Abstract—We describe a case of withdrawal from the gamma hydroxybutyric acid (GHB) precursors gamma butyrolactone and 1,4-butanediol. Symptoms included visual hallucinations, tachycardia, tremor, nystagmus, and diaphoresis. Administration of benzodiazepines and phenobarbital successfully treated the withdrawal symptoms. As predicted from the metabolism of gamma butyrolactone and 1,4-butanediol to GHB, the symptoms were nearly identical to those reported from GHB withdrawal. Because GHB is now illegal in the United States, individuals have begun abusing the legal and easier to acquire GHB precursors. More frequent cases of both abuse and withdrawal from these GHB precursors can be expected. © 2001 Elsevier Science Inc.

Keywords— gamma-hydroxybutyrate; gamma-butyrolactone; 1,4-butanediol; withdrawal; GHB; GBL

INTRODUCTION

In 1992, the Food and Drug Administration began aggressive enforcement actions against the manufacture and interstate distribution of gamma-hydroxybutyric acid (GHB) after serious adverse effects and increasing cases of abuse became evident (1). On March 13, 2000, GHB was made a schedule I drug by the Drug Enforcement Agency (2). Two chemical precursors of GHB, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), have been marketed as legal alternatives to GHB. Toxicity from ingestion of these precursors has been previously reported, with the manifestations being identical to those seen with GHB (3–5). This is predicted based on the in vivo metabolism of these compounds to GHB. Gamma hydroxybutyric acid withdrawal has been documented in patients who chronically abuse the drug (6–12). Two abstracts document withdrawal from GBL (13,14). We report a case of withdrawal from chronic abuse of GHB precursors.

CASE REPORT

A 36-year-old man presented to the Emergency Department (ED) from jail with altered mental status. The police who accompanied the patient informed us that he might have been suffering from GBL withdrawal. When arrested approximately 10 h before ED presentation, he had warned the arresting officers that without consumption of GBL he would likely soon suffer withdrawal. During custody he had developed worsening agitation, hallucinations, and delirium. On arrival at the ED, he had the following vital signs: blood pressure 132/84 mm Hg, pulse 127 beats/min, respirations 18 breaths/min, and temperature 37.1°C (98.4°F). He was alert, occasionally responding to absent visual stimuli with occasional episodes of staring. Eye examination revealed normal size and reactive pupils with occasional lateral and rotary nystagmus. The mucous membranes were moist, and the neck was supple. Examinations of the heart, lung,
abdomen were normal. The skin was cool and moist. The patient was alert and oriented with thought processes that were extremely tangential. He would occasionally not respond to questions. The rest of the neurologic examination was normal except for a symmetrical tremor in both hands and a few beats of clonus in both lower extremities.

He was initially administered an empiric 2 mg of intravenous (i.v.) lorazepam and 65 mg of i.v. phenobarbital for presumed withdrawal. Within 1 h, the patient became less delirious, less tremulous, and the heart rate declined to 100 beats/min. He was then able to elaborate on his use of GHB precursors. He reported that he first began abusing GHB 8 months prior in an attempt to prevent recurrence of longstanding ethanol abuse. He initially used GHB but then switched to GBL and 1,4-BD as GHB became difficult to acquire. Over the Internet, he was able to obtain the solvent Verve 5.0 (furanone dihydro or GBL). Verve 5.0 contains 5 g of GBL/oz, and he described using 1 oz every 2 h around the clock for the past 6 months. Infrequently, he would ingest an ink jet printer fluid that contained 1,4-BD. He would also occasionally supplement this with illicitly acquired GHB, but stated he had not used any GHB for 1 month. He had attempted to stop the use of these agents multiple times, even self-treating with hydrocodone and diazepam. However, he described fairly rapid onset of tremors and diaphoresis that led him to continue use. His 10-h period in custody was the longest time he had gone without GBL or 1,4-BD for many months. He denied any other drug use or recent use of ethanol.

Initial laboratory values were all normal except for a slightly elevated creatine kinase of 185 IU/L with a normal MB fraction. Urine toxicological screen performed after treatment with lorazepam and phenobarbital was positive only for barbiturates and benzodiazepines. A comprehensive urine drug screen revealed only phenobarbital and benzodiazepines as a class. Specific urine testing confirmed the presence of GHB at a concentration of 870 μg/mL. An electrocardiogram showed sinus tachycardia but was otherwise normal. Sequential creatine kinase measurements revealed a peak at 2704 IU/L approximately 16 h after admission.

