Letter

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Management of GHB acute intoxications

A. Di Trana[1], R. Beck[2], A. Del Rio[3]

[1] Unit of Forensic Toxicology, Section of Legal Medicine, Department of Excellence of Biomedical Sciences and Public Health, Polytechnic University of Marche, Ancona;[2] Anesthesia and Intensive Care Unit, Department of Medical and Surgical Sciences, University of Foggia, Policlinico Riuniti Foggia, Foggia; [3] Department of Anatomical, Histological, Forensic, and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy

Abstract

Intoxications related to γ-Hydroxybutyric acid (GHB), arising from its success as recreational drug due to its psychotropic properties, are significantly and alarmingly jeopardizing public health, posing major challenges to medical staff. In recent years, GHB's prodrug γ-butyrolactone (GBL) has often supplanted GHB in recreational settings, owing to its lower cost and the ease with which it can be obtained, mainly due to its various legal industrial applications. The Authors intend to stress that symptoms should be assessed and confirmed by timely toxicological analyses by highly-trained, expert professionals. Such tests aimed at analytical confirmation are instrumental in providing physicians valuable indications in terms of the proper pharmacological treatments in order to revert the adverse, or even fatal, side effects, particularly when the overall intoxication picture looks ambiguous. At the time being, little is known about the pharmacological therapies effective in GHB intoxication cases; further comprehensive research is therefore essential, if we are to tackle such a burgeoning public health emergency before it is too late. ***Clin Ter 2021; 172 (1):e49-51. doi: 10.7417/CT.2021.2280***

Key words: *GHB, acute intoxication, analytical confirmation*

Dear Editor,

The psychotropic properties of the endogenous short-chain fatty acid γ-Hydroxybutyric acid (GHB) are at the basis of its success as recreational drug (1). This presumptive neurotransmitter is physiologically biosynthesized from γ-aminobutyric acid (GABA) in mammal brain, but it was also detected in peripheral tissues such as brown fat and kidneys. Specific GHB-receptors are the physiological target of the molecule and its presumptive neuroprotective role is still discussed (1). Besides, neuromodulator properties on neurotransmitters such as glutamate and dopamine in rodents and up-regulation of hormones in humans have been suggested by several studies. However, the GHB shows a good affinity for GABAB receptors at high concentration, exerting a depressant effect on the central nervous system (2).

The sodium salt (sodium oxybate) was internationally approved as therapy for the narcolepsy-associated cataplexy, alcohol withdrawal syndrome and maintenance therapy by European Medicines Agency. Moreover, the GHB is used as anesthetic agent, since high GHB doses are associated to the reduced levels of consciousness (3). Other therapeutic effects on humans have been investigated such as treatment of heroin addiction, relief of pain, improvement of sleep fragmentation, decrease of intracranial pressure, hyperkinetic movement disorders and anxiety disorders (1).

Besides, the anxiety decreasing and disinhibiting properties may cause increased sociability and sexual arousal, which are at the basis of its success as recreational drug of abuse (4). In fact, it has been reported that GHB is one of the most commonly used substance in Chem-sex settings (5, 6). GHB is also known to be used with other substances such as mephedrone or methamphetamine (7-9). Furthermore, offenders usually take advantage from side effects occurring at high dosages, like loss of physical control, consciousness, memory lapses, drowsiness, and dizziness, to commit drug-facilitated sexual assault (10). In the past GHB was also used by bodybuilders as a "steroid-accessory drug", in addition to anabolic androgenic steroids such as nandrolone (11); that has been the case particularly in sports activities where stamina and strength play a key role, which has in turn determined illicit substance abuse on an alarming scale (12).

Due to the concerning increase of the abuse potential, the United Nations listed the GHB in schedule IV in the 1971 United Nations Convention on Psychotropic Substances in 2001. Then, other Countries have scheduled this psychotropic agent as controlled substance.

Recently, the prodrug γ-butyrolactone (GBL) has replaced the GHB in recreational settings because it is cheaper and easier to obtain due to several legal industrial applications (13, 14-16). The cyclization of GHB to GBL occurs at acidic pH thanks to acid catalyzation, making the cyclic form the most abundant in acid condition, whereas the linear form is prevalent in basic means (2).

