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Case report: gamma butzrolactone (GBL) withdrawal syndrome

Odtegnitveni sindrom od gama-butirolaktona (GBL): prikaz primera

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Abstract

Gama-butyrolactone (GBL) is an easily accessible and inexpensive recreational drug popular primarily in night clubs. GBL is a precursor of the endogenous neurotransmitter gamma-hydroxybutyrate (GHB), which acts as an agonist at the GABAB and GHB receptors in the central nervous system (CNS). Low doses inhibit dopamine release, resulting in euphoric effects and reduced central inhibition. Higher doses stimulate the secretion of opioid-like substances and rapidly depress CNS. Addiction develops after several weeks to months of everyday usage. The clinical features of withdrawal are in principle similar to those of ethanol and/or benzodiazepine withdrawal. This paper presents the case of GBL withdrawal syndrome, which was clinically manifested with developed delirium, confusion, hallucinations, and agitation. Therapeutic management include high doses of benzodiazepines and, if needed, barbiturates, anticonvulsive and antipsychotic drugs.

Izvleček

Gama-butirolakton (GBL) je zaradi lahke dostopnosti in nizke cene priljubljena rekreativna droga v nočnih klubih. Gre za prekurzor endogenega nevrotransmiterja, gama-hidroksibutirata (GHB), ki deluje kot agonist na receptorje GABAB in GHB v centralnem živčnem sistemu (CŽS). V nižjih odmerkih inhibira izločanje dopamina, povzroča evforične učinke in niža centralno inhibicijo. Višji odmerki spodbujajo izločanje opioidom podobnih substanc in povzročijo hitro depresijo CŽS. Odvisnost nastopi po nekaj tednih do mesecih vsakodnevne uporabe. Odtegnitev načeloma oponaša klinično sliko odtegnitve od alkohola in/ali benzodiazepinov. Predstavljamo primer odtegnitvenega sindroma od GBL, ki se je pokazal z razvojem delirija, zmedenostjo, halucinacijami in agitacijo. Zdravljenje vključuje visoke odmerke benzodiazepinov, po potrebi pa tudi barbiturate, antikonvulzive in antipsihotike.

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Ključne besede: gama-butirolakton; GBL; odtegnitveni sindrom; odvisnost; akutna zastrupitev

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1 Introduction

1.1 Presentation

Gamma-hydroxybutyrate (GHB) and its precursor gamma-butyrolactone (GBL) are popular recreational drugs with strong hypnotic and amnestic effects (1,2,3). GBL was first synthesized in 1964 for use in anaesthesiology (4,5), while its clinical use was limited to the treatment of narcolepsy due to possible toxicity (6) (sodium oxybate, Xyrem®).

GHB was classified as a controlled substance in 1990, which increased the trafficking of its precursors (GBL and 1,4-butanediol) (2,4,7). The use of GHB, GBL, and 1,4-butanediol has been prohibited in Slovenia since 2001 (7). They are still used in the chemical industry as a component of adhesives, solvents, paint, and nail polish removers, as an intermediate factor in the synthesis of plastics, polymers, and pesticides, and as an additive in the textile industry. Production for recreational use, however, has moved to makeshift underground laboratories and is estimated at around 200,000 tonnes annually (8).

1.2 Pharmacology

GHB is an endogenous substance structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA), which acts as an agonist on GABAB and GHB receptors in the central nervous system (CNS) (2,4). They are located in the basal ganglia, cerebral cortex, hippocampus, midbrain and substantia nigra (4). GBL itself is a pharmacologically inactive precursor, but in vivo it is rapidly metabolized to GHB via serum lactonases in the liver, crosses the blood-brain barrier and the placenta, and causes rapid CNS depression (4,5). Being more lipophilic than GHB, GBL is absorbed more quickly and takes effect within 20–30 minutes (2).

One millilitre of pure GBL corresponds to approximately 2.5 g of GHB (2). The effect is the same and without differences in toxicity (9). GBL and its analogues are sold in the form of liquid preparations for oral administration. GHB can form salts and is therefore also available as a powder, but there are no reports of nasal administration (4).

