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CASE REPORT

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A Multi-Drug Intoxication Fatality Involving Xyrem® (GHB)

ABSTRACT: Gamma-hydroxybutyrate (GHB) is best known as a recreational depressant drug, whose use has also been implicated in drug facilitated sexual assault cases. It is also available as a therapeutic agent (Xyrem®) used for the treatment of daytime sleepiness or cataplexy associated with narcolepsy. This is a report of a case of a 53-year-old woman undergoing treatment with Xyrem® for narcolepsy. The decedent was also prescribed tramadol, gabapentin, cetirizine, modafinil, carisoprodol, and Xyrem®. Toxicological analysis of the blood revealed GHB 165.6 mg/L, and 90.7 mg/L in the urine. Blood GHB concentrations in the range 156–260 mg/L have been reported to induce moderately sound sleep. The combined use of central nervous system depressant drugs, together with her problematic sleep apnea, and snoring (both contraindications for GHB use) were determined to have caused this subject's death. The manner of death was determined to be accidental.

KEYWORDS: forensic science, toxicology, postmortem, Gamma-hydroxybutyrate, overdose, sleep apnea, Xyrem

Gamma-hydroxybutyrate (GHB) is a central nervous system (CNS) depressant. Recreationally, GHB has been used as a "rave" drug, and has been implicated as a date-rape drug (1). It has also been marketed illicitly as an alternative to steroids for body building (2) and for weight control (3). The toxic effects of GHB include euphoria, somnolence, nystagmus, ataxia, aggression, and unconsciousness (1). Serious adverse reactions to GHB include hypotension, bradycardia, respiratory depression, seizures, and coma. There are withdrawal symptoms associated with GHB use including tremors, agitation, hallucinations, tachycardia, and hypertension (1). In 2002, the United States Food and Drug Administration (FDA) approved the sodium salt of GHB (sodium oxybate) for the treatment of excessive daytime sleepiness and cataplexy (muscle weakness) associated with narcolepsy (4). Narcolepsy is defined in the current classification as being characterized by "excessive daytime sleepiness that is typically associated with cataplexy (i.e., narcolepsy with cataplexy) and/or with abnormal rapid eye movement sleep phenomena such as sleep paralysis and hypnagogic hallucinations" (5). This prescribed drug is marketed under the trade name Xyrem® by Jazz Pharmaceuticals (Palo Alto, CA), and is a Schedule III controlled substance (6,7). In a 2-week double-blind study, in which some individuals in the study group were given a placebo rather than their typical dose of sodium oxybate, cataplexy attacks increased by a median of 21 in patients receiving the placebo, while there was no increase in patients who continued their previously established sodium oxybate regimen (8). In a 12-month, open-label trial, both cataplexy and daytime sleepiness decreased at all dosage levels of sodium oxybate (9).

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Case Report

The decedent is a 53-year-old woman with a medical history of narcolepsy, sleep apnea, and sarcoidosis. She was prescribed the following medications and doses: Xyrem®: 7.5 mL per dose twice per night (solution – 500 mg/mL, total nightly dose – 7.5 g); tramadol, 650 mg three times per day; gabapentin, 300 mg six times per day; cetirizine, 10 mg once per day; modafinil, 200 mg twice per day; and carisoprodol, 350 mg at bedtime. All of the above medications had been prescribed within 1 month of the date of death and the pill counts were consistent with medication compliance. The subject's husband reports that the subject went to bed at approximately midnight, and noted she was snoring loudly. Approximately 6 h later, the subject was found unresponsive. Emergency personnel responded, but no resuscitation efforts were made as the subject was obviously deceased. The following samples were submitted to the Washington State Toxicology Laboratory (WSTL) for analysis: peripheral blood, urine, vitreous humor, and gastric contents.

Methods

Peripheral blood was analyzed for alcohol using headspace gas chromatography (HSGC). This sample was negative for alcohol. Blood and urine samples were screened for the following ten classes of drugs using Enzyme Multiplied Immunoassay Technique (EMIT®, Siemens Healthcare Diagnostics, Deerfield, IL): cocaine metabolite, opiates, benzodiazepines, barbiturates, cannabinoids, amphetamines, phencyclidine, propoxyphene, methadone, and tricyclic anti-depressants. In addition, the urine was screened for acetaminophen and salicylates. The urine was positive for acetaminophen only, and the blood screened negative.

