggested the diagnosis of GHB withdrawal. Later analysis of a patient drug sample confirmed the presence of GHB. The patient required 507 mg of lorazepam and 120 mg of diazepam over 90 h to control agitation. This is one of the few reported cases of GHB withdrawal and one of the most severe. Given the increasing use of GHB, more cases of severe GHB withdrawal should be anticipated. © 2000 Elsevier Science Inc.

Keywords—gamma-hydroxybutyrate; withdrawal; autonomic dysfunction; tremors; hallucinations

INTRODUCTION

Gamma-hydroxybutyrate (GHB) has been abused for its sedative and euphoric effects as well as by bodybuilders for its claimed anabolic effects. Despite GHB’s abuse potential, it also has been used recently in limited controlled clinical trials for the treatment of alcoholism and opiate withdrawal syndrome (1–5).

The clinical presentation of GHB withdrawal ranges from mild clinical anxiety, agitation, tremors, and insomnia to profound disorientation, increasing paranoia with auditory and visual hallucinations, tachycardia, elevated blood pressure, and extraocular motor impairment (6–9). Reported symptoms have generally resolved without sequelae after varying withdrawal periods.

In this report, we describe a patient who presented with severe GHB withdrawal mimicking alcohol delirium tremens with autonomic dysfunction, and severe agitation requiring large doses of benzodiazepines after abruptly stopping use of GHB.

CASE REPORT

The patient, a 33-year-old computer programmer, was transferred from our Alcohol and Drug Rehabilitation Center to the Roosevelt Hospital Emergency Department (ED) with tachycardia, hypertension, and auditory and visual hallucinations.

The patient had initially requested treatment for his 2.5-year GHB addiction. During his screening interview, he was lucid but slightly anxious. Over a 2-h observation period at the rehabilitation center, the blood pressure and heart rate (HR) were noted to increase. He was given 50 mg of chlordiazepoxide subcutaneously and 2 mg of lorazepam intramuscularly (i.m.) with “slight calming effect.” Eight hours later, the patient was found to be...
disoriented and displayed symptoms of paranoia with auditory and visual hallucinations. The blood pressure was 190/60 mmHg and heart rate was 120 beats/min before transfer. The patient was extremely disoriented on arrival in the ED, and stated that he had taken GHB earlier that day. He denied any history of alcohol or other drug abuse.

Triage vital signs were: temperature 37.4°C (99.4°F) rectally, heart rate 112 beats/min, respirations 22 breaths/min, and blood pressure (BP) 120/90 mmHg. On examination, the patient was hypertensive and disoriented with both auditory and visual hallucinations. During episodes of agitation, he was diaphoretic. The oral mucosa was noted to be moist. Nuchal rigidity was not present. On neurologic examination, the patient was oriented to self only. Short- and long-term memory were poor. Pupils were 4 millimeters and equally reactive though horizontal nystagmus was present. Resting and intention hand tremors were noted. Asterixis, cerebellar signs, and gait abnormalities were notably absent.

An electrocardiogram (EKG) revealed sinus tachycardia with a QRS duration of 76 ms and QTc of 423 ms. A chest x-ray study was normal. Electrolytes were sodium, 134 mEq/L; potassium, 3.9 mEq/L; chloride, 104 mEq/L; bicarbonate, 23 mEq/L; anion gap, 7 mEq/L; blood urea nitrogen, 13 mg/dL; creatinine, 1.1 mg/dL; glucose, 134 mg/dL; calcium, 10.4 mg/dL; magnesium, 1.9 mg/dL; phosphorous, 4.0 mg/dL. Liver function and coagulation profiles were noted to be normal. Arterial blood gases on room air drawn 1.5 h after arrival showed pH, 7.46; PCO₂, 35 mmHg; PO₂, 103 mmHg; HCO₃⁻, 24 mEq/L, and 98% oxygen saturation. Urinalysis was normal. Toxicology screen of blood for alcohol, salicylate, and acetaminophen was negative.

