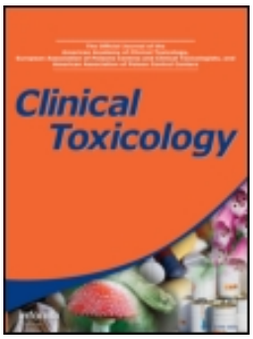

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BRIEF COMMUNICATION

Baclofen overdose mimicking brain death

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Abstract

Context. Brain death guidelines should be used with caution in patients with drug intoxication. It is often suggested that physicians use five half-lives of a drug when observing a patient with an overdose. We report two cases of baclofen intoxication where brain death was entertained as an explanation for prolonged coma, with arousal seen days later, suggesting that routine use of a 5-half-life observation period is insufficient with baclofen intoxication. *Case presentation*. A 40-year-old woman was found unresponsive by her family. Baclofen was found to be the responsible overdose. The patient had absent brain stem reflexes and was intubated and in the ICU for several days. Although EEG and Apnea test were inconclusive, the patient was thought to be brain dead and organ procurement was arranged. On hospital day 5, the patient started having purposeful movements. The patient had progressive arousal and was eventually transferred without neurologic sequelae to psychiatry. The second patient also had a massive baclofen overdose, had absence of almost all brain stem reflexes and was also intubated and in the ICU. Brain death was felt to be imminent, but the patient began to awake on hospital day 7. *Discussion.* Our two cases suggest that baclofen intoxication may result in very prolonged and profound coma and may, in fact, mimic brain death. *Conclusion.* The determination of brain death in the comatose overdose patient must proceed with caution. An adequate period of time to allow drug clearance must be allowed.

Keywords Baclofen; Overdose; Brain death; Half-life; Suicide attempt

Introduction

Guidelines for the determination of brain death have been promulgated by the American Academy of Neurology.[1] These guidelines describe the process for determination of brain death in comatose adults. An important provision of these guidelines is that the etiology and irreversibility of coma be established. Drug intoxication per se, without anoxic or another cause of irreversible brain injury, as a complication of drug toxicity, is insufficient to fulfill these criteria. The use of these guidelines in the drug-intoxicated patient is fraught with hazard. We report two cases of baclofen intoxication where brain death was entertained as an explanation for prolonged coma, with arousal seen days later, in one case after organ procurement plans had already been initiated. These cases highlight the potential hazard associated with brain death determination in the overdose patient.

Cases

A 40-year-old female was found by her family unresponsive. There were empty bottles of baclofen, nabumatone, diphenhydramine, and alprazolam at the scene. Family members believed that baclofen was the primary ingestion. There was no arousal with naloxone, and she was intubated at her residence. On hospital arrival vital signs were BP 113/85 mm Hg, P 68 bpm, no spontaneous respirations, and T 94.1°F rectally. Glasgow Coma Scale was 3 with fixed dilated pupils, absent corneal and ocular reflexes, and flaccid extremities. Cardiac, lung, and abdominal examination were normal. Laboratory testing showed electrolytes and glucose within normal limits. No ethanol, acetaminophen, or salicylate was detected. CBC and liver transaminases were normal. Urine toxicology screen was positive for opioids and benzodiazepines. EKG revealed a sinus rhythm with a normal QRS interval and a QTc of 500 msec. CT of the brain was normal.

The patient was warmed with a Bair Hugger®. A brief period of hypotension was managed with fluids and a vasopressor. A propofol infusion was started on hospital day 2 after seizure like activity was observed. On hospital day 3**,** propofol was discontinued, and no further seizure like activity was observed. The patient remained deeply comatose and an EEG obtained later that day showed a burst-suppression pattern with occasional sharp waves on a flat background, interpreted as portending a poor prognosis. On hospital day 4, neurology consultation was requested for brain death determination. The neurologist found the patient unresponsive to all stimuli with fixed pupils, absent corneal and oculocephalic reflexes, no response with caloric testing, and flaccid areflexic extremities. A weak inspiratory effort was reported after 5 min of apnea and after an increase in the pCO_2 from 34 to 64 mmHg. The neurology consultant did not feel that the patient fulfilled clinical criteria for brain death based on having a spontaneous breath during the apnea test.