A liquid–liquid extraction using *n*-butyl chloride was performed on the blood sample to detect basic drugs. One milliliter of sample was extracted at pH 9 (using 1 mL of 1 N borate buffer) into 3 mL *n*-butyl chloride. Samples were then mixed for at least 5 min, centrifuged at 2000 r.p.m for 5 min, then back extracted into 150 μL of 3 N HCl. The extracts were made alkaline by

adding 100 μL each of ammonium hydroxide and saturated ammonium carbonate. The samples were then back extracted into diphenylamine in chloroform (150 μL). Identification was made using gas chromatography/mass spectrometry (GC/MS) and gas chromatography/nitrogen phosphorous detection (GC/NPD). The drugs were quantitated using four-point calibration curves with metycaine as the internal standard. A solid–liquid extraction was performed on the blood to identify the presence of acidic drugs. Using approximately 1 g of XAD resin (Supelco®, Bellefonte, PA) and 5 mL of distilled water and 100 μL of cyclopal as the internal standard, 1 mL of sample was extracted and vortexed for 1 min. Six milliliter of ethyl acetate was added, followed by vortexing for 1 min. The ethyl acetate was transferred to conical tubes and evaporated to dryness under air at 50°C. The residue was reconstituted in 75 μL of acetonitrile and washed with 500 μL of *n*-heptane. The samples were vortexed and centrifuged. The acetonitrile layer was transferred to injection vials for analysis. Chromatographic analysis was performed by GC with flame ionization detection. Spectral match confirmation was made by GC/MS.

The following liquid–liquid extraction was performed for GHB on the blood, urine, vitreous humor, and gastric contents as reported by Couper and Logan (3) without conversion of GHB to gamma-butyrolactone. One milliliter of sample was used in each extraction. The internal standard was diethylene glycol. The extraction was performed with ethyl acetate and derivitization was performed using BSTFA 1% TMCS. The resulting extracts were analyzed using selective ion monitoring gas chromatography–electron impact mass spectrometry. The experimental limit of detection for this method was 0.5 mg/L in a 1-mL blood or urine specimen. The limit of quantitation for a blood sample is 1 mg/L and 5–10 mg/L for a urine sample. The upper limit of linearity is 100 mg/L.

Results and Discussion

The following analytical results were obtained. GHB was detected in the peripheral blood at 165.6 mg/L, in the urine at 90.7 mg/L, in the gastric contents at 142 mg/L (total volume 5 mL), and was positive in the vitreous humor. The peripheral blood was also positive for the following compounds: tramadol (0.46 mg/L), carisoprodol (1.9 mg/L), meprobamate (3.9 mg/L), acetaminophen (6.1 mg/L), and caffeine. The latter drug concentrations were all within normal therapeutic ranges.

According to clinical trials, the average peak plasma concentration of GHB following a total nightly dose of 9 g of Xyrem® (taken in two 4.5 g doses 4 h apart) were 78 mg/L and 142 g/mL, respectively (7,10). The presence of GHB in the urine, gastric contents, and vitreous humor indicate that the GHB detected was not endogenous. Previous studies have shown that light sleep is associated with levels of GHB ranging from 52 to 156 mg/L and moderate sleep is associated with levels ranging from 156 to 260 mg/L (11). The levels of GHB found in the peripheral blood in this case are consistent with light to moderate sleep. During clinical trials, two individuals who were previously diagnosed with sleep apnea discontinued the use of Xyrem® after it increased breathing difficulties associated with the sleep apnea (10).

The WSTL has encountered only one other case where Xyrem® was a known prescribed medication. That involved a male driver who was stopped by police for erratic driving. He admitted to taking Xyrem® for narcolepsy before he last slept. The measured GHB concentration was 100 mg/L, which is consistent with light sleep (11).

Conclusions

The following are contraindications for the use of Xyrem®: combined use of other CNS-depressant drugs and breathing difficulties, such as sleep apnea and snoring. In this case, the individual was simultaneously taking multiple CNS depressants and had been previously diagnosed with sleep apnea.

The manner of death was determined to be accidental by unintentional overdose of prescription medications. The cause of death was acute intoxication due to the combined effects of GHB, tramadol, and carisoprodol. Other significant contributing conditions were sleep apnea and sarcoidosis.

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