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Case Report

Three deaths associated with use of Xyrem®

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Abstract

Fatalities resulting from popular use of gamma hydroxybutyrate (GHB) have previously been reported. We report three deaths associated with use of Xyrem® (sodium oxybate), a pharmaceutical preparation of GHB initially approved for treatment of narcolepsy with cataplexy. One death appears associated with Xyrem® abuse, with extremely high postmortem blood GHB levels documented. Although postmortem blood GHB levels in two other deaths are consistent with therapeutic levels, cause and effect cannot be established. We discuss these cases and factors which may have exerted contributory respiratory depressant effects, singly or in combination, including concurrent use of sedative hypnotics, obstructive sleep apnea, and obesity.

Keywords: Gamma hydroxybutyrate; Xyrem®; Fatalities; Sodium oxybate; GHB; Deaths; Fatal outcome; Overdose

1. Introduction

Gamma hydroxybutyrate (GHB) is a central nervous system (CNS) depressant. Initially developed as an anesthetic, GHB was subsequently formulated as Xyrem® (sodium oxybate) and initially approved in US and Europe for treatment of narcolepsy with cataplexy. Popular use of GHB and its analogs, gamma butyrolactone (GBL) and 1,4 butanediol (BD), has also been documented among recreational drug users seeking euphoric, sedative, stimulant, and sexual effects, and among users of "dietary supplements" containing GHB or analogs, which were marketed for a fantastic array of purported health benefits [1]. Although adverse events (including death) associated with popular abuse of GHB and its analogs have been widely reported, and although the Xyrem® package insert has related warnings, to date there have been few reports in the clinical literature on adverse effects associated with therapeutic use, misuse, and abuse of pharmaceutical GHB sold as Xyrem®. Here we report three deaths associated with Xyrem®.

2. Case reports

2.1. Case 1

A 52-year-old woman with history of narcolepsy with cataplexy went to bed and was found dead in the morning. A half-bottle of Xyrem® oral solution and a partially filled dosing syringe were found at the scene. No autopsy was performed. Blood toxicology detected GHB, phentermine, paroxetine, and zolpidem, all at therapeutic levels. See Table 1 for toxicology and available medical history.

2.2. Case 2

A 44-year-old man with history of hypertension, mood disorder, anxiety disorder, mild obstructive sleep apnea, and gastric bypass was found dead in bed. He had been prescribed Xyrem® (4g nightly, divided in

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Table 1
Deaths associated with ingestion of GHB and its analogs, gamma butyrolactone and 1,4 butanediol.

Case(s)	Formulation/prescr. dose	History	Toxicology (mg/L unless noted)
Case 1, 52-year old female, obese (Ht. 69", Wt. 224 l bs, BMI 33.1), found dead	Xyrem®, 2 nightly doses, likely 3.375 mg each** (per label)	*Medical history:* Narcolepsy with cataplexy, "tummy tuck" *Duration of use:* 6 months. *Side effects of Xyrem®:* "Feeling that her heart would race and that she could taste the medication through her teeth"	*Postmortem blood:* GHB 141; EtOH 0.02 g%*; Phentermine 0.26; Zolpidem 0.16; Paroxetine 0.3
Case 2, 44-year old male, obese (Ht. 70", Wt. approx. 275 lbs, BMI 39.5), found dead	Xyrem®/7 g, divided in 2 nightly doses (per physician notes)	*Medical history:* Mood disorder, anxiety disorder, mild obstructive sleep apnea, treatment-resistant, intractable insomnia, hypertension; gastric bypass or banding *Duration of Xyrem® use:* Unknown, ⩽2.5 weeks, physician notes it was unknown if patient alternated use of Xyrem with other sedative-hypnotics *Side effects:* "Cognitive side effects;" feelings of sleep paralysis, per family member	*Postmortem blood:* GHB 110; Alprazolam 0.016; Nordiazepam 0.081; Quetiapine 0.045
Case 3, 43-year-old female (Ht. 64 inches, Wt. 114 pounds, BMI 19.6), found dead	Xyrem®/4.5 g, taken at bedtime (per label)	*Medical History:* Unknown, "possible" narcolepsy/cataplexy diagnosis, comatose during ED visit 4 days prior due to Xyrem® toxicity (unknown whether intentional), urine positive for benzodiazepines, cocaine, amphetamines; recent ED intubation for ingestion of large amount of Risperdal and Vicodin *Duration of use:* Unknown *Side effects:* Unknown	*Postmortem blood:* GHB 3500; Methamphetamine 1.1; Amphetamine 0.19; Chlorpheniramine <0.05 *Vitreous:* GHB 1800
Akins 2007, 53-year-old female, found dead	Xyrem®/total nightly dose 7.5 g, divided in 2 doses	*Medical history:* Narcolepsy, sleep apnea, sarcoidosis *Duration of use:* ⩽1 month *Side effects:* None noted	*Postmortem blood:* GHB 165.6/140***; Tramadol 0.46; Carisoprodol 1.9; Meprobamate: 3.9 *Postmortem urine:* GHB 90.7 *Gastric contents:* GHB 142.0
Ferrara 1995, 42-year-old male, found dead	Alcover®, 50 mg/kg divided in 3 daily doses	*Medical history:* Heroin addict treated with Alcover® *Duration of use:* 1 month	*Postmortem blood:* GHB 11.5; Morphine 0.77; 6-monoacetylmorphine 28.5 ng/ml *Vitreous:* GHB 84.3; Morphine 0.3 *Urine:* GHB 258.3
Zvosec 2007, 226 deaths, 155 male, 71 female; age 15–52 yrs (median 27)	GHB, GBL, BD; street supplies, "supplements," doses unknown	*History:* 207 deaths due to respiratory-cardiac arrest, 13 deaths in traumatic events (motor vehicle collisions, drownings, smoke inhalation) *Adverse events:* Agitation, vomiting, seizures, loss of consciousness	*Postmortem blood:* 177 non-traumatic deaths: GHB range 9–4400**** (median 290), 29 deaths with GHB < 142 (therapeutic range), 64 non-traumatic deaths confirmed negative for co-intoxicants: GHB range 18–4400 (median 347)

EtOH, ethanol; Prescr. dose, prescribed dose; Ht, height; Wt, weight; BMI, body mass index.
* Ethanol level is consistent with endogenous postmortem production; this woman was reported to be a non-drinker and non-smoker.
** Dosage recorded in death investigation ("500 mg") is inconsistent with dosing recommendations and likely was inaccurately transcribed by the death investigator. Xyrem oral solution is typically dispensed in a bottle containing 180 ml of 500 mg/ml solution (90 g). Each kit contains one bottle of Xyrem, a 10-ml plastic measuring syringe, and two 90-ml dosing cups. Typical dosing regimens are 3–4.5 g twice nightly. The dosing syringe found at the scene contained 7.5 ml, equal to a 3.75 g dose.
*** A value of 165 mg/L was detected by the jurisdictional laboratory; 140 mg/L was detected in a sample sent to a national laboratory for verification.
**** GHB exists endogenously, in trace amounts, and may increase postmortem; the vast majority of postmortem blood GHB levels are <50 mg/L. Cases included in that range had confirmatory exogenous levels in other specimens as well as (in most cases) histories of acute GHB ingestion.

two doses) one month prior, for treatment-resistant intractable insomnia. "Cognitive side effects" (undescribed) resulted in Xyrem® cessation after several days. Following physician consultation, he resumed Xyrem® (7 g nightly, divided in two doses). Death occurred two weeks later. The decedent was not wearing his CPAP mask. A Xyrem® dosing cup containing an uningested dose was on the bedside table. No autopsy