Sodium Oxybate for Narcolepsy: Explaining Untoward Effects and Recommending New Approaches in Light of Prevailing Receptor Pharmacology

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Abstract

Objective: Gamma-hydroxybutyrate (GHB) has been an abused and illicit substance for decades, but the antinarcotic medication Xyrem (sodium oxybate), the sodium salt of GHB, was approved just in 2002 for increasing wakefulness. We present a case of coma induced by co-ingestion of prescription GHB and ethanol and describe the response to naloxone treatment, by first responders, without evidence of opiate exposure. The purpose of this report is to bridge updated knowledge on GHB and ethanol pharmacology with the clinical sequence of events in a patient co-ingesting these compounds and to theorize on a potentially better pharmacological approach to narcolepsy. **Case Summary:** The patient was a 25-year-old woman with a history of narcolepsy. She suddenly collapsed at home but became transiently responsive after being administered naloxone in the ambulance. She presented to the emergency department with apnea, poor responsiveness with a Glasgow Coma Score of 7, and urinary incontinence. While undergoing intubation, the patient spontaneously and abruptly awoke. Labs were unremarkable except a blood alcohol concentration of 0.123%. The dosage of, and adherence to, GHB was unknown in this case. **Discussion:** The case is described in light of the most recent pharmacological advancements on these co-ingestants. A conceptual dose–response curve is shown to facilitate understanding of the complex pharmacology of GHB. **Conclusions:** Approved and potential alternatives to GHB, for achieving wakefulness, are discussed. Potential new strategies should bear low to no risk of coma with accidental overdose or co-ingestion of ethanol. In addition, promising antidotes for future consideration are discussed.

Keywords

oxybate, Xyrem, gamma-hydroxybutyrate, GHB, narcolepsy, toxicology, naloxone

Gamma-hydroxybutyric acid (GHB) is notorious for its illicit use. The medication sodium oxybate (Xyrem) is the sodium salt of GHB. Thus, the following text will use GHB to refer to either GHB or sodium oxybate. GHB can induce biphasic and contrasting symptoms that are concentration dependent and directly related to its pharmacology. It is produced endogenously¹ and binds to the GHB receptor^{2,3} and some GABA receptor subtypes.^{4,5} It activates GABA_A, GABA_B, and GHB receptors in several brain regions, with higher affinity for GHB receptors.⁵ At low concentrations, a predominant GHB receptor activity induces wakefulness, whereas at high concentrations, the sedating GABA_A and GABA_B effect overrides the excitation, producing the classic obtundation.⁵ GHB is indicated for the treatment of narcolepsy. Specifically, it is taken at night, and initiated at 4.5

g divided into 2 equal doses: one at bedtime and one 2.5 to 4 hours later.⁶ This regimen rapidly induces somnolence, but is proven to enhance wakefulness during the day.⁶ When ethanol is consumed by a patient taking GHB, the threshold for inducing coma can be severely lowered. The following case exemplifies this concept and also illustrates the

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Table 1. Physical Assessment.

Vital signs	Temperature: 96.4; pulse: 74; blood pressure: 118/68, resp. rate: 10 ; O ₂ saturation: 98% RA
General assessment	Poorly responsive, incontinent of urine
Head, ears, eyes, nose, throat (HEENT)	Pupils equal, round, reactive to light; laceration to upper lip; dried blood in nares
Neck	C-collar
Heart	Regular rate and rhythm, +S1, S2, no m/r/g
Lungs	Clear to auscultation bilaterally, periods of apnea , breathes w/painful stimuli
Abdomen	Soft, positive bowel sounds, NT/ND
Extremities	No edema, pulses equal throughout
Neurological	Glasgow Coma Score 7, does not open eyes , groans w/painful stimuli, withdraws w/painful stimuli
Skin	No rash, warm, dry

Note. Boldface text indicates abnormalities.

phenomenon of increased wakefulness once GHB falls below a threshold concentration. A mechanistic explanation for the observed clinical course is presented in the discussion. A conceptual dose–response relationship is presented based on current receptor pharmacology and observed clinical effects of GHB. Approved and potential alternative options for treating narcolepsy are presented. These agents may circumvent the risk of coma with overdose or concomitant alcohol exposure.