Since GBL is absorbed more rapidly, it is considered more pharmacologically potent than GHB. Indeed, the lipophilic property ensures greater bioavailability and a major duration of action, although a shorter effect (13).

Correspondence: Alessandro Del Rio. E-mail address: alessandrodelrio70@gmail.com

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The rapid metabolization of GHB, GBL, and 1,4-BD poses two main problems. First, it complicates therapeutic use, as repeated doses have to be applied in order to cover a clinically relevant time period. Then, the detection of these drugs in clinical and forensic cases is challenging, as the detection period is short and highly specialised equipment is needed (3, 17, 18). Also, the analytical quantification of GHB and its analogues in biological matrices is further complicated by the endogenous production of this molecule, drawing the attention of forensic and clinical analytical scientists in the application of cut-offs for positivity (2, 19-22).

The recent identification of GHB-glucuronide, a direct GHB metabolite, was not promising as expected in prolonging the detection time of this complicated molecule in biological samples (23, 24).

GHB intoxication symptoms are nonspecific and may vary from subject to subject depending on the individual tolerance, dose and route of administration. Relaxation, ataxia, disorientation, dizziness, euphoria, confusion, hallucinations, somnolence, nausea, hypothermia, miosis, slurred speech are the most commonly reported signs of GHB in toxication (1, 25). It has to be noted that most of those are common to alcohol intoxication, making the diagnosis more challenging especially in unintended intoxication (1, 25, 26). Other symptoms are often reported, like dysarthia, confusion, incoordination, hypotonia, hyporeflexia, tremor, myoclonus, horizontal and vertical gaze nystagmus. Rarely, bruxism, vertigo, delusion, extrapyramidal side effects have been reported (1).

To this concern, the strategy used to treat acute GHB intoxication is supportive, requiring the constant monitoring of vital signs. The airways should be ensured to be clear, since emesis is common. Cardiovascular and respiratory symptoms should be carefully evaluated and intubation in suggested for unconscious patient during the first few hours of recovery (26). The possible bradycardia is often treated by atropine. Pharmacological treatments have been proven effective in reverting the sedative effects in both humans and animal models, like benzodiazepines. According to other studies, naloxone, flumazenil and phenobarbital show no effect on GHB intoxication.

In conclusion, GHB intoxications are an alarming public health issue that poses challenges to medical staff, due to the decreasing popularity of this illicit substance. The evaluation of symptoms should be confirmed by promptly toxicological analyses, conducted by expertise personnel. Whenever the intoxication signs are ambiguous, analytical confirmation could direct physician to proper pharmacological treatments to revert the even fatal side effects (27). Anyway, little is still known about the effective drugs on GHB intoxications and further studies should be conducted.

