Psychiatria Danubina, 2024; Vol. 36, No. 1, pp 126-129 https://doi.org/10.24869/psyd.2024.126 *Case Report*

NON-FATAL GAMMA HYDROXY BUTYRATE INTOXICATION WITH UNUSUALLY HIGH BLOOD LEVEL

Milica Pjevac, Anja Kokalj Palandacic & Peter Pregelj

University Psychiatric Clinic Ljubljana, Ljubljana, Slovenia

received: 1. 2. 2023; revised: 31. 7. 2023; accepted: 7. 9. 2023

* * * * *

INTRODUCTION

Gamma Hydroxy Butyrate (GHB) has emerged as a relatively new psychoactive substance that is gaining significant traction in illicit drug markets. This increase in popularity poses an escalating health concern globally and in Slovenia (Šegrec et al. 2015). While GHB is sanctioned for medical use in certain countries for conditions such as narcolepsy and alcohol withdrawal, its notoriety primarily stems from its frequent abuse (Felmlee et al. 2021).

Moreover, GHB is often misused in combination with other substances like alcohol and amphetamines, and recently it has been associated with newer psychoactive substances such as mephedrone (Busardo et al. 2016).

In this paper, we discuss an exceptional case of non-fatal GHB intoxication that led to an unusually high concentration of GHB in the patient's bloodstream. To the best of our knowledge, this is the inaugural report documenting a patient who survived an intoxication episode of this magnitude.

OBJECTIVE

Gamma-hydroxybutyric acid is a short-chain fatty acid present in both peripheral tissues and the central nervous system. Produced endogenously, GHB is a metabolic byproduct of gamma-aminobutyric acid (GABA) and is thought to serve as both a central neurotransmitter and a neuromodulator (Galloway et al. 2000). Although GHB is structurally akin to GABA, it binds to GABA B receptors at high concentrations but does not bind to GABA A receptors (Carai et al. 2001). Specific receptors for GHB have also been identified, with the highest concentrations found in the hippocampus, cortex, and dopamine-rich areas such as the striatum, olfactory tract, and substantia nigra (Heckler et al. 1992). Some studies suggest that GHB inhibits dopamine release, while others report that it increases dopamine levels. However, the prevailing view is that GHB generally reduces dopamine release while encouraging its accumulation, with lower doses producing the opposite effect (Galloway et al. 2000).

GHB can be consumed in multiple forms, either in its original state or synthesized from externally administered precursors such as gamma-butyrolactone (GBL) or 1,4-butanediol (also known as butane-1,4-diol or 1,4-BD). Due to their similar molecular structures, GHB, GBL, and 1,4-BD are collectively referred to as »GHB and its analogues.« (Felmlee et al. 2021).

GHB is most commonly ingested orally as a tasteless and odorless liquid, often mixed into a beverage. It is also available in a powdered form, which is typically inhaled (Šegrec et al. 2015). The desired effects of GHB consumption include feelings of euphoria, relaxation, lowered inhibitions, and heightened sexual desire. However, taking it in elevated doses can result in cognitive impairment, memory loss, and seizures (Sumnall et al. 2008).

When taken orally, GHB is quickly absorbed from the gastrointestinal tract, reaching peak concentration in the plasma within 20-60 minutes. Its absorption is both dose-dependent and saturable. GBL and 1,4-BD are absorbed more rapidly than GHB and have higher bioavailability, along with a non-saturable absorption process. GBL can be transiently stored in muscle and fat tissues, which can delay its conversion to GHB, as well as the onset of its psychotropic effects and toxicity. All of these molecules can cross the blood-brain barrier; however, GBL and 1,4-BD pass through this barrier more easily than GHB does (Dufayet et al. 2023).

Following intestinal absorption, GBL is converted to GHB by blood lactonases. The expression of lactonases is increased with chronic GBL exposure (Felmlee et al., 2021). Furthermore, 1,4-BD is converted to 4-hydroxybutyraldehyde by alcohol dehydrogenases and then to GHB by aldehyde dehydrogenases (ADHs) (Felmlee et al., 2021). GHB undergoes rapid and almost complete metabolism mainly by the liver and brain with a half-life

of 20-60 minutes, and less than 5% of an oral dose is excreted unchanged in the urine. Typically, exogenous GHB becomes undetectable in blood within about six hours and in urine within twelve hours (Castro et al. 2014).

CASE DESCRIPTION

A 24-year-old female patient with no notable medical history was treated for severe GHB intoxication at a medical emergency unit. Following her discharge, she was referred to the psychiatric emergency service for an evaluation of suicidal intentions. The day prior, she had consumed several shots of tequila with her boyfriend and friends while having eaten very little. She later had a disagreement with her boyfriend. Amid the argument, she ingested GHB, hoping to experience its euphoric and mood-lifting effects. However, shortly thereafter, she became drowsy and eventually lost consciousness.