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Despite the failure to satisfy objective brain death criteria the neurologist and the medical service felt the prognosis was poor, and after discussion with the family, plans for organ donation and withdrawal of support were made. The next day, hospital day 5, with organ procurement imminent, eye opening and extremity movement were observed. There was progressive arousal although her recovery was prolonged by delirium. The patient was discharged to psychiatry on hospital day 15. The patient admitted to a large baclofen overdose after she had recovered.

The second case was a 51-year-old female with multiple medical problems found by her family unresponsive with a suicide note. She was last seen 8 h earlier. The patient was on multiple medications that included clorazepate, hydroxyzine, paroxetine, phenobarbital, phenytoin, digoxin, warfarin, and baclofen. On arrival to the emergency department (ED), the patient was unresponsive, with a temperature of 95°F, a systolic blood pressure of 70 mmHg, and breathing 8–12 bpm. Pupils were nonreactive and 4 mm, extremities were flaccid, and there was no response to stimuli. The patient was intubated and saline and dopamine corrected her blood pressure. Electrolytes, glucose, renal function, and liver tests were all normal and a head computed tomography (CT) unrevealing. Drug levels for phenobarbital, phenytoin, and digoxin were all therapeutic, and international normalized ratio (INR) was 1.6.

The patient remained deeply comatose, and on hospital day 5, with no arousal, anoxic brain injury was entertained as a complication of her overdose. Consultation for brain death examination by neurology was placed. Because of the weekend, this evaluation was delayed and on hospital day 7, prior to actual neurology evaluation, the patient showed signs of arousal and the consultation cancelled. By the next day, she was awake and following commands. The patient was ultimately discharged on hospital day 24 in her usual state of health.

A baclofen level obtained on hospital day 1, and estimated to be 15 h post ingestion, returned elevated at 2.7 mcg/mL (therapeutic 0.080–0.400 mcg/mL).

Discussion

The impetus to define brain death took shape in the 1960s with advances in critical care and transplant medicine. An ad hoc committee at Harvard Medical School addressed this issue and presented their definition of irreversible coma in 1968.[2,3] They defined irreversible coma, or brain death, as "unresponsiveness and lack of receptivity, the absence of movement and breathing, the absence of brain stem reflexes, and coma whose cause has been identified."[4] To address this evolving concept of death, which traditionally had been considered an irreversible cessation of breathing and cardiac activity, and to attempt to have consistent guidelines in place nationwide, the National Conference of Commissioners on Uniform State Laws proposed a Uniform Determination of Death Act in 1980. The act defined death as (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem.[5] Both the American Medical Association and the American Bar Association approved this Act by 1981.

An expert panel in 1995 published guidelines for the determination of brain death.[6] These guidelines were recently updated in 2010.[1] Brain death is primarily a clinical diagnosis, with the judicious use of ancillary tests to augment the clinical evaluation. Reversible causes such as drug intoxication, hypothermia, and metabolic or endocrine disturbances must be excluded. Clinical evaluation should demonstrate no evidence of activity of the cerebral hemispheres and brain stem. Examination should demonstrate no response to noxious stimuli, absence of cranial nerve reflexes, and failure to spontaneously breathe in the face of hypercarbia during an apnea test. The use of ancillary tests such as electroencephalography (EEG), conventional angiography, CT or Magnetic resonance (MR) angiography, or nuclear brain flow study is considered optional in adults by the most recent expert guidelines and should not supplant a good clinical evaluation.[1] These ancillary tests may allow for a more rapid declaration of brain death and may provide supportive findings when the clinical evaluation is uncertain or incomplete.