References

1. Bosch OG, Seifritz E. The behavioural profile of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol in humans. Brain Res Bull. 2016; 126:47-60
2. Busardò FP, Jones AW. Interpreting γ-hydroxybutyrate con centrations for clinical and forensic purposes. Clin Toxicol. 2019; 57:149-63
3. Busardò FP, Kyriakou C, Napoletano S, et al. Clinical applications of sodium oxybate (GHB): from narcolepsy to alcohol withdrawal syndrome. Eur Rev Med Pharmacol Sci. 2015; 19:4654-4663
4. Bourne A, Reid D, Hickson F, et al. Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: Findings from a qualitative study. Sex Transm Infect. 2015; 91:564–8
5. McCall H, Adams N, Mason D, et al. What is chemsex and why does it matter? BMJ 2015; 351:h5790
6. Marinelli S, Berretta P, Pacifici R, et al. Sex enhancers: challenges, threats and the need for targeted measures. Clin Ter. 2019; 170:e181-e183
7. Zaami S. New psychoactive substances: concerted efforts and common legislative answers for stemming a growing health hazard. Eur Rev Med Pharmacol Sci. 2019; 23:9681-9690
8. Orsolini L, Chiappini S, Corkery JM, et al. The use of new psychoactive substances (NPS) in young people and their role in mental health care: a systematic review. Expert Rev Neurother. 2019; 19:1253-1264
9. Zaami S, Busardò FP, Pichini S, et al. The value of toxicological and forensic analyses in the global challenge to health risks caused by new psychoactive substances. Eur Rev Med Pharmacol Sci. 2019; 23:6008-6010
10. Busardò FP, Varì MR, di Trana A, et al. Drug-facilitated sexual assaults (DFSA): a serious underestimated issue. Eur Rev Med Pharmacol Sci. 2019; 23:10577-10587
11. Busardò FP, Frati P, Sanzo MD, et al. The impact of nandrolone decanoate on the central nervous system. Curr Neuropharmacol. 2015; 13:122-131
12. Palmi I, Berretta P, Tini A, et al. The unethicality of doping in sports. Clin Ter. 2019; 170:e100-e101
13. Busardò FP, Gottardi M, Tini A, et al. Replacing GHB with GBL in Recreational Settings: A New Trend in Chemsex. Curr Drug Metab. 2018; 19:1080-1085
14. Raposo Pereira F, McMaster MTB, Schellekens A, et al. Effects of Recreational GHB Use and Multiple GHB-Induced Comas on Brain Structure and Impulsivity. Front Psychiatry 2020; 11:166
15. Ciarimboli E, Pirani F, Beck R, et al. The health threat of γ-butyrolactone (GBL): Hair analysis in a case of intoxication. Toxicologie Analytique et Clinique. Published online ahead of print June 19 2020
16. Beck R, Matanovi SM, Zibar L. Gamma-hydroxybutyric acid, gamma-butyrolactone, and 1,4-butanediol addiction: a serious health threat. Arh Hig Rada Toksikol. 2019; 70:149- 150
17. Busardò FP, Mannocchi G, Giorgetti R, et al. Stability of endogenous GHB in vitreous humor vs peripheral blood in dead bodies. Forensic Sci Int. 2017; 274:64-69
18. Andresen-Streichert H, Jensen P, Kietzerow J, et al. Endogenous gamma-hydroxybutyric acid (GHB) concentrations in post-mortem specimens and further recommendation for interpretative cut-offs. Int J Legal Med. 2015; 129:57-68
19. Busardo FP, Kyriakou C. GHB in Biological Specimens: Which Cut-off Levels Should be Taken into Consideration in Forensic Toxicological Investigation?. Recent Pat Biotechnol. 2014; 8:206-214
20. Kintz P, Cirimele V, Jamey C, et al. Testing for GHB in hair by GC/MS/MS after a single exposure. Application to document sexual assault. J Forensic Sci. 2003; 48:195-200
21. Busardò FP, Pichini S, Zaami S, et al. Hair testing of GHB: an everlasting issue in forensic toxicology. Clin Chem Lab Med. 2018; 56:198-208
22. Busardò FP, Zaami S, Baglio G, et al. Assessment of the

stability of exogenous gamma hydroxybutyric acid (GHB) in stored blood and urine specimens. Eur Rev Med Pharmacol Sci. 2015; 19:4187-94
23. Piper T, Mehling LM, Spottke A, et al. Potential of GHB phase-II-metabolites to complement current approaches in GHB post administration detection. Forensic Sci Int. 2017; 279:157-164
24. Marchei E, Tini A, Pirani F, et al. Is GHB-glucuronide useful as a biomarker for the exogenous use of GHB? Eur Rev Med Pharmacol Sci. 2019; 23:2311-2313
25. Kamal RM, van Noorden MS, Franzek E, et al. The Neurobiological Mechanisms of Gamma-Hydroxybutyrate Dependence and Withdrawal and Their Clinical Relevance: A Review. Neuropsychobiology 2016; 73:65-80
26. Morse BL, Chadha GS, Felmlee MA, et al. Effect of chronic γ-hydroxybutyrate (GHB) administration on GHB toxicokinetics and GHB-induced respiratory depression. Am J Drug Alcohol Abuse 2017; 43:686-693
27. Marinelli E, Beck R, Malvasi A, et al. Gamma-hydroxybutyrate abuse: pharmacology and poisoning and withdrawal management. Arh Hig Rada Toksikol. 2020; 71:19-26