Burst Suppression Electroencephalography (EEG) Pattern with Coma and Loss of Brain Stem Reflexes Following a Baclofen Overdose with Subsequent Full Recovery

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Financial support: None declared

Conflict of interest: None declared

Patient: Female, 37-year-old

Final Diagnosis: Baclofen toxicity

Symptoms: Coma

Medication: —

Clinical Procedure: None

Specialty: Neurology

Objective: Unusual clinical course

Background: When taken in overdose, baclofen can produce a unique pattern of clinical findings and EEG abnormalities that contrasts to that seen with other sedative hypnotic medications. This includes profound lethargy and coma, loss of basic brainstem reflexes and pupil reactivity, myoclonic jerks and seizures, and a burst suppression pattern on EEG. In the absence of a clear history of ingestion, clinicians may presume the presence of anoxic brain injury and that a progression towards brain death may be imminent.

Case Report: We report a case of a middle-aged woman found unresponsive who presented with apnea, loss of rudimentary neurologic findings on physical exam, burst suppression EEG findings, and a prolonged comatose state for nearly 48 h, followed by rapid resolution of symptoms secondary to a supratherapeutic baclofen ingestion.

Conclusions: Baclofen toxicity can present both clinically and with EEG abnormalities consistent with anoxic brain injury, suggesting an inevitable progression to brain death. When provided with appropriate supportive care and prolonged observation, improvement with full neurologic recovery is often seen despite the initial grim clinical picture.

Keywords: Baclofen • Brain Death • Seizures

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936280

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Background

A rapid decline in mental status occurring in a previously healthy individual presents clinicians with a diagnostic challenge. While the differential is broad, toxicological causes are not uncommon. Significant sedation is common following overdose of many substances, although a thorough physical examination and neurologic assessment will typically identify preservation of very basic neurologic function and, often, maintenance of higher degrees of cortical functioning [1]. In their absence, an alternative diagnosis, including the possibility of anoxic brain injury occurring in relationship to medication or substance misuse, will often be considered. We present the case of a patient with large-volume baclofen ingestion with presenting features highly suggestive of anoxic brain injury and imminent progression to brain death that made a rapid and full recovery.

Case Report

A woman in her late 30s presented after being found unresponsive in her garage approximately 2 h after last being seen normal. Pre-hospital medical providers found the patient completely unresponsive to verbal and physical stimuli, with minimal respiratory effort and a cyanotic appearance. Her pulse was described as faint. Administration of 4 mg of intravenous naltrexone was without response. No combustible devices were noted to be operated in this enclosed space. Emergency medical service (EMS) providers designated her a Level 1 acuity for respiratory distress using the 5-tiered Emergency Severity Index, as is common-place in the United States, where this patient resided. Family contact was initiated a short time later, who reported a history of ADHD and peripheral neuropathy, but she was otherwise healthy. She had been in a normal state of health just 2 h prior to being found in the garage. She had no history of depression or misuse of her prescribed medications or other substances. She smoked 1 pack of cigarettes per day and was currently taking only amitriptyline and modafinil. She had a more distant history of back pain issues for which she previously took baclofen, but it was not believed she was currently taking this medication.

Upon Emergency Department (ED) arrival, the patient was noted to be without respiratory effort, her skin was cool and dry, and her pupils were dilated to 6 mm and non-reactive. A brief neurologic exam demonstrated absent verbal response, eye opening, or extremity movement despite the application of painful stimuli. The patient had no appreciable gag reflex. There were no signs of trauma and the remainder of the exam was grossly unremarkable, with a limited neurologic exam performed. Initial vital signs included a blood pressure of 98/58 mmHg, pulse of 68 beats per minute, rectal temperature of 33.7°C (92.6°F), and a room air pulse oximetry of 82%. Following the unsuccessful administration of an additional 6 mg of naltrexone, the patient was subsequently intubated without sedation.

