

Clinical Reasoning:

A 41-year-old comatose man with absent brainstem reflexes



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SECTION 1

A 41-year-old obese man was stopped by the police for driving erratically. He was confused, dysarthric, ataxic, and vomited repeatedly before collapsing and becoming rapidly obtunded, eventually requiring rapid sequence intubation (RSI). He arrived at the emergency department (ED) with a Glasgow Coma Scale score of 3, hypothermia (35.3°C), and hypotension (78/38 mm Hg), with a heart rate of 80. He was treated with warm IV fluid boluses and warming blanket. He was examined by the attending and resident neurologists approximately 2.5 hours from the time of RSI. He was mechanically ventilated but had received no sedation since intubation. Nothing was known about his medical history and no collateral information was available.

He did not respond to naloxone or thiamine. Clinical examination was performed with a temperature of 36°C and a blood pressure of 120/80 mm Hg. He remained mechanically ventilated without spontaneous respirations. No meningismus, external signs

of trauma, needle puncture marks, or tongue or buccal lacerations were observed. Spontaneous movements were absent. He did not open his eyes, grimace, withdraw, or posture to noxious stimuli (nailbed and supraorbital pressure). Neuromuscular blockade was excluded with a train of 4 twitches with maximal ulnar nerve stimulation. His pupils were fixed at 2 mm and unreactive to light. Corneal and oculoccephalic (vertical and horizontal) reflexes were absent. Irrigation of each ear canal with ice water produced no eye deviation. No gag or cough reflexes were elicited with posterior pharyngeal stimulation and tracheal suctioning respectively. His extremities were flaccid and areflexic. Babinski sign was absent. No gaze deviation, nystagmoid eye movements, facial twitching, or jerking movements were observed. Cardiovascular, lung, and abdominal examinations were unremarkable.

Questions for consideration:

1. How do you approach a comatose patient?
2. What are the differential diagnoses?

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SECTION 2

The comatose patient who presents to the ED is a challenge. The list of potential causes is vast and the clinician's approach must be systematic.

Once the airway, breathing, and circulatory status are secured, IV thiamine is given followed by glucose or dextrose since hypoglycemia is a common reversible cause of coma. In this patient, capillary blood glucose was 125 mg/dL. IV naloxone is given empirically as an antidote for possible opioid toxicity.

Metabolic causes of coma are a very important consideration. Electrolyte derangements (sodium, calcium, magnesium), hypoglycemia or hyperglycemia, acid-base disorders, severe hypothyroidism, hypoadrenalism, hypoxia, hepatic failure, uremia, and hypercarbia should be considered.

Illicit drugs, medication overdosage (accidental or intentional), certain toxins, and alcohol deserve noteworthy attention. Major offenders include narcotics, benzodiazepines, lithium, antipsychotics, salicylates, antiepileptic medications, heroin, cocaine, inhaled solvents, methanol, ethylene glycol, and carbon monoxide.

Infectious causes (encephalitis, meningitis, sepsis, neurosyphilis, and HIV-related infections) and increased intracranial pressure should be considered. Coma may result from trauma leading to intracranial

hemorrhage or diffuse axonal injury. Ischemic or hemorrhagic strokes (especially those involving the posterior circulation, including the top of the basilar syndrome) are important causes. Unresponsive states may be due to postictal states or nonconvulsive status epilepticus.

Given the aforementioned differential diagnoses, laboratory tests included complete blood count, electrolytes, urea, creatinine, liver enzymes, coagulation profile, arterial blood gas, lactate, ammonia, troponin, thyroid stimulating hormone, vitamin B12, blood alcohol level, HIV, syphilis serology, C-reactive protein, erythrocyte sedimentation rate, blood cultures, and urinalysis. These were within normal limits. CSF analysis for cell count, protein, glucose, Gram staining, cultures, and herpes simplex virus PCR were unremarkable. Blood and urine toxicology screen were negative for benzodiazepines, cocaine, phencyclidine, cannabinoids, methamphetamine, opiates, tricyclic antidepressants, salicylates, and acetaminophen. EKG and CT head were normal. Brain MRI was not performed due to metallic hardware in the cervical spine visualized on radiography.

Questions for consideration:

1. What was the cause of coma in this patient?
2. Is this clinical picture compatible with brain death?

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SECTION 3

Despite the absence of pupillary light, corneal, oculocephalic, vestibulo-ocular, pharyngeal, and tracheal reflexes, the patient's examination did not meet the current American Academy of Neurology guidelines¹ for brain death in adults. Firstly, the constricted pupils were suggestive of drug toxicity¹; secondly, there was no identifiable cause of the profound coma. We therefore did not proceed with apnea testing but elected to institute supportive care while searching for a cause of the coma.

No CNS-depressant drugs were administered or detected on routine toxicology screening. Severe electrolyte, acid-base, or endocrine abnormalities were absent. Head and neck CT angiogram (CTA) revealed normal flow. Empiric acyclovir and antibiotics were started. As he did not appear to be nonconvulsive status epilepticus, an EEG was not performed at the time of presentation. About 10 hours later, he regained spontaneous movement and respirations. He was agitated, hypertensive, tachycardic, and diaphoretic. Tone was normal but diffuse hyperreflexia and prominent fasciculations in his leg muscles were noted. EEG at this time showed generalized theta slowing with reactivity.