Intravenous fluid was initiated with one-half normal saline with 5% dextrose. Dextrose 50 g, thiamine 100 mg, and naloxone 0.4 mg were given i.v. without change in mental status. Fifty grams of activated charcoal with sorbitol was given orally. For the patient’s worsening agitation, lorazepam 2 mg was given i.v. without significant effect. Maximum heart rate and BP during episodes of agitation were noted to be 149 beats/min and 160/119 mmHg, respectively. Additional lorazepam was given to a total of 6 mg before beginning diazepam. Diazepam 20 mg by i.v. bolus was given approximately every 40 min over the ensuing 5.5 h to a total of 120 mg. High-dose benzodiazepines had a slight calming effect with reduction of BP and HR. The patient was transferred to the intensive care unit where a lorazepam infusion was begun. Toxicology screen of the urine returned negative for amphetamines, barbiturates, cocaine, methadone, and opiates.

Family members had been called, and both wife and mother-in-law reported that the patient had been abusing GHB for the past 2.5 years. On several occasions, he had reportedly tried to stop but each time developed severe hand tremors, diaphoresis, and anxiety, and he subsequently reverted to his typical pattern of GHB abuse. Both relatives denied a patient history of abusing alcohol or other illicit substances.

For the next 51 h in the ICU, the patient was maintained on a lorazepam drip at 8 mg/h (for a total of 408 mg) but remained confused with occasional episodes of agitation. After the lorazepam infusion was tapered and discontinued, lorazepam 12 mg i.v. soluset every 4 h was continued. The total dose of lorazepam received over a 90-h ED-ICU stay was 507 mg (497 mg i.v. and 10 mg oral). In addition, 5 mg of haloperidol had been given i.m. Thiamine was administered daily. Approximately 21 h after the initial presentation in the ED, HR and BP normalized. On day 4 of hospitalization, the patient’s mental status was clearing, and he was transferred to a regular floor. Lorazepam was continued orally every 6 h and then tapered. The patient was alert and oriented in all spheres by day 8.

Further history obtained from the patient as he became more lucid revealed that he had been taking 5 to 6 oz of GHB per day in divided doses for 2.5 years. He initially started taking 1/2 oz with the effect lasting from 1 to 2 h, and proceeded to increase dosing because of tremulousness, anxiety, and diaphoresis experienced several hours after each dose. The milligram dose of GHB the patient was taking was unclear; he ordered the powder over the Internet and mixed it with water at home.

On day 10, the patient was discharged with plans for further outpatient treatment at the drug rehabilitation center. A sample of the GHB solution provided by the wife during her husband’s ICU course was later analyzed by the Mayo Medical Laboratory (Rochester, Minnesota) and found to contain 230 g/L of GHB.

**DISCUSSION**

Gamma-hydroxybutyrate (sodium oxybate) has a structure similar to that of gamma-aminobutyric acid (GABA) and glutamic acid and is found naturally in the mammalian brain (10). It exhibits properties of a neurotransmitter or neuromodulator (11). Unlike GABA and glutamic acid, GHB can cross the blood-brain barrier and induce sedation and anesthesia. Originally investigated in the 1960s as a surgical anesthetic, it was found to have little analgesic effect and was frequently associated with seizures and tonic-clonic jerking movements of the limbs and face with the onset of coma (12). In the 1970s, GHB was used to treat sleep disorders, and presently remains under investigation for the treatment of narcolepsy because of its ability to alter sleep cycles (13). Throughout
the 1980s, GHB gained increasing popularity among body builders as a "growth hormone stimulator," and was marketed as a health food product capable of “building muscle mass and burning fat while you sleep” (14). However, after multiple reports of acute intoxication, over-the-counter sales were banned by the federal Food and Drug Administration (FDA) in 1990 (15).

Despite the FDA’s prohibition of over-the-counter sales, GHB—also known under such street names as “Grievous Bodily Harm,” “Liquid Ecstasy,” “Liquid X,” “Scoop,” and “Salty Water”—still may be purchased in liquid or solid form (for reconstitution with water) through the Internet or by illicit means. Currently, GHB is abused in the U.S. and abroad for its sedative, euphoric, aphrodisiac, and purported “muscle building” properties as well as by dieters for its claimed “fat burning” metabolic effects. Symptoms of severe GHB overdose have been well documented and include bradycardia, clonic muscle movements, seizures, coma, and respiratory arrest (16–18). Other adverse reactions associated with GHB ingestion include euphoria, drowsiness, confusion, dizziness, temporary amnesia, dyspnea, uncontrollable shaking, increased libido, headache, nausea, vomiting, incontinence, mild hypothermia, and mild acute respiratory acidosis (17–19).

