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The Use of Intravenous Baclofen as Therapy for the γ-hydroxybutyric Acid Withdrawal Syndrome

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Abstract

Introduction: In this case series with three patients, we introduced baclofen, a γ-aminobutyric acid type B(GABA-B) receptor agonist, for treatment of the γ-hydroxybutyric acid (GHB) withdrawal syndrome.

Materials and Methods: Single center case series performed on three patientswith a GHB withdrawal syndrome. They initially received massive doses of benzodiazepines, without sufficient effect. Two patients also received an unsuccessful continuous dexmedetomidine drip. In all patients, intravenous baclofen was started, with an intravenous loading dose between 0.5 and 2 milligrams (mg) to achieve a therapeutic level. Thereafter a continuous intravenous dose between 0.5 and 1 mg per hour for 12 h was administered to maintain a steady state. After that, baclofen was substituted orally with a daily oral dose varying between 20 mg and 40 mg which could be downgraded and stopped over the next days. They all continued to receive a standard benzodiazepine regimen during the baclofen trial.

Results and Discussion: Main outcome measurements were the degree of withdrawal symptoms and the need for benzodiazepines during baclofen treatment. In all patients, a significant reduction of the GHB withdrawal syndrome was noted. A standard daily regimen of baseline benzodiazepine dosing between 40 mg and 80 mg diazepam was sufficient. Adverse effects of baclofen use were absent.

Conclusion: This case series suggests the benefit of intravenous baclofen as additive to the standard benzodiazepine treatment for a GHB withdrawal syndrome in order to limit life-threatening symptoms, to reduce the total amount of benzodiazepines needed and to shorten the length of stay in an observational unit with monitoring facilities.

Keywords: Gamma hydroxybutyric acid; Withdrawal; Baclofen

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Introduction

Gamma Hydroxybutyric acid (GHB) is a short-chain fatty acid and occurs naturally in mammalian brain tissue, where it is derived from the neurotransmitter γ-aminobutyric acid (GABA). There is a structural similarity between GHB and GABA. It is designed in the sixties in an attempt to produce an analogue of the inhibitory brain neurotransmitter GABA able to cross the blood-brain barrier. In the subsequent years, GHB turned out not to be a valuable anesthetic agent. Thereafter, it was used in the treatment of narcolepsy and alcoholism [1]. Since the nineties, GHB has been abused by body builders because these products were thought to stimulate the production of growth hormone, and in night club life, in circuit parties and raves as a recreational drug.GHB has two prodrugs, γ-butyrolactone and 1,4-butanediol [1]. The GHB withdrawal syndrome is a frequent problem at the emergency department, due to an increase in chronic GHB abuse. It is serious, long-lasting and a challenge to treat. Therapeutic options are limited. In this case series with three patients, we introduced baclofen, a γ-aminobutyric acid type B (GABA-B) receptor agonist, as treatment of the withdrawal syndrome. It has been hypothesised that a substitution for GHB on the GABA-B receptor could prevent withdrawal [2,3].

Materials and Methods

Single center case series performed on three patients between July2013 and August 2016 with a GHB withdrawal syndrome. All patients, males aged between 25 and 31 years, suffered from a serious GHB withdrawal syndrome at arrival at the emergency department (ED) with symptoms

Table 1: Patient characteristics.

Patient characteristics	1	2	3
Age (years), gender	25, male	27, male	31, male
GHB use at time of presentation	Yes	Yes	Yes
Toxicology screening	None	Amfetamine, benzodiazepine, cocaine	Benzodiazepine
Respiratory rate at time of presentation (/min)	40	27	18
Heart rate at time of presentation (/min)	110	120	116
Blood pressure at time of presentation (mmHg)	120/80	120/70	144/82

GHB= γ-hydroxybutyrate

Table 2: Treatment characteristics.

Treatment characteristics	1	2	3
Total benzodiazepine dose before start baclofen (diazepam/ lorazepam), mg	44/30 over 3 h	0/280 over 12 h	10/710 over 21 h
Dexmedetomedine drip (µg/kg/h)	No	1,03 for 34 h	1,00 for 17 h
Baclofen initial loading dose IV (mg)	0,5	1	2
Baclofen continuous dose (mg/h) for 12 h	0,5	1	1
Baclofen oral decremental dose (mg/24 h)	40	40	20

Table 3: Evaluation after treatment with baclofen.

Evaluation after baclofen administration	1	2	3
Total benzodiazepine dose first 24 h after start baclofen (diazepam / lorazepam), mg	0/140	0/130	0/60
Total benzodiazepine dose after start baclofen (diazepam/ lorazepam), mg	0/160 over 27 h	0/270 over 104 h	0/210 over 144 h
Respiratory rate (/min)	NA	18	18
Heart rate (/min)	NA	83	65
Blood pressure (mmHg)	NA	110/63	93/54
Adverse effects	No	No	No

NA= Not Available

of tremor, restlessness, insomnia, nausea, autonomic dysfunction, anxiety and delirium. Patient characteristics are summarised in Table 1. They all initially received massive doses of benzodiazepines, without sufficient effect. Two patients also received an unsuccessful continuous dexmedetomidine drip, which is an alpha 2 adrenergic receptor agonist, with doses up to 1.03 µg/kg/hour. In all patients, intravenous baclofen was started, with an intravenous loading dose between 0.5 and 2 milligrams (mg) to achieve a therapeutic level. Thereafter a continuous intravenous dose between 0.5 and 1 mg per hour for 12 h was administered to maintain a steady state. After that, baclofen was substituted orally with a daily oral dose varying between 20 mg and 40 mg which could be downgraded and stopped over the next days. They all continued to receive a standard benzodiazepine regimen during the baclofen trial. Treatment characteristics are summarised in Table 2.