The patient’s ED course included both a negative computed tomography (CT) scan without contrast of the head and a negative CT angiogram of the neck and brain. Laboratory studies included an unremarkable complete blood cell count, electrolyte, and hepatic panel except for a potassium of 3.1 mEq/L, a serum HCO₃⁻ of 21 mEq/L, and an anion gap of 14. Other noteworthy laboratory studies included a lactic acid level of 2.4 mmol/L, CPK of 28 mcg/L, acetaminophen and salicylate levels <10 mcg/mL, serum ethanol level of 82 mg/dL, carboxyhemoglobin level of 10.2%, procalcitonin <0.02 ng/mL, and a 12-item urine drug screen positive solely for tricyclic antidepressants. An ECG showed a sinus rhythm of 88 beats per minute, a QRS interval of 80 msec, and a QT interval of 460 msec. Serum amitriptyline levels were not measured given a low suspicion provided the absence of tachycardia and QRS prolongation. Approximately 2.5 h after arrival, spontaneous respirations were assessed with no respiratory efforts noted despite 45 s without ventilations provided. The patient had not received sedation at any time while intubated in the ED or during the first 7 h of hospitalization.

Her hospital course was remarkable for a rapid improvement in her body temperature to normal over the initial 6 h, as well as continued normal or near-normal vital signs throughout her hospital stay. Between 7 and 10 h following initial presentation, 2 episodes of head arching and bilateral rhythmic upper-extremity extension lasting approximately 45 s, with a third similar episode that progressed to a full-body generalized tonic-clonic seizure were observed. The patient was treated with a bolus and then infusion of propofol in addition to 2 g of levetiracetam. The propofol was stopped shortly after the levetiracetam load was completed.

An electroencephalography (EEG) obtained 12 h after hospital admission without external stimuli showed evidence of a burst suppression pattern as well as profound encephalopathy concerning for hypoxic-ischemic encephalopathy. Neurologic consultation obtained during day 1 and 2 of hospitalization following a prolonged period in which minimal-to-no sedation had been provided identified both absent corneal reflexes and negative cold caloric testing. With the patient off all sedation at approximately 36 h after initial arrival, she remained intubated with no generation of spontaneous respiratory effort or extremity movement despite aggressive stimulation.

Approximately 48 h after initial presentation, the patient began to breathe over the ventilator with eye opening and purposeful movements followed by extubation 8 h later. She had returned to her baseline mental status approximately 72 h
after hospital arrival. At this time, she reported the ingestion of a large, yet difficult-to-quantify, number of baclofen tablets that she had previously been prescribed, which she took due to the numerous life stressors she was experiencing. She was discharged 6 days after her initial hospital presentation.

**Discussion**

Baclofen is a gamma-aminobutyric acid (GABA) derivative, unique among medications utilized as muscle relaxants in its function as a agonist on the GABA-B receptor. At therapeutic levels, effects occur at the level of the spinal cord, with supra-therapeutic dosages acting as a potent generalized central nervous system depressant. GABA-B receptors are G protein-coupled receptors found at both the presynaptic and postsynaptic interface. Baclofen acts post-synaptically by increasing potassium efflux, leading to cell membrane hyperpolarization, producing the sought-after muscle-relaxant effects. Presynaptically, baclofen’s action at the GABA-B receptors leads to decreasing calcium influx and a resultant decrease in both inhibitory neurotransmitter GABA and excitatory neurotransmitter glutamate release. While the primary effect is a reduction in postsynaptic membrane depolarization, inhibition of further presynaptic GABA release is postulated to result in the occurrence of myoclonic jerks and seizures that may be seen following baclofen overdose [2].

Taken in overdose, the clinical effects of baclofen are typically that of profound sedation, muscular hypotonia, and areflexia, with full flaccid paralysis and respiratory failure requiring mechanical ventilation occurring in severe cases. A similar pattern can be seen with other sedative hypnotic ingestions such as opioids and benzodiazepines. Consideration should be given to large-dose naloxone administration, given the frequency in which both short- and long-acting opioids are misused and can present in a very similar manner. Patients who have ingested large quantities of baclofen are often mildly-to-moderately hypothermic, with autonomic disturbance common, including bradycardia more commonly than tachycardia, and both hypotension and hypertension have been reported [3,4]. Lack of pupillary reactivity is common, with pupils often noted to be mid-sized or dilated [5]. The use of routine drug screening will not detect baclofen given its unique chemical structure. While ascertaining specific baclofen levels can be used to confirm the diagnosis in patients in which a clear history is not available, this is unlikely to be readily available and therefore may not impact management decisions.

