A Snapshot of GHB and Drug-Facilitated Crimes

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SOFT-DFC Snapshots are short reports of critical information about the more common drugs associated with drug-facilitated crimes (DFCs). They are not complete literature reviews about the drug or drug class. One key aspect is their focus on the ability to detect a drug after a single-dose administration, as is often the situation in DFC investigations. As such, these summaries also point out instances in which available data is limited in the hopes that this will encourage further research studies. Finally, SOFT-DFC Snapshots point to the use of these drugs in actual DFC cases, as cited in the medical and open literature.

Gamma-hydroxybutyrate (GHB) was originally developed in the 1960s for use as an anesthetic.[1] In the 1980s, it was sold as a nutritional supplement to weight builders to aid in building muscle mass and a sedative.[2] Its increased abuse and public health risk resulted in its ban by the FDA in 1990.[3] Continued use as a "Club Drug" or "Date Rape Drug" led to it being scheduled to a Schedule I drug in 2000.[4] As it pertains to DFC cases, it's odorless and tasteless nature allows it to be easily and covertly added to alcoholic drinks of unsuspecting victims.[5] Its rapid onset of action, strong sedating, and memory-impairing effects, as well as its ability to increase libido, make it a favorable drug of choice in DFCs.[6,7]

Drug Class: CNS Depressant[8]

Generic Name: Sodium oxybate (sodium salt of GHB and Schedule III)[9]

Brand Name(s): Xyrem® (immediate-release solution), LUMRYZ® (extended-release suspension)

Dosage Forms: Immediate release (initial, 4.5 g divided into two doses per night, max of 9 g divided into two doses per night). Extended-release (initial 4.5 g per night, titrated max of 9 g per night)[10]

FDA Approval: GHB is not approved for medical use by the FDA. Sodium oxybate is used to treat cataplexy and excessive daytime sleepiness associated with narcolepsy.[9] The exact mechanism of action is not well understood. Still, agonism of $GABA_B$ receptors at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons, is thought to play a role in the treatment of narcolepsy.[11,12] There is also evidence that it binds at a GHB-specific G protein-coupled pre-synaptic receptor.[13]

International Approval: Alcover® (sodium oxybate) used in Italy and Austria for the treatment of alcohol detoxification and withdrawal.[14,15]

Illicit Use:

Low GHB doses produce sedative and euphoric effects, but higher doses can result in loss of consciousness, seizures, bradycardia, body temperature, decreased respiratory depression, coma, and death.[8] Combining it with other CNS depressants, such as ethanol, can result in increased CNS depression.[8,16,17]

Gamma-butyrolactone (GBL) is a precursor in the illicit manufacture of GHB, and if ingested, it can be converted to GHB within the body. After ingestion, 1,4-Butanediol (BD) can also be metabolized to GHB.[18] GBL is regulated as a List I chemical, while BD remains uncontrolled.[18,19] Both analogs are abused due to their sedative and euphoric effects.

Metabolism/Elimination:

The major metabolic pathway for GHB is via oxidation by GHB dehydrogenase, which produces succinic semialdehyde. This is then oxidized to succinic acid, which enters the Krebs cycle and metabolizes to water and carbon dioxide. The secondary pathway is beta-oxidation, followed by Krebs cycle metabolism.[15] GHB has an elimination half-life of 0.5 – 1.0 hours.[11,12,16] The half-life appears to increase with higher doses or be absent with intravenous administration, suggesting zero-order or saturation kinetics.[17,20] Only about 1-5% of unchanged GHB is eliminated in the urine.[15]

Single Dose Studies:

Endogenous levels of GHB are present in the body, and suggested cutoffs of 10 µg/mL for urine and 2 µg/mL for blood are currently used to distinguish exogenous vs. ingestion of GHB in living individuals. [21–24]

Urine:

ANSI/ASB Standard 122 recommends not testing urine samples for GHB when more than twelve hours have elapsed between the alleged incident and the time of collection.[22]

In one study, 16 adults were administered an oral 50 mg/kg dose of GHB (Xyrem®) alone and combined with 0.6 g/kg of ethanol. 12.5% of urine samples collected from 3 to 6 h, 81.3% collected from 6 to 12 h, and 100% collected from 12 to 24 h after dosing were below the 10 µg/mL threshold level. It concluded that the detection time for GHB in urine may be shorter than the previously reported 12-h window in some people taking therapeutic doses of GHB.[25]

Another study involving 11 naïve volunteers that were administered an oral 25 mg/kg dose, resulted in urinary t_{max} of one hour and a mean c_{max} of 67.6 (32.6 – 161.3) mg/L.[26]