We contacted the patient's recently divorced wife, who believed he was taking baclofen, duloxetine, and desvenlafaxine, and had been very depressed and distraught lately. With this information, a presumptive diagnosis of intentional baclofen overdose was made. Delirium, hyperreflexia, fasciculations, and autonomic changes were attributed to acute baclofen withdrawal. Serotonin syndrome was a possible differential diagnosis.

He received meticulous supportive care. Lorazepam and haloperidol were used to control agitation. Baclofen 5 mg 3 times daily was started to treat acute baclofen withdrawal. Cyproheptadine was given to treat possible serotonin syndrome.

He recovered completely by day 5 of hospitalization. He was alert, attentive, and oriented. His vital signs were stable. His reflexes were normal and fasciculations resolved. He admitted to attempting suicide by ingesting at least 600 mg of baclofen. He denied taking other drugs. He was transferred to the medical ward and later, for psychiatric care.

Although measurement of blood baclofen levels were unavailable at our institution, his medical history and clinical course pointed to a diagnosis of intentional baclofen overdose.

DISCUSSION

Baclofen [4-amino-3-(4-chlorophenyl)-butanoic acid] is a lipophilic derivative of γ -aminobutyric acid (GABA), one of the primary inhibitory neurotransmitters of the CNS, and acts by agonism of the GABA_B receptors of

the spinal cord.² The recommended regimen for adults is 5 mg 3 times daily and may be increased to a maximum dose of 80 mg per day.

Baclofen toxicity can occur in the setting of oral ingestion or intrathecal administration. Reports of toxicity are predominantly single case reports with one report of 14 adolescents overdosing in a single event.² One study³ consisted of a retrospective review of prospectively collected data on 23 cases of baclofen overdose.

Overdose presents with nausea, ataxia, and agitation followed by profound coma with flaccid areflexia and respiratory depression.⁴⁻⁶ Other manifestations include absent brainstem reflexes, hypotension, bradycardia, tachycardia, hypothermia, hypersalivation, and supraventricular tachycardia.^{2-4,6-8} Miosis is more common than mydriasis^{2,6,7} and pupil reactivity is typically lost.⁵ Ventilatory support (mean length of 40 hours²) is often required, particularly when ingestion exceeds 200 mg.³ Seizures may be related to baclofen toxicity or withdrawal.⁵ Myoclonus (epileptic or encephalopathic in origin) has been reported.⁷

The most common EEG findings in baclofen toxicity are burst suppression^{4,8} and nonspecific diffuse slowing⁹ but other EEG patterns have been reported as well.⁸ Laboratory abnormalities include transient elevation of hepatic enzymes, hyperglycemia, and leukocytosis.⁵

In most settings, measurement of serum baclofen levels is not readily available. Furthermore, animal experiments indicate that the apparent rate of baclofen elimination from nervous tissue is slower than from serum,⁴ which may explain the prolonged neurologic manifestations following overdose despite normal or negligible serum levels.² There is no antidote for toxicity and therefore, treatment is supportive therapy. Coma may occur rapidly but with supportive care, full neurologic recovery can be expected, provided no cerebral hypoxic-ischemic insult occurred.^{4,5}

Though recommended, gastric lavage and activated charcoal may be of little use given the rapid absorption of baclofen from the alimentary tract.⁷ Atropine,^{2,5} physostigmine,^{2,4} flumazenil,⁴ ondansetron,⁵ and hemodialysis⁶ have been used but none are supported by controlled studies. Baclofen withdrawal syndrome may occur in patients on chronic therapy and is typically more severe in intrathecal baclofen therapy. Manifestations include pruritus, seizures, myoclonus, delirium, psychosis, diplopia, dyskinesias, rebound spasticity, autonomic instability, and hyperthermia. In severe cases, rhabdomyolysis, renal failure, multisystem organ failure, and death may occur.^{6,8,9}

This case underscores the importance of meeting all the prerequisites of the AAN practice guidelines for determining brain death. Apart from excluding

hypotension, hypothermia, and severe acid-base, electrolyte, or endocrine abnormalities, it is important to identify the cause of the coma either by neuroimaging or laboratory studies.¹ This case illustrates how certain CNS-suppressing drugs that cannot be readily tested for, like baclofen, may induce a coma mimicking brain death. It may be argued that confirmatory tests like CTA and EEG would exclude the diagnosis of brain death in such cases, but it is imperative to remember these studies can produce false-negative results.¹⁰ In coma with absent brainstem reflexes, the clinical determination of brain death should not be made if the cause of the coma remains unidentified. We emphasize the importance of elucidating the cause of profound coma prior to the consideration of formal brain death declaration.

AUTHOR CONTRIBUTIONS

Dr. Beh was involved in drafting and revision of the manuscript. Drs. Vernino and Warnack were involved in revision of the manuscript.

DISCLOSURE

Dr. Beh reports no disclosures. Dr. Vernino has served on a scientific advisory board and as consultant for Athena Diagnostics, Inc.; serves as an Associate Editor for *Clinical Autonomic Research* and on the editorial board of *Archives of Neurology*; receives/has received research support from Chelsea Therapeutics, the NIH/NINDS, and the US Department of Veterans Affairs; and receives license fee payments from Athena Diagnostics, Inc. for technology re: Antigen material for antibody testing. Dr. Warnack reports no disclosures.

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