Binding of endo- or exogenous GHB to receptors in the CNS stimulates the release of opioid-like substances in the prefrontal cortex (5,10). The effect is biphasic: at low doses it inhibits dopamine signalling, and at high doses it stimulates it (2,9). Lower (initial) doses cause a euphoric effect, relaxation, increase self-confidence and reduce inhibition, while higher doses have an inhibitory effect, similar to benzodiazepines (2). Other CNS effects of GHB/GBL include induction of delta waves and REM (rapid eye movement) sleep, decreased cerebral glucose metabolism, generalized hypothermia, cerebral vasodilation, increased cerebral blood flow (2,4), and increased secretion of prolactin and growth hormone via the neuroendocrine system (4,5,11).

The half-life of GHB/GBL is between 20 and 50 minutes (2,4,5). Elimination is primarily via CO2 exhalation (5); only 1–5% of GHB is excreted in the urine (4,7). Due to rapid metabolism and elimination, the clinical presentation can change from acute intoxication to withdrawal within 30 minutes (2,12).

The excess concentration of GHB/GBL in the urine and blood is measurable a few hours after the last dose. Endogenous concentration of GHB in urine is usually 1 mg/L and slightly lower in plasma, and arbitrary excess values are above 10 mg/L in urine and above 5 mg/L in plasma (4,7). Gas chromatography is used to detect it in urine, blood and serum samples, which is carried out in Slovenia by the Institute of Forensic Medicine in Ljubljana (7).

1.3 Acute poisoning and overdose

Retrospective case studies (10,13) report that 53–83% of users had at least one overdose experience. In Slovenia, the first case of GHB poisoning was found in 2002 at the University Medical Centre Ljubljana (UMCL) (7). Acute poisoning manifests with impaired consciousness and is accompanied by bradycardia, bradypnea, hypotension and hypothermia (4,7,9). The period of unresponsiveness is usually transient, with most patients recovering within 2–3 hours of coma onset (4,16). During wakening, the patient may be aggressive and confused, and vomiting is also common (7).

Reported deaths from GHB/GBL have generally resulted from respiratory depression or subsequent complications of aspiration due to vomiting (4,5). Death occurs more frequently when alcohol or illicit drugs are used together (5,9,14). Interactions between GHB/GBL and ethanol in animal models have shown that ethanol acts synergistically on sedative effects by competitively blocking the metabolism of GHB/GBL (4,15). In practice, however, agitation is more common with concurrent alcohol use (9). It can be assumed that ethanol at

lower doses of GHB/GBL promotes disinhibition and euphoria. Cocaine and ecstasy (3,4-methylenedioxymethamphetamine, MDMA) in combination with GHB/GBL more frequently cause prolonged coma (9), since stimulant addicts generally require a higher dose of GHB/GBL for a sedative effect, which is manifested by deeper depression of consciousness.

Acute poisoning treatment is supportive. There is no specific antidote. Preventive administration of naloxone is not recommended, as GHB/GBL's mechanism of action is different from opioids (16). Gastric lavage is not effective, and only activated charcoal is recommended (7). Between 2000 and 2014, the UMCL treated 74 people for GHB poisoning, of which 80% of patients needed symptomatic treatment, 5% were treated in the intensive care unit, and 14% required mechanical ventilation (17). 18% of patients received benzodiazepines to alleviate symptoms of agitation upon awakening, and 4% required atropine for bradycardia (17).

1.4 Chronic dependence and withdrawal

Dependence typically develops after a few weeks to months of daily GHB/GBL use (4). It is assumed that the minimum duration of use is two to three months, at least three to four times a day (16). Withdrawal occurs rapidly (1–6 hours after the last dose), and symptoms last from 48 hours to 15 days, or an average of 9 days (2,4,5).

Withdrawal symptoms may resemble the clinical presentation of ethanol withdrawal and/or benzodiazepines and are therefore often difficult to distinguish from the latter (2,4,5,9,14,18). The most common milder withdrawal symptoms from GHB/GBL are tremors, hallucinations, tachycardia, insomnia, nausea, and vomiting. More severe symptoms such as delusions, psychosis, agitation, convulsions, and rhabdomyolysis occur less frequently (4,19). Delirium develops more frequently than with withdrawal from ethanol and/or benzodiazepines and within a shorter period since the last dose