Result

Main outcome measurements were the degree of withdrawal symptoms and the need for benzodiazepines during baclofen treatment. In our three patients, a significant reduction of the GHB withdrawal syndrome and benzodiazepine administration was noted, with improved hemodynamic and respiratory stability. In one patient, cardio-respiratory parameters after baclofen treatment were not available. A standard daily regimen of baseline benzodiazepine dosing between 40 mg and 80 mg diazepam was sufficient, without the need for additional doses. Adverse effects of baclofen use were absent. Evaluation after treatment with baclofen is summarised in Table 3.

Discussion

Use of GHB is far more prevalent in young man than women. It is a club drug, taken for its disinhibitory effects, leading to euphoria and heightened sexual awareness. It is a frequent cause of drug-induced coma in young people. Addiction occurs in occasional users, but mostly in bodybuilders or people with a history of anxiety or insomnia. They drink the drug every 2 to 4 hours around the clock because of the rebound insomnia that leads to escalation of the dosage. Occasional GHB users may have a mild withdrawal syndrome [1]. Chronic use is an upcoming problem leading to a severe and life-threatening withdrawal syndrome. It leads to tolerance associated with down-regulation of inhibitory GABA-B and GHB receptors. Abstinence after chronic use of GHB results in decreased GABA- and GHB-mediated neuro-inhibition and thus in unopposed excitatory neurotransmission [1].

GHB has diverse pharmacologic and biologic properties and has several neuronal mechanisms of action that includes activation of the GABA-B receptor and a GHB-specific receptor [1]. It has both a direct effect on the GABA-B receptor, and an indirect effect via the conversion to GABA that activates the GABA-A receptor [1,4]. Many of the clinical, toxicological and pharmacologic effects of exogenously administered GHB are mediated primarily through the GABA-B receptor [1]. Withdrawal symptoms can develop fast, become severe and can be long-lasting. The symptoms occur 4-8 h after abstinence and can last for up to 21 days. Withdrawal symptoms consist of anxiety, tremor, confusion, aggression, disorientation, agitation, hallucinations and autonomic dysfunction such as tachycardia, restlessness, insomnia, hypertension, sweating and vomiting.

In severe cases, they can ultimately lead to delirium, psychosis, rhabdomyolysisand seizures [1,5]. This may lead to an admission at the ED.

The treatment of GHB withdrawal is primarily supportive, with administration of sedatives to control agitation, injury, delirium, hyperthermia, and seizures. Benzodiazepines, which are GABA-A receptor agonists, appear to be the treatment of choice [5]. The need for high doses is readily explained by the fact that cross-tolerance is not complete, because the lack of action of these drugs on the GABA-B receptor [2]. The use of benzodiazepines can result in a sedative state needing monitoring and induce risks such as benzodiazepine tolerance, dependency and addiction. These arguments induce the search for an additional treatment. Antipsychotic agents are not indicated as they lower the seizure threshold. There is also no evidence that anticonvulsant drugs are effective in the treatment of GHB withdrawal [1].

Recent publications suggest the use of baclofen, a GABA-B receptor agonist [2,3]. Baclofen is available as oral and intrathecal formulations. It has a good absorption after oral administration (75%) and has a half-life of 2 to 6 h [3,6]. It has already been used as off-label therapy for alcohol withdrawal syndrome (AWS) [7]. A recent study even suggests the potential use of intravenous (IV) baclofen [6]. Baclofen appears to reduce abuse and dependency of GHB due to modulation of the GABA-B receptor, and might exert an inhibitory action on the dopamine neurons. Adding a daily dose of baclofen to a symptom triggered regime of benzodiazepines reduced significantly the need for high doses of benzodiazepines in the treatment of AWS, without producing obvious side effects [7]. In an ED setting, IV off-label use could be an option as oral administration is often impossible in these cases and rapid onset is mandatory, but is it safe?

One animal study describes IV use and no toxicity was described [8]. However, limited animal and human data are available. One study demonstrated that IV baclofen in a bolus dose of 3 up to 5 mg was well tolerated [6]. Based on the absence of toxic effects of high doses baclofen with intrathecal use, taken into account the physio-chemical aspects of the solution for intrathecal use, the need for medical treatment, and no other therapeutic options, we decided to administer baclofen intravenously [9]. Considering the risk of baclofen overdose, we choose an arbitrary but conservative dose in the first patient, and an incremental dose in the second and third patient. First a loading dose was given to achieve a potential therapeutic level followed by a continuous infusion to maintain a steady state. In addition, we observed a low need of additional doses of benzodiazepines. Duration of GHB withdrawal has been described between 5 and 12 days [5]. In our experience, such highly addicted patients need at least 2 to 3 days of admission to get adequate symptomatic control. With the addition of baclofen, the GHB withdrawal syndrome is shorter and better controlled.

Conclusion

This case series suggests the benefit of intravenous baclofen as additive to the standard benzodiazepine treatment for a GHB withdrawal syndrome in order to limit life-threatening symptoms, to reduce the total amount of benzodiazepines needed and to shorten the length of stay in an observational unit with monitoring facilities. A reduction of abuse and dependency of GHB due to modulation of the GABA-B receptor was noted. Further trials are needed to confirm our findings and a dose finding study is needed to provide more information on the appropriate dose of IV baclofen within safe limits.

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