Abanades et al., administered oral doses of 40, 50, 60 and 72 mg/kg to eight volunteers and yielded urinary c_{max} of 31.8, 61.7, 45.8, and 85.5 mg/L and t_{max} of 0 – 3 hours, respectively. [27]

Blood/Plasma/Serum:
Exogenous GHB is only detectable in blood for up to eight hours.[17]

An Italian study using single doses of 12.2, 25 and 50 mg/kg were administered orally to 8 volunteers and yielded peak plasma concentrations of 23, 46, and 80 mg/L with median t_{max} 25 (20-30), 30 (20-45) and 45 (30-60) minutes, respectively.[28]

Another study involving 12 naïve volunteers that were administered an oral 25 mg/kg dose, resulted in t_{max} of 24.6 minutes and a mean c_{max} of 48.0 mg/L in whole blood while the serum resulted in t_{max} of 23.3 minutes and a mean c_{max} of 59.4 mg/L.[26]

Abanades et al. administered oral doses of 40, 50, 60 and 72 mg/kg to eight volunteers and yielded plasma c_{max} of 79.1, 83.1, 113.5 and 130.1 mg/L and t_{max} of 0.7, 0.6, 0.6 and 0.9 minutes, respectively. [27]

Hair:
Currently, there is not a consensus on endogenous GHB levels in hair due to high intra and inter-individual variation.[29]

In 2020, Strickland et al. drew the following conclusions and recommendations for testing hair. “(i) the collection should take place 8 weeks or more after the suspected dosing event and a length of at least 3 to 5 cm be gathered from the scalp; (ii) GHB ratios are discouraged as a test for GHB ingestion, especially for male subjects; (iii) based on our data, a concentration above 2 ng/mg along with a positive indication from the adjacent segment difference is likely to indicate exogenous dosing; and (iv) hair preparation should be standardized/limited for parameters such as segment length and we recommend using 1 cm segments.”[29]

DFC Cases:

A 2016 publication reported the death of a 6-year-old girl who was the victim of a DFSA following sedation by GHB. The following levels were reported: cardiac blood: 150 mg/L; bile: 292 mg/L;

vitreous humor: 58 mg/L; liver: 100 mg/kg; kidney: 124.5 mg/kg, brain: 110 mg/kg. Segmental hair analysis showed high GHB levels in the proximal part of the hair sample (~40.9 ng/mg).[20]

In 2016, Stephen Port was convicted of the murder of four men and numerous rapes and sexual assaults. He spiked his victims' drinks with GHB.[30]

A 2009 report documented a case involving a 24-year-old woman who was repeatedly and unknowingly dosed with GHB and morphine while studying abroad for a year. After returning home, she received video clips capturing the assaults. She had her hair tested, and both morphine and GHB were detected.[31]

Another case involved a 38-year-old woman who exhibited symptoms of confusion, hyperactivity, and slurring. She also appeared to be experiencing hallucinations and convulsions. She also claimed to have experienced memory loss. A blood sample that was collected within 8 hours of the assault contained 3.2 mg/L of GHB as well as other CNS depressants. [32]

References:

1. Waiters P. Executive Office of the President Office of National Drug Control Policy PROPERTY OF National Criminal Justice Reference Service (NOJRS) Box 6000 Rockvilte, MD 20849-6000. www.whitehousedrugpolicy.gov/streetterms/default.asp. Accessed November 24, 2023.
2. O'CONNELL T, KAYE L, JOHN J. PLOSAY I. Gamma-Hydroxybutyrate (GHB): A Newer Drug of Abuse. *Am Fam Physician*. 2000;62(11):2478-2482. https://www.aafp.org/pubs/afp/issues/2000/1201/p2478.html. Accessed November 24, 2023.
3. Kapoor P, Deshmukh R, Kukreja I. GHB acid: A rage or reprive. *J Adv Pharm Technol Res*. 2013;4(4):173. doi:10.4103/2231-4040.121410
4. Carter LP, Pardi D, Gorsline J, Griffiths RR. Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem ®): differences in characteristics and misuse. doi:10.1016/j.drugalcdep.2009.04.012
5. Felmlee MA, Morse BL, Morris ME. γ-Hydroxybutyric Acid: Pharmacokinetics, Pharmacodynamics, and Toxicology. doi:10.1208/s12248-020-00543-z
6. Varela M, Nogué S, Orós M, Miró Ò. Gamma hydroxybutirate use for sexual assault. *Emergency Medicine Journal*. 2004;21(2):255-256. doi:10.1136/EMJ.2002.002402
7. LeBeau MA, Montgomery MA, Miller ML, Burmeister SG. Analysis of Biofluids for Gamma-Hydroxybutyrate (GHB) and Gamma-Butyrolactone (GBL) by Headspace GC-FID and GC-MS. *J Anal Toxicol*. 2000;24(6):421-428. doi:10.1093/JAT/24.6.421