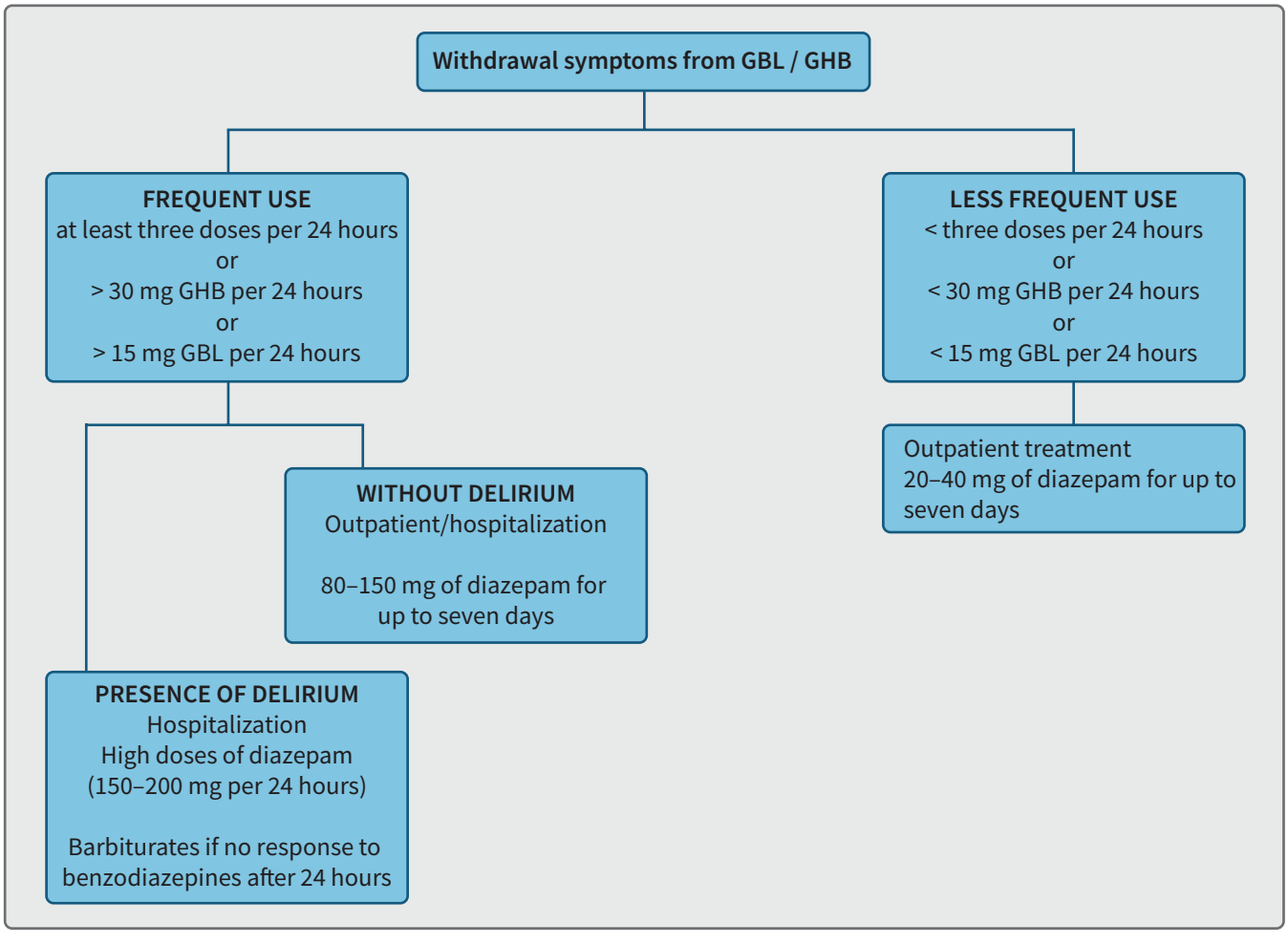

Figure 1: Algorithm for the treatment of gamma-butyrolactone (GBL). Adapted from Henderson DL, 2008 (19).

(4). Long-term effects such as more severe anxiety and depression, fear of leaving home and answering phone calls may persist for weeks to months after GHB/GBL use is stopped (2).

In 2004, the GHB/GBL addiction and withdrawal treatment algorithm was published for the first time (16). It is based on the frequency of intake, daily dose of GHB/GBL, and the clinical presentation (Figure 1). In case of less frequent use, outpatient treatment with diazepam is recommended (2). The recommended initial daily dose of diazepam is 20–40 mg, divided into three doses, which is appropriately adjusted to the individual according to gender, age, comorbidities, and clinical deterioration. Similar to the treatment of alcohol withdrawal, other benzodiazepines may be used at diazepam-equivalent doses (16).

