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Commentary on: Akins BE, Miranda E, Lacy M, Logan BK. A multi-drug intoxication fatality involving Xyrem® (GHB). J Forensic Sci 2009;54(2):495-6.

Sir,

We appreciate the timely report of a Xyrem®-associated fatality by Akins et al. in the March issue of JFS (1). We have several questions. First, what was the decedent's bodyweight? The total nightly prescribed dose in the current case was listed as 7.5 g; it would be helpful to know the mg/kg dose. Second, were all of the medications listed prescribed by the same physician? And third, gabapentin may also exert sedative effects; was gabapentin quantified postmortem?

Further, we report three Xyrem®-associated fatalities in Sleep Medicine (2), two of which bear similarities to the current case report and raise several important issues. First, as with the current case report, which documents a postmortem blood GHB level of 165.6 mg/L, Cases 1 and 2 in our series also occurred with postmortem blood GHB (141 and 110 mg/L, respectively) consistent with therapeutic levels. Importantly, the current report also documents low postmortem urine GHB (90.7 mg/L) and gastric GHB (142 mg/L) levels, which not only support exogenous origin, as noted by the authors, but also support ingestion of a therapeutic dose. This level is similar to the mean urine level (157.3 mg/L) documented in living subjects receiving a 50 mg/kg dose of GHB (3). Taken together, these three cases give cause for increased caution among clinicians prescribing Xyrem®. Further, overlap of endogenous, therapeutic, and toxic GHB levels in these and other cases (4) underscores the importance of thorough death investigation and integration of toxicologic, pathologic, and historical data for accurate identification of GHB as causal or contributory to death.

Second, Cases 1 and 2 in our series occurred with depressant co-ingestants documented at therapeutic levels (zolpidem 0.16 mg/L in Case 1; alprazolam 0.016 mg/L, nordiazepam 0.081 mg/L, and quetiapine 0.045 mg/L in Case 2). The current case report similarly documents depressant co-ingestants within normal therapeutic ranges (tramadol 0.46 mg/L and carisoprodol 1.9 mg/L). Akins et al. note that combined use of CNS depressant drugs with Xyrem® is contraindicated, but we find that Xyrem® informational material (5) is not clear on this point: specifically, warnings against the use of Xyrem® with CNS depressants or alcohol do not specify whether they apply only to concurrent nightly use of sedative-hypnotics with Xyrem® or also to all daytime doses of muscle relaxants and anxiolytics, which the decedents may have been taking as instructed by their physicians. Furthermore, if patients were warned against any kind of use (not just bedtime use), then was it patient noncompliance or inadequate oversight of multiple medications prescribed by multiple physicians that led to their use?

Third, two decedents in our series had conditions that may have contributed to respiratory compromise (obesity in Case 1; obesity and sleep apnea in Case 2). Similarly, the current case report documents a history of sleep apnea and a report of snoring heard prior to death. However, while Akins et al. state that "breathing difficulties, such as sleep apnea and snoring" are contraindications for use of Xyrem®, our review of informational materials located no such instruction. The only specific contraindications listed in Xyrem® informational material online are: (i) use of sedative-hypnotic agents and (ii) succinic semialdehyde dehydrogenase deficiency. A section on "Warnings" describes clinical trials in patients with sleep apnea and concludes simply that "caution should be observed if Xyrem® is prescribed to patients with compromised respiratory function" (5). What does this mean for clinical practice? Additionally, while snoring may be an indication of breathing difficulty, it is not listed in Xyrem® materials as a contraindication or warning but, rather, is listed solely as an adverse event (5) and it has also been documented in reports of GHB toxicity (6). Furthermore, it is not specified in the current report whether the decedent had a history of snoring prior to use of Xyrem®; it may have been a result of Xyrem® administration. In any case, there is need for greater clarity regarding what "caution" means when prescribing Xyrem® to patients with compromised respiratory function.

Fourth, as best we can determine, these cases were the first to: (i) document association of pharmaceutical GHB (Xyrem®) with death and (ii) document postmortem levels consistent with therapeutic use. In such cases, pathologic confirmation of potentially contributory natural disease processes in cause of death would be particularly valuable. However, neither the current case nor two of the three cases in our series had an autopsy performed. Although sarcoidosis was documented in the current case and listed as a possible contributory factor, no autopsy was done. Conversely, despite the absence of autopsy findings in Case 1 of our series, cause of death was listed as "atherosclerotic cardiovascular disease." Significant variability among medical examiners regarding autopsy performance and death certification practices in drug-related cases has previously been documented, with potentially significant ramifications for compilation of drug mortality statistics (7) as well as for appreciation of lethal risk posed by prescription medications taken singly or in combination with other drugs and/or natural disease processes.

A minor point of correction: Xyrem® was approved only for the treatment of narcolepsy patients with cataplexy in 2002; approval for treatment of excessive daytime sleepiness was not obtained until 2005 (8).

Lastly, Akins et al. describe a narcoleptic stopped for erratic driving under the influence of Xyrem®. Whether this was a case of sleep-driving or abuse, it is important to note that deaths have been reported among GHB-intoxicated drivers as well as resulting directly from overdose. We have reported a series of 226 GHB-associated fatalities which include 13 that resulted from fatal trauma, of whom three were GHB-intoxicated drivers and three were GHB-intoxicated pedestrians (9).

References

1. Akins BE, Miranda E, Matthew Lacy J, Logan BK. A multi-drug intoxication fatality involving Xyrem® (GHB). J Forensic Sci 2009;54(2):495–6.
2. Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem®. Sleep Med 2009;10(4):490–3.
3. Haller C, Thai D, Jacob P, Dyer JE. GHB urine concentrations after single-dose administration in humans. J Anal Toxicol 2006;30:360–4.
4. Zvosec DL, Smith SW, Porrata T, Strobl AQ, Dyer JE. 226 Gamma hydroxybutyrate (GHB)-associated fatalities: overlap of postmortem GHB levels with endogenous, therapeutic, and non-fatal GHB toxicity cases and factors supporting exogenous origin. Proceedings of the 41st Annual Meeting of the National Association of Medical Examiners, October 13–17, 2007, Savannah, GA. Atlanta, GA: National Association of Medical Examiners, 2007.

5. Xyrem® (sodium oxybate) oral solution, http://jazzph.isat-tech.com/media/PI.pdf (accessed 2/5/2009).
6. Arneson AH, Goetze J. Dietary supplement or dangerous drug? Two case reports of gamma-butyrolactone toxicity. J Emerg Nurs 2000;26:425–9.
7. Graham JK, Hanzlick R. Accidental drug deaths in Fulton County, Georgia, 2002: characteristics, case management and certification issues. Am J Forensic Med Pathol 2008;29:224–30.
8. Xyrem approved for the treatment of EDS in patients with narcolepsy, http://www.drugs.com/news/xyrem-approved-eds-patients-narcolepsy-1624.html (accessed 3/20/2009).
9. Zvosec DL, Smith SW, Porrata T, Strobl AQ, Dyer JE. Fatal motor vehicle collisions while gamma hydroxybutyrate (GHB)-intoxicated. Proceedings of the 45th International Meeting of the Association of Forensic Toxicologists (TIAF) and First Joint Meeting with the International Council on Alcohol, Drugs and Traffic Safety (ICADTS), August 26–30, 2007, Seattle, WA, http://www.icadts2007.org/scientific/proceedings/index.html (accessed 6/21/2009).

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