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Letter to the Editor

Is GHB-glucuronide useful as a biomarker for the exogenous use of GHB?

Dear Editor,

Detection of gamma-hydroxybutyric acid (GHB) in biological matrices of conscious and unconscious consumers has become crucial in many clinical and forensic settings, due to its increasing use for recreational purposes, including "chemsex" and drug-facilitated sexual assault[1-5]. It has to be mentioned that the drug itself as well as its precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), are currently restricted in several countries (e.g. United States, United Kingdom, Italy) and also the UN Commission on Narcotic Drugs has listed GHB among Psychotropic Substances[6-8]. The main issue in the analytical determination of GHB concentrations in biological fluids (e.g. blood, urine, cerebrospinal fluid) and in keratin matrices (e.g. hair, nails) derives from the importance of being able to distinguish endogenous GHB from exogenous administration of an illegal drug, as reported above, and in the latter hypothesis, the challenge is the detection of single doses unknowingly consumed by victims of suspected sexual violence[1]. GHB naturally occurs in the human body, so caution must be taken in the interpretation of positive results. Furthermore, GHB has a narrow window of detection (about 3-12 h in both blood and urine) and quickly reaches concentrations overlapping the endogenous ones[1]. In the search of a biomarker of its use with a longer detection window, the *in vivo* existence of a glucuronated GHB metabolite (GHB-glucuronide) was investigated[9]. Successfully, the glucuronated metabolite was determined in different biological matrices (plasma, urine, hair, nails, cerebrospinal fluid and whole blood) with hyphenated techniques[10-18] and a longer window of detection than the parent drug was demonstrated. Unfortunately, in all the reported studies, GHB-glucuronide was quantified in negligible concentrations (Table I) regardless of whether the parent drug had been administered as a medication or abused as a recreational drug. This evidence has raised some questions concerning the real importance of this metabolic pathway for GHB and in agreement with the conclusions of reported studies[6-13], it is likely that this glucuronated metabolite does not provide any diagnostic information regarding GHB exogenous intake[10-13,15,17,18]. However, an important aspect that has to be taken into account is that the metabolite analyzed to date is the glucuronate at the level of the hydroxyl group of GHB and not the glucuronate at the level of the carboxylic group, due to the unavailability of the standard compound. Therefore, the possibility of monitoring the carboxylic glucuronated metabolite of GHB, when the chemical standard will be available, could allow to evaluate if this other metabolite is useful in detecting GHB exogenous administration with a better diagnostic time-frame.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Table I. GHB-Glucuronide concentration in different biological matrices after GHB intake.

Reference	Matrices	GHB-Glucuronide concentration
10	Hair	Case 1 abuser: 1.7-3.1 ng/mg Case 2 abuser: < LOQ*
11	Hair	Case 1 narcoleptic patients-chronical user: < 0.32-0.68 ng/mg Case 2 narcoleptic patients-chronical user: < 0.48-1.20 ng/mg Case 3 narcoleptic single exposed patient: 0.99-1.01 ng/mg
12	Plasma	Case 1 narcoleptic patients-chronical user: < LOQ** Case 2 narcoleptic patients-chronical user: < LOQ** Case 3 narcoleptic patients-chronical user: < LOQ**
	Cerebrospinal fluid	Case 1 narcoleptic patients-chronical user: 1.05 µg/ml Case 2 narcoleptic patients-chronical user: < LOQ§ Case 3 narcoleptic patients-chronical user: 1.36 µg/ml
13	Plasma	Case 1 narcoleptic patients-chronical user: < LOQ** Case 2 narcoleptic patients-chronical user: < LOQ** Case 3 narcoleptic patients-chronical user: < LOQ** Case 4 narcoleptic patients-chronical user: < LOQ**
	Urine	Case 1 narcoleptic patients-chronical user: < LOQ** Case 2 narcoleptic patients-chronical user: 0.62 µg/ml Case 3 narcoleptic patients-chronical user: < LOQ** Case 4 GHB fatal intoxication: 0.55 µg/ml
	Cerebrospinal fluid	Case 1 narcoleptic patients-chronical user: 1.53 µg/ml Case 2 narcoleptic patients-chronical user: < LOQ§ Case 3 narcoleptic patients-chronical user: 1.22 µg/ml
	Hair	Case 1 narcoleptic patients-chronical user: 0.32-0.86 ng/mg
15	Nails	Children and Adolescents endogenous levels: 0.160 ng/mg Adult Females endogenous levels: 0.153 ng/mg Adult Males endogenous levels: 0.156 ng/mg
17	Whole blood	Post-mortem cases: GHB-Glucuronide not found
18	Serum	1,4-butanediol intoxication: 13.7 µg/ml

*LOQ = 0.48 ng/mg; **LOQ = 0.5 µg/ml; § LOQ = 1.0 µg/ml.

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