Treatment of withdrawal with more frequent use of GHB/GBL (Figure 1) depends on clinical severity and presence of delirium. The main symptomatic treatment is sedation with high benzodiazepine doses for up to seven days (4). Guidelines recommend 75–200 mg of diazepam in the first 24 hours (2,16). In case of non-responsiveness to benzodiazepines or refractory symptoms, the drug of choice is baclofen, a receptor agonist, at a dose of 30 mg/day for the first five days (2,4). Baclofen is said to have beneficial effects on subsequent treatment, as patients reported better concentration and sleep and reduced desire for GBL (2).

In the symptomatic treatment of advanced delirium and withdrawal, other barbiturates and propofol as well as antipsychotics have also proven to be effective. In case of convulsions or seizures, it is reasonable to start treatment with anticonvulsants (4,8,13,20). Although cases of Wernicke-Korsakoff syndrome have been described, the routine use of vitamin B is not recommended (4,21), but clinical judgment can still be used, depending on the patient's history.

1.5 Purpose of the report

In the case presentation, we will describe the course of treatment of a patient with GBL withdrawal syndrome who progressed to delirium. Due to the similarity of the clinical presentation to other poisonings, the toxidrome is rarely clinically recognized, because despite the increasing frequency of use, healthcare workers are not yet well acquainted with the substance. For the first time in the Slovenian literature, we present the latest guidelines for the treatment of GBL withdrawal.

2 Case report

In February 2020, the emergency clinic of the Department of Psychiatry of the University Medical Centre Maribor treated a 34-year-old detainee with a referral diagnosis of unspecified delirium. The judicial officers said that he "has been behaving strangely for several days", and on the day of admission he was said to be "purely in his own world", "confused and aggressive". He had never been hospitalized or seen by a psychiatrist before. At the first examination, he was unable to establish meaningful contact, his reality control was greatly reduced, and delirium was observed. We observed disturbances in perception; he acted under the influence of visual and auditory hallucinations, and his behaviour was disorganized. The somatic and neurological examinations were difficult to perform due to agitation and suspected psychosis, although they were grossly without abnormalities. There were wounds on both wrists from resisting handcuffing.

The patient was involuntarily admitted to the Forensic Psychiatry Unit for observation and diagnosis. In the prison infirmary he received 2 mg of lorazepam (2 mg intramuscularly); on the ward, he received zolpidem (5 mg daily for seven days), diazepam (initially 10 mg three times a day for three days, followed by 5 + 5 + 10 mg daily for two days, followed by 5 + 0 + 5 mg daily for three days, and before discontinuation another 5 mg in the evenings for three days) and quetiapine (25–50 mg in the evening when he stabilized). Physical restraint with belts was required. Laboratory results showed marked leucocytosis (K-leukocytes: 26.14 * 109/L; normal values: 4.00–10.00 x 109/L) with low C-reactive protein (S-CRP: 9 mg/L; normal values: < 5 mg/L) and elevated ammonia concentrations (plasma ammonia: 57 µmol/L; normal values: < 50 µmol/L).

A computed tomography (CT) scan of the brain was performed (unremarkable), along with an abdominal ultrasound, which showed mild liver injury. Hepatitis markers were negative. Due to subfebrile body temperature (body temperature: 37.4°C), chest radiography was performed, which did not show evidence of a bacterial or viral respiratory infection. Infectious disease specialists performed a lumbar puncture (unremarkable findings) and started empiric antibiotic treatment with levofloxacin 500 mg/12h.

On the third day of hospitalization, the patient's mental condition improved and was able to have a meaningful conversation. Physical restraints were no longer necessary. The patient denied the abuse of alcohol and illegal drugs. His condition continued to improve daily.

Occasional psychomotor agitation was still present, but his behaviour was completely normal.

After 10 days of hospitalization, the patient admitted to having abused GBL for many years. He bought it online for €100/L. Initially it had a euphoric effect, but later he took it to sleep better. Doses were "depending on the day", one to five times a day, about three to five drops. We were unable to obtain information about what substance and in what quantities the patient used to dilute GBL.

On the 17th day of hospitalization, the patient was transferred back to custody. Upon discharge, his consciousness was not impaired; he was generally well-oriented, formally and substantively organized in his thinking, adequate in contact, without obvious productive psychopathological symptoms. His cardiorespiratory system was without abnormalities.

