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Baclofen and Gamma-Hydroxybutyrate Withdrawal

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Abstract

Introduction—Benzodiazepine treatment of life-threatening gamma-hydroxybutyrate (GHB) withdrawal is frequently unsatisfactory. Animal studies suggest strongly that treatment with $GABA_B$ agonists, such as baclofen, will be a more effective strategy.

Methods—A case report from the medical intensive care unit (ICU) of the university tertiary care hospital.

Results—A 61-year-old woman was admitted to the medical ICU for severe withdrawal symptoms from chronic GHB use. This manifested as delirium, tremor, and seizures despite only small decreases in GHB dose and treatment with benzodiazepines. The addition of baclofen allowed the rapid sequential decreases in the GHB dose without seizure or delirium and resulted in long-term improvement of her tremor.

Conclusions—Baclofen, a $GABA_B$ agonist, may be a useful agent in the treatment of severe GHB withdrawal.

Keywords

Gamma-hydroxybutyrate dependence; Baclofen; Intention tremor

Introduction

Gamma-hydroxybutyrate (GHB) is a popular drug of abuse used for its euphoric, anabolic, sedative, and amnestic properties [1]. A low therapeutic index and common use have led to it being a significant cause of drug-induced coma [2], observed in association with bradycardia, myoclonus, and respiratory depression [3]. Furthermore, GHB is now prescribed for the treatment of cataplexy in patients with narcolepsy [4], for excessive daytime sleepiness [5], as a treatment for alcohol withdrawal [6] and is also being tested for the treatment of fibromyalgia [7].

Gamma-hydroxybutyrate is a short-chain fatty acid that is an endogenous precursor and metabolite of gamma-aminobutyric acid (GABA). It acts in the central nervous system at two G-protein-coupled receptors, the $GABA_B$ receptor, and the GHB receptor [3]. Addiction to GHB develops rapidly in patients using it regularly [8–10]. Cessation of GHB may be life-threatening and results in tremor, tachycardia, insomnia, anxiety, delirium, hypertension, coma, or death [10]. Difficulty with the detection of the metabolites and the similarity of the clinical features to alcohol and benzodiazepine withdrawal mean that it may be under-recognized in intensive care unit (ICU) patients [11]. The severity of the associated symptoms led to recommendations that elective withdrawal occur in ICUs [12]. Case reports have described the use of $GABA_A$ agonists such as benzodiazepines [11,13]. However, this approach requires

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prolonged intensive monitoring and is fraught with complications [13]. Lack of activation of $GABA_A$ receptors by GHB may explain why benzodiazepines are unsatisfactory [14]. In contrast, blocking the $GABA_B$ receptor was recently shown to trigger GHB withdrawal in primates [15] indicating a $GABA_B$ agonist could be a more specific treatment for GHB withdrawal. In this report, we describe the successful treatment of a patient with severe GHB withdrawal symptoms using the $GABA_B$ receptor agonist, baclofen.

Case History

A 61-year-old woman was transferred to the ICU from the psychiatric unit following two tonic-clonic seizures during the monitored detoxification from GHB. She was first prescribed GHB 18 months earlier for insomnia, but the dose and frequency were steadily increased to ameliorate anxiety and improve sleep. During this time she developed a severe GHB-sensitive tremor that prevented her from eating or dressing independently. Prior to hospital admission she was taking 4 g GHB every 3 h and an additional 1 g every 3 h as needed in order to avoid severe tremor and delirium. She was admitted to our hospital for elective withdrawal of GHB. Initially, GHB was prescribed 6 g every 4 h to match her previous daily dose and lorazepam was increased to 2 mg every 2 h as needed for anxiety. All other medications were prescribed as per her outpatient regimen (see below). A 1-h delay in the administration of the GHB dose resulted in a witnessed tonic-clonic seizure. With the 4-h dosing regimen, she became confused and agitated in the hour before the next dose but improved with administration of GHB. After 24 h, the dose was reduced to 5 g every 4 h. This resulted in another tonic-clonic seizure within 30 min of the second dose. She was transferred to the ICU for closer monitoring.

Her past medical history included post-traumatic stress disorder, anxiety, hypertension, gastric bypass surgery, hypothyroidism, chronic fatigue syndrome, fibromyalgia, depression, tremor, and recent ankle fracture. There were no reports of previous seizures. Her outpatient medications included GHB 4 g every 3 h and 1 g every 3 h as needed, alprazolam 2 mg every 6 h, escitalopram 10 mg daily, gabapentin 900 mg every 6 h, liothyronine 25 mg daily, conjugated estrogen 0.625 mg daily, hydrochlorothiazide 25 mg daily, hydrocortisone 20 mg every am, 10 mg every pm, lisinopril 40 mg daily, oxycodone 10 mg every 6 h, lorazepam 1–2 mg twice daily, metoclopramide 10 mg thrice daily, paroxetine 50 mg daily, quetiapine 400 mg twice daily, warfarin 5 mg daily, medroxyprogesterone 10 mg daily.