The patient was admitted to the hospital and did well for the first 18 h of admission. During this period he received occasional doses of 2 mg lorazepam (total of 8 mg). However, the following morning, and 4 h after his most recent dose of lorazepam, he once again became delirious, tachycardic, diaphoretic, and tremulous. He was given escalating doses of lorazepam, diazepam, and additional i.v. phenobarbital, which successfully treated his symptoms. Intravenous diazepam was then used intermittently to treat recurrence of his withdrawal symptoms. Varying doses of phenobarbital were administered every 12 h, and by the third hospital day the patient was asymptomatic. During his hospital stay, the patient was treated with a total of 38 mg of lorazepam, 110 mg of diazepam, and 455 mg of phenobarbital. He was transferred back to jail with a 2-day prescription of 60 mg of phenobarbital to be taken twice per day. Follow-up 3 days following hospital discharge to jail revealed that he had no signs of recurrent withdrawal.

**DISCUSSION**

We report a patient who suffered significant withdrawal symptoms from GBL and 1,4-BD. He described in detail the dose and frequency of GBL ingestion and repeatedly denied abusing ethanol. The withdrawal symptoms that he suffered, including agitation, hallucinations, tachycardia, nystagmus, tremor, and diaphoresis, are identical to those reported from GHB withdrawal. The symptoms are also identical to those observed in two of the three reported patients suffering from GBL withdrawal (13,14). The similarity between withdrawal from GHB and GHB precursors would be predicted based on the metabolism of GBL and 1,4-BD to GHB. Gamma butyrolactone is converted by serum and liver lactonases to GHB (15). 1,4-Butanediol is converted by alcohol dehydrogenase to GHB (16). This patient’s multiple failed attempts at curtailing GHB precursor use also mirrors the unsuccessful attempts reported by patients suffering from chronic GHB abuse (6).

The withdrawal symptoms reported from GHB, GBL, and those in this patient from GBL and 1,4-BD are very similar to those of ethanol withdrawal. Although the exact mechanism of action of GHB is not completely understood, it seems to share a common pathway with ethanol. This is supported by the cross tolerance of GHB and ethanol, the successful use of GHB in ethanol abstinence programs, and the symptom similarity of both drugs in withdrawal (17,18). A study using GHB in an abstinence program from ethanol detailed that 10% of patients began to abuse GHB (18).

Treatment of GHB and GBL withdrawal has included the use of benzodiazepines, phenobarbital, and haloperidol. Case reports have detailed the very large doses of benzodiazepines required to successfully treat these patients (6,14). Benzodiazepines and phenobarbital both act through enhancement of γ-aminobutyric acid (GABA) activity. GABA is one of the main inhibitory neurotransmitters in the central nervous system (19). GHB in high doses may act through the GABA-B receptor and may also exert its effect by actual conversion to GABA (20). Use of agents that enhance GABA, therefore, may be effective in treating GHB withdrawal.
Treatment with benzodiazepines and phenobarbital were successful in this patient. The combined use of lorazepam and diazepam was empiric. Phenobarbital was initially administered based on the experience of one of the authors using the drug for ethanol withdrawal. Phenobarbital was chosen as outpatient therapy because of its long half-life.

Gamma-butyrolactone is a common household and industrial solvent. Although most of the effects of GBL are likely from the conversion to GHB, GBL has greater bioavailability (21,22). Consequently, an equal dose of GBL has been shown to produce a greater central nervous system effect than GHB (23). Chemical synonyms of GBL include dihydro-2(3H)-furanone, butyrolactone, 4-butyrolactone, and 4-butanolide. Gamma butyrolactone has been sold under various product names including Blue Nitro, Renewtrent, Revivarant, and Verve 5.0. Although the Food and Drug Administration has asked for a voluntary recall, GBL remains legal. Chemical synonyms of 1,4-BD include butanediol, 1,4-tetramethylene glycol, tetramethylene glycol, and 1,4-butyleneglycol. Products containing 1,4-BD include Enliven, Pine Needle Extract, Serenity, and Zen (24). These products are either marketed as solvents or as GHB alternatives.

This is one of the first reported cases of withdrawal from GHB precursors. It is unknown exactly how many people are currently abusing GHB or its precursors GBL and 1,4-BD. This patient warned us that many individuals are currently using these drugs. As highlighted in the presented case, features of withdrawal include rapid onset, and treatment requires large doses of sedatives.

REFERENCES