Case Presentation

A 25-year-old woman with a history of narcolepsy was brought into the emergency department (ED) poorly responsive. Prior to presenting, the patient was sitting at the dinner table with her father when she suddenly collapsed, hit her head on the table, and became unresponsive. The emergency medical services team administered 2 mg of naloxone per protocol after which the patient became tachycardic and combative. The patient had a normal prehospital blood glucose reading. On arrival in the ED the patient again became poorly responsive, apneic, and incontinent of urine (Table 1). The ED team began preparations for intubation when interrupted by the patient's boyfriend. The boyfriend indicated that the patient's father made her take the medication (drug identity not revealed at the time) despite knowing that she has responded with untoward symptoms in the past. However, the boyfriend did not elaborate on the nature of the past undesirable symptoms. He denied that the patient had a history of drug or alcohol abuse, or any suicidal ideations/attempts. The patient exhibited several abnormalities on physical assessment. She was poorly responsive with a

Glasgow Coma Score of 7. She was apneic and unresponsive unless receiving painful central or peripheral stimuli, that is, sternal rub or pressure to the lunulae of her finger/toenails. Routine labs were normal with the exception of a blood ethanol concentration of 0.123%. Urine was negative for opiates. Head and cervical spine computed tomography and chest X-ray were unremarkable. As intubation was underway the patient awoke spontaneously with the ability to follow commands. She reported taking Xyrem for narcolepsy. She administered a dose (undisclosed amount) prior to dinner, but specific timing was not provided. She reported having a few glasses of wine with dinner, but an accurate quantity was not provided in the history. In addition, her degree of adherence to the prescribed GHB regimen was not disclosed, but subjective assessment suggested that she took it sporadically. She indicated that she was not taking any medications other than GHB.

Discussion

An understanding of the pharmacological basis for the biphasic response to GHB is essential for designing both safer therapeutic agents for narcoleptic disorders and antidotes for intoxication. The time course of symptoms and response to naloxone in this case may be best explained with this mechanistic knowledge. That is, the past 40 years of research on GHB and its targets has revealed that GHB receptors exist that are distinct from GABA receptors.^{2,3} These GHB receptors are high-affinity and excitatory,³ thus promoting alertness. High-affinity GABA_A receptor subtypes may also be activated with low concentrations of GHB,⁴ which would be expected to be inhibitory. However, it is apparent that at such low GHB concentrations excitation predominates via the GHB receptor.⁵ However, with GHB's recommended dosage regimen at night it is clear that its concentration rises to a level that activates additional, low-affinity, GABA_A and GABA_B receptors.^{5,7} These receptors are inhibitory, promoting somnolence. When inhibitory GHB stimuli overcome excitatory inputs, obtundation, and perhaps loss of consciousness, is observed in a patient. Whether GHB, when used as recommended, promotes daytime wakefulness because of more productive sleep, or because of the low-concentration-induced excitation produced by GHB during the day, or both, is unknown. We consider the latter a potential contributing factor, as the half-life of GHB is 40 minutes.⁸ That is, when taken as directed, patients will administer a second dose of GHB approximately 4 hours after falling asleep. The GHB plasma concentration can plausibly reach the level required for wakefulness within 4 hours after the second dose (more than 5 half-lives).

Ethanol is a positive allosteric modulator of GABA_A receptors,⁹ and when consumed with GHB the combination produces synergistically greater levels of central nervous

Figure 1. Current knowledge of γ -hydroxybutyrate (GHB) targets and theoretical dose–response relationship.