GHB withdrawal, yet to be fully elucidated, has been reported in association with prolonged GHB use. Although typically characterized by anxiety, insomnia, and tremors, it also may be associated with extraocular motor impairment, profound disorientation, increasing paranoia with auditory and visual hallucinations, tachycardia, and elevated blood pressure (6–9). The presentation of GHB withdrawal mimics sedative-hypnotic withdrawal syndrome; however, there have been no reported instances of seizures or elevated temperature. In 1994, Galloway et al. described the first case of GHB dependence and withdrawal symptoms in a patient who had been abusing 25 g of GHB on a daily basis (in 5 divided doses) for 2 years (6). Table 1 presents a synopsis of GHB withdrawal cases (6–9,20).

Of the cases listed, Friedman et al. report a more complex case of GHB withdrawal in a patient who had been abusing GHB for 18 months after giving up alcohol (9). She made 12 independent attempts at detoxification, but tremors, restlessness, and insomnia associated with paranoia developed. Large quantities of alcohol were again consumed for relief of insomnia while she concurrently maintained her typical GHB dosing pattern of 2 teaspoons every 2 h. The patient was observed to be paranoid, tremulous, with auditory and visual hallucinations, and “crossed eyes.” Thiamine was administered daily. Lorazepam therapy was instituted but seemed to worsen her psychomotor agitation, and alternatively, chlorpromazine therapy was started. Physical examination by a neurologist 2 days later revealed “eyes less crossed,” sleepiness, dysarthria, a severely impaired and patchy memory, a left VI nerve palsy, left beating nystagmus on left gaze, and a gait disorder that appeared to be astasia-abasia although an accurate assessment was precluded by her mental status. Brain magnetic resonance imaging, cerebral spinal fluid analysis, and blood studies were all normal. Within the succeeding 4 days, the eyes returned to normal, and by day 5, orientation was normal. Her symptoms were attributed to Wernicke-Korsakoff syndrome (WKS) and GHB withdrawal.

More recently, Dyer and Andrews describe a case of a young college woman taking 3 to 5 “capsful” of liquid GHB on a daily basis for 1 year for body-building purposes (8). With withdrawal of the drug at a detoxification center, the patient developed increasing symptoms of paranoia with visual and auditory hallucinations and an elevated heart rate (112 beats/min) and blood pressure (138/98 mmHg) with a normal temperature. A history of co-ingestants was not documented, and urine toxicology returned negative. The 9-day withdrawal period was characterized by paranoia, agitation, and delirium (8). The patient was treated with propranolol, benzodiazepines, and phenothiazines. The GHB solution she had been using was analyzed and found to contain 721 mg/mL of GHB.

Our case describes acute and severe withdrawal associated with abrupt cessation of GHB use. Several parallels are found between our case and prior reports: a history of prolonged GHB abuse; a gradual progression of increased GHB dosing; drug cessation leading to anxiety and tremor; and a history of several unsuccessful GHB cessation attempts.

There are several unique aspects to this case of GHB withdrawal. Unlike most GHB withdrawal cases previously reported, no other drugs were reportedly being used by our patient. He denied using alcohol, sedative-hypnotics, or other recreational drugs. This was confirmed by the patient both at the rehabilitation center and after recovery from the withdrawal state, by multiple family members, and by urine toxicology.