Electroencephalography (EEG) was the first ancillary test used for the evaluation of brain death. The EEG should demonstrate electrocerebral silence, with very specific criteria and instructions for the performance of this study.[1] Both "false positive" and "false negative" EEG recordings have been observed. Electrical activity was observed in several cases at the time of death, with brain stem autolysis in one case and hemorrhage in the other observed at autopsy.[7] Isoelectric EEGs have been reported with toxic levels or following overdose of diazepam, methaqualone, meprobamate, and trichloroethylene.[8] Children with very elevated levels of pentobarbital have been observed to have electrically silent EEGs.[9] It has been suggested that an EEG be considered more of a "negative test," that is, it can demonstrate that the patient is not dead but cannot demonstrate the converse with any confidence.[2]

In our first case, the patient's EEG was not isoelectric but rather showed disorganized electrical activity; burst suppression and occasional sharp waves superimposed on a flat background. In the setting of coma following resuscitation from cardiopulmonary arrest, a burst suppression pattern is associated with a grim prognosis.[10] This may have influenced the decision of the medical team caring for this patient to proceed towards organ procurement. However, this EEG pattern has also been described with coma from drug overdose.[11]

Baclofen is an analog of the inhibitory neurotransmitter γ-aminobutyric acid. The inhibitory effects of baclofen on gamma-aminobutyric acid (GABA)-B receptors in the spinal cord are the basis for its use to treat muscle spasm associated with spinal cord diseases and injury. In overdose, it is a potent central nervous system (CNS) depressant. Numerous case reports describe profound sedation and coma from overdose,[12–15] including a prior report of baclofen mimicking brain death. In that case a 59-year-old male presented in deep coma with no spontaneous movements or response to noxious stimuli, absent cranial nerve reflexes, and hypoventilation.

Similar to our first case, EEG showed burst suppression. Contrary to our cases, signs of arousal were evident within 12 h of presentation to hospital.[16]

With therapeutic dosing, the half life of baclofen is about 2–4 h.[17] About 85% of baclofen is eliminated unchanged in the urine.[17] More prolonged elimination half-lives have been measured in overdose. In one case, an elimination half-life of 8.6 h was measured based on levels between 12 and 36 h post overdose.[12] In another case an elimination half-life of 34.5 h was calculated based on levels done between 36 and 60 h post ingestion, following which even a small increase in plasma baclofen level was observed.[13] It is not clear from these cases if this prolonged elimination is due to prolonged or erratic absorption or represents some other toxicokinetic effect. Renal failure results in delayed clearance of baclofen. Toxicity following therapeutic dosing has been reported in patients with renal failure.[18] Neither of our patients had evidence of renal disease.

Cerebral spinal fluid (CSF) concentrations of baclofen after oral administration are approximately 1/8–1/9 those of plasma levels in adults measured 4 h after the last dose of baclofen.[19] In rats, administered radiolabeled baclofen distribution to the brain occurs quickly. Over the first 24 h, blood baclofen levels decrease rapidly while brain levels decrease more slowly.[17] A study by Deguchi et al. using microdialysis probes in rats found that CNS baclofen levels were about 30-fold lower than plasma baclofen levels. Brain tissue and CSF concentrations were similar, and the clearance of baclofen from the brain was greater than clearance (efflux) into the brain. Pretreatment of rats with probenecid resulted in a three-fold increase in brain baclofen concentrations. Direct administration of probenecid into the brain led to even greater increases in brain baclofen levels.[20] As probenecid is an inhibitor of organic anion transporters, this suggests that an active transport system may account for the greater clearance of baclofen from the CNS while entry is more a function of its moderate lipid solubility.

Based on these animal studies it seems unlikely that delayed clearance of baclofen from the CNS would explain prolonged coma in our patients. Other possibilities for prolonged coma include persistent elevated plasma levels as a result of continued GI absorption or co-ingestion of another xenobiotic that impedes the clearance of baclofen from the CNS via an organic anion transporter, or some other mechanism. Though not described in humans, the potential alteration of active transporters seems to be a plausible mechanism. Other unknown toxicodynamic effects of massive baclofen overdose remain possibilities.

Hypothermia slows the metabolism of many drugs, affecting not only the rate of metabolism but also the down regulation of Cytochrome P450 (CYP) enzymes.[21,22] The effect of hypothermia on the clearance of baclofen has not been reported. Although both our patients were modestly hypothermic on presentation, they were rapidly rewarmed and we do not feel this contributed to their prolonged coma.