A friend quickly took her to a nearby emergency unit, where her vital signs were found to be critical. She had shallow breathing with an oxygen saturation level of 85%, a slow heart rate of 30 beats per minute, and low blood pressure measuring 69/41 mmHg. Despite being administered 0.8 mg of naloxone and 500 mcg of flumazenil intravenously, she did not show any positive response to the treatments. Owing to her rapidly deteriorating condition, she was intubated and placed on mechanical ventilation. Additionally, she received 0.25 mg of atropine. Following these interventions, her condition stabilized, and she was transferred to the intensive care unit (ICU).

Upon her admission to the ICU, the patient remained unconscious, registering a Glasgow Coma Scale score of 3. She did respond to painful stimuli, had stabilized blood pressure at 117/80 mmHg, and had a pulse rate of 45 beats per minute. Her pupils were constricted and displayed a weak reaction to light exposure. Computerized tomography scans of her head and X-rays of her chest and heart appeared normal. Given these clinical signs, GHB intoxication was suspected. Immediate intervention was undertaken: Her stomach was lavaged, and she was given activated charcoal along with a laxative. Blood, urine, and stomach content samples were sent for toxicological analysis.

Toxicology results indicated high levels of GHB across all samples: 661 mg/l in blood, 2752 mg/l in urine, and 1123 mg/l in stomach content. Additional traces of benzodiazepines (administered earlier to induce coma) and tetrahydrocannabinol (THC) were found in her urine. Notably, no alcohol was detected in any of the samples. The next day, the medically induced coma was discontinued, allowing the patient to regain consciousness. She was then extubated. Due to hypokalemia, she was also administered potassium. Twenty-four hours after her admission, the effects of GHB had worn off, and she was referred for psychiatric evaluation.

During the psychiatric evaluation, the patient showed no signs of psychotic or depressive behaviors. She strongly denied having any suicidal thoughts or intentions. With no further concerns, she was subsequently discharged.

DISCUSSION

Blood concentrations of GHB between 300-500 mg/l can be life-threatening, often leading to respiratory depression and circulatory collapse (Busardo and Jones 2015). The case we've discussed showed a rapid onset of GHB intoxication and an exceptionally high blood concentration of 661 mg/l. This far exceeds the median level of 240 mg/l reported in a 2002-2015 study on 78 non-fatal GHB intoxications (Liakoni et al. 2016). According to the most comprehensive UK report, blood GHB concentrations ranged from 86-551 mg/l and urine concentrations from 5-5581 mg/l (Elliot 2007).

A Hamburg-area study from 2006 to 2016 found a decrease in GHB intoxication cases, although a consistent rate still requires intensive care (Abid 2022). This study also noted that the severity of consciousness alterations depends on variables like GHB concentration, the use of other substances, and individual tolerance. All patients with GHB levels exceeding 250 mg/L were comatose (Abid 2022). An Australian study revealed that half of recreational GHB users had experienced an overdose, characterized by loss of consciousness and unresponsiveness (Degenhardt et al. 2002).

When interpreting these results, it's crucial to account for the body's endogenous production of GHB, which is present in both the central nervous system and peripheral tissues. Blood and urine samples with GHB concentrations exceeding 5 mg/l and 10 mg/l, respectively, are typically considered to be exogenous. However, in the rare genetic condition known as GHB aciduria, elevated levels of GHB (ranging from 100-200 mg/l) can occur due to an enzyme deficiency that results in GHB accumulation (Castro et al. 2014).

CONCLUSION

The perils associated with GHB intoxication warrant serious attention from both the medical community and the public at large. The increasing prevalence of GHB use, as evidenced by both casual and habitual users, underscores the urgency of this issue. Despite a decline in cases over certain periods, such as from 2006 to 2016 in the Hamburg area, GHB intoxications continue to pose a critical health risk requiring intensive medical care.

Standard drug screenings often fail to detect GHB, making prompt diagnosis and intervention even more vital. The range of symptoms and the severity of the poisoning can vary substantially, influenced by factors such as the concentration of GHB in the bloodstream, the presence of other substances, and individual tolerance levels. Given the rapid onset of GHB intoxication and the potential for life-threatening complications like respiratory depression and circulatory collapse, timely medical treatment is imperative.

The extraordinarily high blood concentration of GHB seen in our case report—661 mg/l— exceeding usual levels, should serve as a stark reminder of the drug's unpredictability and potential lethality. Furthermore, recreational use of GHB is fraught with risk, as evidenced by an Australian study where half of the users experienced an overdose leading to loss of consciousness and an inability to be roused. Therefore, our paper aims to contribute to an increased awareness and understanding of the complexities and dangers of GHB intoxication.