In addition, this case of GHB withdrawal is unique because of the severity of the withdrawal symptoms and the need for large doses of benzodiazepines. Three other cases have been reported using a sedative-hypnotic to treat GHB withdrawal. Galloway used phenobarbital on an outpatient basis to treat a very mild case of GHB withdrawal; Dyer and Hernandez, in cases similar to ours, used benzodiazepines, but the dosing was not documented; and finally, in Friedman’s case report, lorazepam therapy was switched to chlorpromazine for psychomotor agitation, which seemed to worsen while on lorazepam (7–9,20). By comparison, our patient was in
<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Age/Sex</th>
<th>Initial GHB</th>
<th>GHB Dose at Presentation</th>
<th>Length of Time</th>
<th>Coingestions at Presentation</th>
<th>Prior Drug Abuse History</th>
<th>Signs &amp; Symptoms</th>
<th>Treatment</th>
<th>Withdrawal Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Galloway (6,7)</td>
<td>30/F</td>
<td>INA*</td>
<td>25 g/day</td>
<td>2 years</td>
<td>ETOH</td>
<td>ETOH, MDMA, heroin, marijuana, methamphetamine</td>
<td>Tremors, anxiety, insomnia</td>
<td>None</td>
<td>12 days</td>
</tr>
<tr>
<td>2</td>
<td>Galloway (7)</td>
<td>39/M</td>
<td>INA</td>
<td>One bottle/day</td>
<td>INA</td>
<td>ETOH</td>
<td>ETOH</td>
<td>Muscle cramps, anxiety, insomnia</td>
<td>INA</td>
<td>INA</td>
</tr>
<tr>
<td>3</td>
<td>Galloway (7)</td>
<td>40/M</td>
<td>2.5 g q HS</td>
<td>20 g/day</td>
<td>2 years</td>
<td>Methamphetamine, phenobarbital, LSD, ETOH</td>
<td>Diazepam</td>
<td>Insomnia</td>
<td>None</td>
<td>INA</td>
</tr>
<tr>
<td>4</td>
<td>Galloway (7)</td>
<td>31/F</td>
<td>2.5 g twice per day</td>
<td>3 capsful TID</td>
<td>1.5 years</td>
<td>Marijuana</td>
<td>Anabolic steroids, cocaine, marijuana</td>
<td>Insomnia, mydriasis, mild HTN</td>
<td>Phenobarbital</td>
<td>INA</td>
</tr>
<tr>
<td>5</td>
<td>Friedman (9)</td>
<td>24/F</td>
<td>2 tsp. per day</td>
<td>2 tsp. q 2 hr.</td>
<td>1.6 years</td>
<td>ETOH</td>
<td>Diazepam</td>
<td>Tremors, insomnia, restlessness, paranoia, hallucinations, impaired memory, L. nystagmus, L. CN VII deficit, gait abnormality</td>
<td>Thiamine</td>
<td>5 days</td>
</tr>
<tr>
<td>6</td>
<td>Dyer (8)</td>
<td>23/F</td>
<td>3–5 capsful per day</td>
<td>1.5 capsful q 3 hr.</td>
<td>1 year</td>
<td>None</td>
<td>Benzodiazepines</td>
<td>Anxiety, tremors, agitation, delirium, mild HTN, tachycardia</td>
<td>Propranolol, benzodiazepines, phenothiazines</td>
<td>9 days</td>
</tr>
<tr>
<td>7</td>
<td>Hernandez (20)</td>
<td>35/F</td>
<td>INA</td>
<td>2 tsp. q 2 hr.</td>
<td>1 year</td>
<td>Marijuana</td>
<td>Phenytoin, alprazolam, lorazepam, amitriptyline</td>
<td>Insomnia, hostility, impaired memory, hallucinations, delirium</td>
<td>Benzodiazepines, phenothiazines</td>
<td>9 days</td>
</tr>
<tr>
<td>8</td>
<td>Present Case</td>
<td>30/M</td>
<td>0.5 oz/day</td>
<td>5–6 oz/day</td>
<td>2.5 years</td>
<td>None</td>
<td>Benzodiazepines, Thiamine</td>
<td>Anxiety, tremors, diaphoresis, hallucinations, paranoia, nystagmus, impaired memory, HTN, tachycardia</td>
<td>Benzodiazepines, Thiamine</td>
<td>8 days</td>
</tr>
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</table>

Key: INA = Information not available or not documented.
* Concentration = concentration of an isolated patient drug sample
Severe withdrawal, requiring 507 mg of lorazepam and 120 mg of diazepam over 90 h to control agitation. If equivalent dosing of diazepam was used (1 mg lorazepam = 5 mg diazepam) (21), we would have used an estimated 2,655 mg of diazepam. This is a large dose of benzodiazepines, even when compared with those used for alcohol withdrawal.

Thiamine deficiency leading to WKS has been suggested as an etiology for some of the findings in GHB withdrawal. To what extent thiamine deficiency contributed to our patient’s condition, as Friedman hypothesizes in his report, is unclear (9). Antecedent history obtained later was negative for loss of weight or appetite. Our patient did have some of the findings of Wernicke’s encephalopathy including oculomotor dysfunction (horizontal nystagmus) and global confusion; however, he lacked an ataxic gait or gait abnormality. A computed tomography (CT) scan did not demonstrate abnormality in the mamillary bodies. The global confusion in our case can be attributed to severe sedative-hypnotic withdrawal; however, all of the patient’s symptoms did resolve after being given large doses of benzodiazepines plus daily doses of thiamine.