3 Discussion

GHB/GBL is a "club drug" (20) or "date rape drug" (8), popular in nightclubs and known under the names "Ruffles", "Roofies", "GG", "G-Riffick", "Easy Lay", "Liquid X" or "Liquid ecstasy" (5,22), etc. Until the 1990s, GHB/GBL was sold over the counter in the United States as a performance enhancer, in bodybuilding formulas, and in dietary supplements (4), purported to burn fat and increase muscle mass, slow aging, and boost libido (2,5). It was supposed to have a favourable effect on the individual's communicativeness, relaxation, and openness, similar to alcohol, but without side effects such as smell on the breath, hangover and the possibility of detection in urine samples or police breathalysers (20). Because of these properties, the substance initially attracted individuals who were not (yet) aware of its side effects and the high possibility of developing dependence. Compared to other stimulants (cocaine, amphetamines), GHB/GBL is also relatively cheap and easily ordered through online platforms based in countries where the substance is still legal (8).

In a retrospective study (2), GHB/GBL abusers cited the three most common reasons for use: to gain confidence in social interactions, to increase sexual activity, and to improve sleep. Consumption usually began for the first two reasons, followed by higher doses that induced sedation and sleep. This establishes a "circular pattern" of taking smaller stimulant doses in the morning and during the day and larger doses before bed (20). Addicts reported that they "liked the person they became when on GHB/GBL" (2). However, the initial effect of euphoria, satisfaction and relaxation gradually wore off, and consumption of higher doses transformed them into introverted "zombies" lacking motivation, who were often unable to maintain a normal social life and daily functioning, such as going to school, college, or service (2).

Our patient ordered GBL online at a relatively low price and reported no problems with procurement or shipment delivery. In the initial period, he reported increased self-confidence and better physical performance. Soon he needed higher doses, which no longer achieved the initial stimulating effects. The main purpose of continued consumption was to sleep better. Long-term use of the substance numbed the patient, induced psychomotor retardation, and gradually pushed him into isolation. After his unexpected arrest, he abruptly stopped using the substance after several years of continued use; the clinical presentation of withdrawal manifested on the first day in detention and escalated until he was hospitalized. After appropriate treatment, the symptoms disappeared completely within a few days.

We did not know about the substance abuse at the beginning of treatment. The patient had no history of alcohol or illicit drug use. During diagnosis, organic pathology, toxic encephalopathy, CNS infection and hepatitis were excluded. Toxicology tests were negative. The presence of GHB/GBL in urine or blood is not routinely determined in our laboratory, but in any case, the window of possible detection had already expired by the time of admission. The patient received treatment with benzodiazepines and an antipsychotic, which resulted in improvement. The cause of delirium was unclear until the patient's impairment of consciousness subsided, and he admitted that he had consumed GBL. Treatment was not suboptimal despite not knowing the cause of the delirium.

We conclude from the case that the patient was not fully aware of the severity of his addiction, did not expect withdrawal symptoms, and did not initially associate them with stopping GBL consumption.

Patients addicted to GHB/GBL are frequently not recognized. Many describe difficulties in seeking treatment due to a lack of familiarity with the substance on the part of healthcare workers or the inaccessibility of detoxification facilities (2). Before seeking proper help, many GHB/GBL addicts attempt to self-medicate with benzodiazepines and alcohol (4).

4 Conclusions

Based on the clinical case of treatment of a patient with GBL withdrawal, we confirmed that it is a cheap and easily accessible recreational drug that causes severe addiction. Patients normally start using the substance for the initial euphoric effects and are not aware of the

long-term consequences. Dependence develops quickly and requires gradual increases in sleep-inducing doses. Long-term use, dosing several times a day, and combining with ethanol or other drugs are predictive criteria for risky consumption that may cause acute intoxication and/or more severe withdrawal symptoms. The clinical presentation of withdrawal can vary from mild symptoms to advanced delirium. Diagnosing can be difficult due to the rapid metabolism and elimination of the substance from the body, as well as the non-specificity of the toxidrome, which can mimic intoxication with other central nervous system depressants (ethanol, benzodiazepines), or the clinical features of the toxidrome are masked by substances with opposite effects (cocaine) (4). Acute poisoning is frequently unrecognized since the detection of the substance in blood or urine is not routinely performed. GHB/GBL addicts frequently abuse more than one substance, or they try to alleviate withdrawal symptoms empirically with other illegal substances or prescription drugs. Our patient was most likely not even aware of the depth of his problems and would have hypothetically continued his substance abuse if he had not been arrested.

Conflict of interest

None declared.

Inform consent of the patient

The patient has given his written consent for the publication of the paper, which is kept at UMC Maribor.

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