In our second case, a toxic baclofen level on hospital day 1 confirmed exposure. Although we were unable to obtain a baclofen level in our first case, we have evidence of baclofen overdose from examination of pill bottles at the scene by the family and the patient's subsequent affirmation of the ingestion after she recovered.

The role of CSF baclofen levels in patients following baclofen overdose is not well studied. A 12-year-old male with baclofen pump failure and overdose presented with bradycardia, hypotension, and bradypnea. A CSF baclofen concentration 3 h after presentation was 4.47 ug/mL, a level within the therapeutic range.[23] A serum baclofen level on this patient at the same time was 0.38 ug/mL, again therapeutic. Although CSF baclofen levels can be measured, there is limited information on how this correlates with level of consciousness. The absence of baclofen in the CNS might be useful to rule this out as the etiology of persistent coma.

Brain death evaluation in the drug overdose patient must proceed with caution. The American Academy of Neurology Guidelines are very clear that before brain death evaluation proceeds a) there should be either clinical or neuroimaging evidence of a CNS event incompatible with CNS recovery, and b) complicating medical issues and intoxication have been excluded.[1] The guidelines suggest allowing a period of 5 half-lives for the clearance of drugs, or if available, measuring drug levels, prior to performance of the clinical exam for brain death. Although this makes pharmacologic sense, there appears to be little data to support the 5-half-life recommendation. The toxicokinetics and toxicodynamics of a drug may be very different with overdose. Additionally, in some cases the xenobiotic(s) involved may be unknown.

Drug intoxication uncomplicated by clear evidence of anoxic brain injury, cerebral edema, and herniation or some other CNS catastrophe is insufficient alone to proceed to brain death evaluation. What the proper duration of time to allow clearance of a drug and any lingering drug effect is not well defined.

Ancillary testing attempts to confirm brain death in one of the two ways is a) cessation of electrical activity (EEG or evoked potentials) or b) loss of cerebral blood flow (angiography by catheter/MR/CT or nuclear brain flow studies). Although ancillary tests are not considered routinely necessary in the evaluation of brain death in adults, these tests should be considered in cases where drug intoxication is in the differential diagnosis, and other injuries incompatible with neurologic recovery are not apparent on clinical exam and routine imaging. However, the ancillary testing of electrical activity can certainly be influenced by the effects of drugs (as discussed above). It is not yet clear how drug effects may influence testing of cerebral blood flow in brain death determination, but there is some evidence that baclofen itself can modify cerebral blood flow in the setting of therapeutic use.[24] Therefore, the limitations of ancillary testing and the potential for a falsely positive result should be kept in mind.[25]

Our two cases suggest that baclofen intoxication may result in very prolonged and profound coma, and may in fact mimic brain death. The caveat here is that neither of our patients truly fulfilled the criteria necessary to proceed to formal evaluation since neither had clinical evidence of an irreversible catastrophic CNS event and persistent drug

intoxication had not been ruled out. Despite this, our first patient had a brain death evaluation preformed by a neurologist and was determined that all criteria were not met for a formal diagnosis of brain death. Concerning here is that the clinicians elected to proceed to organ procurement based on their clinical impression of futility. In this case it appears a lax institutional approach to the process of brain death determination was partly at fault. Several recent studies document wide variation in the criteria and process for brain death determination in US Hospitals.[26,27]

A limitation of our report is a failure to obtain baclofen levels in case 1 to confirm exposure and comprehensive drug screening to account for any confounding exposures.

Conclusion

The decision to proceed to brain death declaration in the poisoned patient should be done with vigilance and a recognition that coma may be very prolonged. In the absence of clear clinical or imaging findings of brain injury incompatible with life, one should proceed with caution. The toxicokinetic and toxicodynamic properties of a drug may differ from expected behavior at therapeutic doses, and even the utilization of a 5-half-life observation period without the availability of drug concentrations may not be adequate. A multidisciplinary approach should be considered in the assessment of the poisoned patient with prolonged coma.

These cases underscore the need for more precise criteria to define brain death in intoxicated comatose patients.

Declaration of interest

No authors have any financial, personal, or any other interests to disclose. There are no conflicts of interest and all ethical standards of our institutions and profession were followed.

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