Many pharmacologic similarities are reported between GHB and ethanol (22). Ethanol increases endogenous levels of GHB and acts synergistically with GHB to produce central nervous system and respiratory depression (23). Cross-tolerance was demonstrated in a study by Colombo examining the development of tolerance to the motor-imparing effects of GHB and ethanol in rats (24). GHB also has been used to suppress tremors and seizures in rats with alcohol withdrawal, and has been used clinically to suppress withdrawal symptoms in patients presenting in acute alcohol withdrawal (3,5,22). These findings suggest a shared common mechanism of central action of GHB and ethanol. Thus, it is not surprising that an alcohol withdrawal-like syndrome follows after abruptly stopping GHB use, nor that a sedative-hypnotic agent such as a benzodiazepine would be an effective treatment for GHB withdrawal.

The development of a severe withdrawal syndrome from GHB appears to depend on the individual’s ingest- ing high doses over a prolonged duration. GHB abusers presenting in withdrawal and recreational users take a significantly higher dose of GHB than would any subject participating in therapeutic studies. For example, if the 67-kg patient in Galloway’s index case had been participating in Gallimberti’s controlled clinical trials to treat alcohol withdrawal syndromes, she would have consumed a total of 50 mg/kg/day or 3.25 g per day maximum for 3 months. Instead, she had ingested 25 g of GHB per day for approximately 2.5 years (3,5,7).

Correspondingly, if our patient had consistently ingested the same solution as provided for analysis (con-}

<table>
<thead>
<tr>
<th>Effects of GHB</th>
<th>Usual Dosage of GHB Required</th>
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<tbody>
<tr>
<td>Amnesia/hypotonia</td>
<td>10–20 mg/kg</td>
</tr>
<tr>
<td>Normal sequence of REM* &amp; non-REM sleep</td>
<td>20–30 mg/kg</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Decreased cardiac output, increasingly severe respiratory depression, seizure-like activity, coma</td>
<td>&gt; 50 mg/kg</td>
</tr>
</tbody>
</table>

* REM = Rapid eye movement

centration: 230 g/L) at 5 to 6 oz/day, he would have been consuming 34 to 41 g/day (395 to 477 mg/kg/day). For further comparison, Table 2 reports usual dosages to induce amnesia and hypotonia, and anesthesia (15). Given the patients’ histories of progressively increased GHB dosing and the above, the development of tolerance is evident (7–9). Although initial clinical trials using much smaller doses of GHB in treating alcohol and opiate withdrawal appear favorable, at least one author reports that 10.1% of the patients began abusing GHB (6–7 times the recommended dose) for its psychotropic effects with only a mild increase in anxiety levels and insomnia after GHB discontinuation (1–5,25).

Unlike clinical trials in which the quality and amount of GHB ingested is rigorously controlled, the amount and quality of the drug ingested by the recreational user or the patient in withdrawal is difficult to assess. GHB is available as a sodium salt (sodium oxybate) in white powder, tablet, and clear liquid form, and is usually dissolved in water before use. It may be mixed with other drugs or alcohol. Further confounding the issue, GHB abusers report the amount ingested in either “capsful,” ounces, or teaspoons, making accurate conversion and quantitation difficult. One teaspoon of GHB powder is estimated to be between 2.5 g and 2.8 g, and in liquid form, one “capsful” is equal to one teaspoon, but no claim of purity can be made (7,17).

Detection of the GHB is difficult. Its absorption is rapid, within 20–60 min (26). Although the actual pathway is uncertain, most GHB is biotransformed to carbon dioxide through the tricaboxylic acid cycle and expired, with only 2–5% eliminated in the urine (26). Urine analysis for GHB by gas chromatograph via its lactonic form, gamma-butyrolactone (GBL), is possible if the urine specimen is collected within 12 h of the last ingestion (27). Patient samples of GHB have been verified by analysis though infrared spectroscopy on a limited basis (6,7). Recently, a gas chromatograph-mass spectrometric method for determining levels of GHB by way of GBL in urine and plasma has been reported (28). Of course, none
of these methods is readily available. Since no conventional laboratory means exist for its detection, diagnosis depends on clinical presentation.

As demonstrated by this case, in patients presenting with severe symptoms consistent with sedative-hypnotic withdrawal, GHB withdrawal should be included in the clinician’s differential diagnosis. The role of benzodiazepines in the management of GHB withdrawal is unclear but appears to be beneficial because of the similarities to alcohol withdrawal. The incidence of reported cases of GHB withdrawal is expected to increase because of the popularity of the drug.

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