Baclofen produces a global encephalopathy and profound sedation similar to other sedative hypnotic substances. Baclofen is unique, however, in that generalized tonic-clonic seizures and myoclonic jerks are frequently reported, at times occurring unexpectedly in patients otherwise in a profoundly comatose state appearing with an essentially flaccid paralysis [6]. A series of 37 patients reported by Lee et al identified 59% as experiencing myoclonic or generalized tonic-clonic seizures in the setting of profound global encephalopathy [7]. Another series of 13 patients presenting with baclofen overdose of greater than 200 mg identified 3 patients with seizures occurring in the midst of a prolonged state of profound central nervous system depression [8].

The utilization of EEG when confronted with both severe mental status depression and seizure activity may provide some suggestion of baclofen toxicity in the appropriate clinical setting. Farhat et al identified 9 patients with a similar burst suppression pattern on EEG, of which 5 developed generalized tonic-clonic seizures following significant baclofen ingestions [5]. Our patient’s EEG findings and clinical presentation are consistent with these patients, demonstrating a similar triad of findings, including profound deep coma and absent brain stem reflexes, seizures and myoclonic jerks, and a burst suppression EEG pattern. Given the lack of specificity of this EEG finding, and with no alternative diagnosis, further observation with an understanding that prolonged sedation may occur prior to a dramatic improvement may be necessary should this be secondary to a baclofen ingestion. While the duration of sedation may vary, up to 5-7 days of essentially no signs of meaningful central nervous system activity have been reported prior to a rapid progression to full neurologic recovery [9].

Baclofen’s half-life when taken at therapeutic dosages in patients with normal renal function ranges from 4 to 6.5 h, but the persistence of prolonged symptoms highlights variation in drug half-lives that can occur following supratherapeutic ingestion [10,11]. The often-cited rule of observation for a period of time equal to 5 drug half-lives suggested as appropriate to eliminate the likelihood of medication related effects is problematic in light of evidence of medications such as baclofen possessing half-lives up to 34.6 h in the setting of large ingestions [12]. Prolonged respiratory support may be needed due to the lack of an effective reversal agent. The utilization of hemodialysis remains controversial, as supportive care, combined with short-acting benzodiazepines and propofol to treat seizures should they occur, and time, are effective options until drug elimination has occurred [13].

Our case demonstrates the unique features of prolonged coma following a baclofen overdose in a patient with a neurological examination concerning for possible anoxic brain injury. A review of 58 cases in which potential brain death was considered, identified baclofen as the most common cause (11 cases) among ingested substances [1]. Other, less commonly reported medications included bupropion, barbiturates, tricyclic antidepressants, lidocaine, and valproic acid, among others [1,14,15].
Professional organizations, including the American Academy of Neurology, the American College of Medical Toxicology, and the Society of Critical Care Medicine, agree on the importance of excluding drug intoxication or poisoning prior to determination of brain death [14]. An observation period of at least 72 h in patients appearing comatose, if not longer, in the setting of ingestions such as baclofen, would be appropriate prior to determining with a high level of certainty that meaningful recovery is unlikely. While brain death remains a diagnosis that may be performed by clinical means, the utilization of advance imaging such as CT angiogram or magnetic resonance angiography or nuclear brain flow studies should be considered if uncertainty exists about the reliability of components of the neurologic examination [16].

Conclusions

In the absence of a history suggesting baclofen ingestion, this diagnosis may be extremely challenging. Physical examination and clinical course are somewhat non-specific, but there is a well-described pattern of profound coma accompanied by depressed brainstem activity on examination and a burst suppression EEG pattern that may prompt the astute clinician to consider this diagnosis. Prolonged observation and consideration of this ingestion are important given the potential for full recovery, despite what may initially appear to be a very grim prognosis.

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