(A) GHB receptor targets in the central nervous system. GHB activates GHB receptors to increase glutamate release from neurons. GHB also activates inhibitory receptors, GABA_A and GABA_B. Ethanol activates GABA_A receptors to enhance the overall inhibitory potential in the neuron. (B) GHB exhibits a dose-dependent biphasic effect on clinical symptoms as a result of its receptor targeting. At low concentrations GHB has a predominant excitatory effect from GHB receptor activation. At higher concentrations, that is, micromolar to millimolar, GHB begins to activate low-affinity inhibitory receptors (GABA_A and GABA_B). Thus, toxicity equates to loss of consciousness. Whether enhanced daytime wakefulness from taking GHB at night is a result of more productive sleep or GHB-induced stimulation at low concentrations experienced in the morning, or both, is unknown. Ethanol allosterically raises the inhibitory GABA_A activity, thus reducing the threshold for coma via GHB.

system depression. Naloxone, although an opioid receptor antagonist, is also known to inhibit these same GABA receptors.¹⁰ This may explain the transient gain of consciousness of the patient prior to presenting to the ED. An alternative possibility, perhaps acting in parallel with ethanol inhibition, is that naloxone may be blocking endogenous opioids. This hypothesis is supported by the observation that GHB can upregulate mRNA of endogenous enkephalin precursors.¹¹ The abrupt gain of consciousness of this patient in the ED likely reflects the reduction of GHB concentrations to below the threshold for obtundation, and within the window for wakefulness (Figure 1). Other case

studies have also reported respiratory depression in cases of GHB toxicity.¹² This effect is mediated primarily by GHB agonism at GABA_B receptors.¹³ Alone, GHB produces only mild respiratory depression as it affords for a compensatory increase in tidal volume; however, this normally observed compensatory mechanism is lost on ingestion of ethanol,¹³ which may explain this patient's observed periods of apnea.

It may be of great interest to practitioners that specific agonists of the excitatory GHB receptor have been reported.³ Unlike GHB, these congeners do not interact with GABA receptors, thus raising the possibility that the risk of obtundation will be lower or nonexistent with such agents. That

is, in theory, specific excitatory GHB receptor agonists can be used in the morning to achieve the daytime wakefulness observed with GHB without the risk of coma. Noncompliant patients, particularly those consuming alcohol, may be protected to some extent by employing such a specific agent. Moreover, patients with daytime sleepiness but relatively productive nighttime sleep may benefit more from a daytime-exclusive mechanism of action.

An approved alternative treatment to GHB for narcolepsy that has stronger evidence for improving patient outcomes is modafinil. In addition to providing efficacy through reduced daytime sleepiness and reduced sleep latency, modafinil has high-quality evidence showing that it improves quality-of-life measures.¹⁴ Overall, GHB does not possess the robust body of patient-oriented evidence that modafinil does for narcolepsy treatment. Unlike GHB, modafinil functions through diverse, partially sympathomimetic-like (but poorly elucidated), pathways—interacting with norepinephrine, serotonin, dopamine, GABA, adenosine, histamine, melatonin, and benzodiazepine receptors.¹⁵ The prescribing information cautions against the use of ethanol with modafinil; however, given the multiple sites of activity, and the seemingly predominant stimulatory effect, it is unlikely that modafinil would produce the dramatic synergism with ethanol observed in this case. Although modafinil is typically the initial agent used for treating narcolepsy, it is unknown if the patient had failed this therapy prior to being prescribed GHB. Potential for continued ethanol consumption should be part of the clinical risk–benefit analysis when deciding on narcolepsy treatment.

Regardless of pharmacotherapy for narcolepsy, a need exists for antidotes to reverse GHB intoxication. Morse and Morris recently recognized this need in their report on toxicokinetics and toxicodynamics of GHB.¹³ As an alternative to GHB receptor activation, the authors proposed antagonizing the GABA_B receptor for a pharmacodynamic reversal, or inhibiting the renal reabsorptive monocarboxylate transporter to increase clearance of GHB. Morse and Morris showed that both strategies are effective in rats.¹³

Improved treatment of narcolepsy and reversal or avoidance of GHB toxicity appear to be realistic goals at this juncture. This case exemplifies the complex pharmacology of GHB with concomitant ethanol. In the interim, ethanol should undoubtedly continue to be strongly discouraged in patients taking GHB; however, alternatives with more evidence should be chosen, and more effective options can be developed in the near future using our detailed knowledge of this complex system.

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