On examination she was alert and oriented but had dysarthric speech and a coarse, severe tremor affecting her trunk and limbs. Attempts to perform tasks led to a large amplitude tremor involving the whole limb. Dysdiadochokinesia and dysmetria were present bilaterally but worse on the left. Her vitals signs were within normal limits. The examination was otherwise unremarkable.

An MRI of the brain demonstrated generalized age-related volume loss, but no tumor or evidence of demyelination.

Despite the use of benzodiazepines, the patient experienced withdrawal seizures. Upon admission to the ICU, we initiated baclofen at 5 mg every 8 h. Within hours her tremor and speech improved and she had no episodes of confusion. We steadily decreased the GHB dose while increasing the baclofen dose. Over the next 5 days, the GHB was tapered by reducing the dose by 25–50% per day. At 1 g of GHB every 4 h, baclofen was increased to 10 mg every 8 h. The following day the GHB was discontinued, but the baclofen was continued at 10 mg thrice daily. No further seizures were observed and there was a remarkable improvement of her tremor permitting her to perform independent activities of daily living. At 10 weeks, the patient reported that she had experienced no further seizures, tremor was minimal, she was taking baclofen 10 mg thrice daily, and she had not required GHB.

Conclusions

We report here the use of baclofen to facilitate the smooth, rapid transition from GHB in a patient with severe withdrawal symptoms. Despite receiving benzodiazepines, which are currently recommended to treat GHB withdrawal [13], the patient had seizures, delirium, and worsening of an intention tremor with modest reductions in the GHB dose. Introduction of low-dose baclofen led to resolution of the tremor and anxiety, and prevented further seizures during completion of the GHB withdrawal.

GHB and $GABA_B$

Originally manufactured as a GABA analog, GHB mediates its major effects as a $GABA_B$ agonist [16,17]. Endogenous GHB, which is both a GABA precursor and metabolite, also activates GHB receptors and increases endogenous GABA levels [18]. Release of GABA activates chloride channels [19,20] and $GABA_B$ receptors, but the GHB-modulated GABA has been proposed to have only the latter action [18]. The activation of $GABA_B$ receptors by GHB has been supported by multiple studies. Cruz et al. [21] demonstrated that GHB showed a similar pattern of $GABA_B$ receptor activation in rats as baclofen, albeit at higher concentrations because of its low receptor affinity. After GHB or gamma-butyrolactone (a GHB precursor) application, $GABA_B$ receptor deficient mice did not show the behavioral or electroencephalogram changes seen in wild-type mice. This suggests that all the effects of GHB studied were $GABA_B$ receptor dependent [22]. Furthermore, chronic administration of GHB caused cross-tolerance to baclofen, but not to flunitrazepam (a $GABA_A$ agonist) [23]. Similarly, withdrawal from GHB has been shown to be a $GABA_B$-mediated effect in primates [15]. These data all point to baclofen being effective at replicating many effects of GHB, and thus being a putative treatment for GHB withdrawal.

GHB Withdrawal may have Significant Morbidity

Gamma-hydroxybutyrate quickly produces addiction and physical dependence at higher doses and can produce severe withdrawal symptoms after only short-term use [24]. Much like alcohol withdrawal, GHB withdrawal symptoms are serious and include tachycardia, hallucinations, and coma [13]. Seizures have been reported rarely [11,25] as part of the GHB withdrawal syndrome but are well recognized in animal-based studies of GHB withdrawal [26]. Seizures were a major manifestation of GHB reduction in our patient, and should probably be recognized as part of the GHB withdrawal syndrome.

GHB Withdrawal Management

In a recent review of GHB withdrawal, benzodiazepines were the most common agents employed, often in combination with other drugs [13]. For our patient, benzodiazepine dose was increased during GHB tapering but seizures were still observed. Despite their common use in this setting, benzodiazepines have limited efficacy that has been attributed to the lack of action of these drugs on $GABA_B$ receptors [27]. Only when the $GABA_B$ receptor agonist baclofen was added in modest doses, did we gain control over her seizures. Baclofen has a favorable side effect profile compared with GHB at the doses required to relieve severe withdrawal symptoms, and baclofen withdrawal is usually only seen with abrupt discontinuation of the intrathecal form [28].

Therapeutic and recreational use of GHB can lead to dependence. The withdrawal syndrome may be difficult to diagnose in the ICU because of similarities with delirium tremens. Seizure may be an important feature of the withdrawal syndrome. Baclofen, a $GABA_B$ agonist, may be a useful agent in the treatment of severe GHB withdrawal and further research is warranted.

List of Abbreviations

g, Grams; GABA, Gamma-aminobutyric acid; GHB, Gamma-hydroxybutyrate; h, Hours; ICU, Intensive care unit; mg, Milligrams.

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