Acknowledgments: The authors would like to thank the participant for her willingness to share the clinical details of her treatment.

Ethical Considerations: Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest: None to declare.

Funding sources: The authors received no funding from an external source.

Authors contribution: M.P. and A.K.P. made equal contributions to the case report in terms of drafting, writing, and obtaining the patient's consent, P.P. revised the paper and approved the final version of the manuscript.

References

Šegrec N, Paš M, Kastelic A: New psychoactive substances and comorbidity. Viceversa 2015; 59: 28-33.

Felmlee, MA, Morse, BL & Morris, ME: γ-Hydroxybutyric Acid: Pharmacokinetics, Pharmacodynamics, and Toxicology AAPS J **23***, 22 (2021). https://doi.org/10.1208/s12248-020-00543-z*

*Busardò FP, Bertol E, Mannocchi G, Tittarelli R, Pantano F, Vaiano F, Baglio G, Kyriakou C, Marinelli E: Determination of GHB levels in breast milk and correlation with blood concentrations, Forensic Science International, Volume 265, 2016, Pages 172-181, ISSN 0379-0738. https://doi.org/10.1016/j.forsciint.2016.02.020***.**

Galloway GP, Frederick-Osborne SL, Seymour R, Contini SE, Smith DE: Abuse and therapeutic potential of gamma-hydroxybutyric acid. Alcohol 2000 Apr;20(3):263-9. doi: 10.1016/s0741-8329(99)00090-7. PMID: 10869868.

Carai MA, Colombo G, Brunetti G, Melis S, Serra S, Vacca G, Mastinu S, Pistuddi AM, Solinas C, Cignarella G, Minardi G, Gessa GL: Role of GABA(B) receptors in the sedative/hypnotic effect of gamma-hydroxybutyric acid. Eur J Pharmacol 2001 Oct 12;428(3):315-21. doi: 10.1016/s0014-2999(01)01334-6. PMID: 11689189.

Hechler V, Gobaille S, Maitre M: Selective distribution pattern of gamma-hydroxybutyrate receptors in the rat forebrain and midbrain as revealed by quantitative autoradiography. Brain Res 1992 Feb 14;572(1-2):345-8. doi: 10.1016/0006-8993(92)90498-x. PMID: 1319274.

Sumnall HR, Woolfall K, Edwards S, Cole JC, Beynon CM: Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). Drug Alcohol Depend 2008 Jan 1;92(1-3):286-90. doi: 10.1016/j.drugalcdep.2007.07.009. Epub 2007 Sep 4. PMID: 17766059.

Dufayet L, Bargel S, Bonnet A, Boukerma AK, Chevallier C, Evrard M, Guillotin S, Loeuillet E, Paradis A, Pouget AM, Reynoard J, Vaucel JA: Gamma-hydroxybutyrate (GHB), 1,4-butanediol (1,4BD), and gamma-butyrolactone (GBL) intoxication: A state-of-the-art review, Regulatory Toxicology and Pharmacology, Volume 142, 2023, 105435, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2023.105435.

Castro AL, Dias M, Reis F, Teixeira HM: Gamma-hydroxybutyric acid endogenous production and post-mortem behavior – the importance of different biological matrices, cut-off reference values, sample collection, and storage conditions. J Forensic Leg Med 2014 Oct;27:17-24. doi: 10.1016/j.jflm.2014.07.008. Epub 2014 Aug 1. PMID: 25287794.

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 Jan;13(1):47-70. doi: 10.2174/1570159X13666141210215423. PMID: 26074743; PMCID: PMC4462042.

Liakoni E, Walther F, Nickel CH, Liechti ME: Presentations to an urban emergency department in Switzerland due to acute γ-hydroxybutyrate toxicity. Scand J Trauma Resusc Emerg Med 2016;24:107.doi:10.1186/s13049-016-0299-z

Elliott SP: Nonfatal instances of intoxication with gamma-hydroxybutyrate in the United Kingdom. Ther Drug Monit 2004 Aug;26(4):432-40. doi: 10.1097/00007691-200408000-00014. PMID: 15257074.

Degenhardt L, Darke S, Dillon P: GHB use among Australians: characteristics, use patterns and associated harm. Drug Alcohol Depend 2002 Jun 1;67(1):89-94. doi: 10.1016/s0376-8716(02)00017-0. PMID: 12062782.

Correspondence:
Milica Pjevac, MD
University Psychiatric Clinic Ljubljana, Chengdujska 45, 1000 Ljubljana, Slovenia;
milica.pjevac@psih-klinika.si / +386 1 5872 100