8. Dea. Drug-Facilitated Sexual Assault DEA Victim Witness Assistance Program. http://www.DEAdiversion.usdoj.gov/fed_regs/rules/2010/fr06293.htm. Accessed November 24, 2023.
9. Xyrem (sodium oxybate) Information | FDA. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/xyrem-sodium-oxybate-information. Accessed November 22, 2023.
10. Drug Summary. https://www.pdr.net/drug-summary/?drugLabelId=24474. Accessed November 24, 2023.
11. gamma-Hydroxybutyric acid: Uses, Interactions, Mechanism of Action | DrugBank Online. https://go.drugbank.com/drugs/DB01440. Accessed November 22, 2023.
12. Fda. XYREM (sodium oxybate) oral solution, CIII. www.fda.gov/Medwatch. Accessed November 30, 2023.
13. Snead OC. Evidence for a G protein-coupled γ-hydroxybutyric acid receptor. *J Neurochem*. 2000;75(5):1986-1996. doi:10.1046/J.1471-4159.2000.0751986.X
14. Alcover and associated names | European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/referrals/alcover-associated-names. Accessed December 2, 2023.
15. Busardò FP, Jones AW. GHB Pharmacology and Toxicology: Acute Intoxication, Concentrations in Blood and Urine in Forensic Cases and Treatment of the Withdrawal Syndrome. *Curr Neuropharmacol*. 2015;13(1):47. doi:10.2174/1570159X13666141210215423
16. Drug Summary. https://www.pdr.net/drug-summary/?drugLabelId=281. Accessed December 2, 2023.
17. A Special Issue Devoted to the Topic on DFSA. *Forensic Sci Rev*. 2010;22(1).
18. Dea. 1,4-Butanediol.
19. Gamma-Butyrolactone (GBL). 2023.
20. Couper A, Farrell LM, Huestis M, Jeffrey WM, Raemakers J, FFrank served J. April 2014 (Revised) 6. Performing Organization Code The following toxicologists made significant contributions to both the drafting and review of the Fact Sheets: Michael. 2000.
21. Society of Forensic Toxicologists (SOFT) Drug-Facilitated Crimes (DFC) Committee Recommended Minimum Performance Limits for Common DFC Drugs and Metabolites in Urine Samples.
22. Standard for the Analytical Scope and Sensitivity of Forensic Toxicological Testing of Urine in Drug-Facilitated Crime Investigations. www.asbstandardsboard.org. Accessed November 30, 2023.
23. Unodc. Guidelines for the forensic analysis of drugs facilitating sexual assault and other criminal acts. www.unodc.org. Accessed November 24, 2023.
24. Elian AA. Determination of endogenous gamma-hydroxybutyric acid (GHB) levels in antemortem urine and blood.
25. Haller C, Thai D, Jacob P, Dyer JE. GHB Urine Concentrations After Single-Dose Administration in Humans. *J Anal Toxicol*. 2006;30(6):360-364. doi:10.1093/JAT/30.6.360
26. Brailsford AD, Cowan DA, Kicman AT. Pharmacokinetic Properties of γ-Hydroxybutyrate (GHB) in Whole Blood, Serum, and Urine. *J Anal Toxicol*. 2012;36(2):88-95. doi:10.1093/JAT/BKR023

27. Abanades S, Farré M, Segura M, et al. γ-hydroxybutyrate (GHB) in humans: Pharmacodynamics and pharmacokinetics. *Ann N Y Acad Sci*. 2006;1074:559-576. doi:10.1196/ANNALS.1369.065
28. Palatini P, Tedeschi L, Frison G, et al. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol*. 1993;45:353-356.
29. Strickland EC, Thomas JL, Lloyd EW, et al. Endogenous GHB in Segmented Hair Part II: Intra-individual Variation for Exogenous Discrimination. *J Anal Toxicol*. 2020;44(7):637-650. doi:10.1093/JAT/BKAA086
30. R v Stephen Port Sentencing Remarks of Mr Justice Openshaw Central Criminal Court. 2016.
31. Rossi R, Lancia M, Gambelunghe C, Oliva A, Fucci N. Identification of GHB and morphine in hair in a case of drug-facilitated sexual assault. *Forensic Sci Int*. 2009;186(1-3):e9-e11. doi:10.1016/J.FORSCIINT.2009.01.017
32. Couper FJ, Logan BK. Determination of γ-Hydroxybutyrate (GHB) in Biological Specimens by Gas Chromatography-Mass Spectrometry. *J Anal Toxicol*. 2000;24(1):1-7. doi:10.1093/JAT/24.1.1