Baclofen Toxicity Responsive to Hemodialysis in a Pediatric Patient with Acute Kidney Injury

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Abstract

Background Baclofen (para-chlorophenyl-gamma-aminobutyric acid) is widely used for its therapeutic effect of providing muscle relaxation from the persistent muscle spasms and posturing often related to spinal and central nervous system injuries. However, baclofen is also a potent neuronal depressant which is most evident in cases of toxicity. In severe toxicity, respiratory failure and obtundation may occur.

Case-diagnosis/treatment We present the case of a neurologically devastated 16-year-old on chronic baclofen therapy for bilateral spastic cerebral palsy (Gross Motor Function Classification System level V) who presented with fever, leukocytosis, and hypotension. Initial management with fluid resuscitation and antimicrobials for presumed infection did initially improve the patient's mental status; however, he subsequently became comatose later during the same hospitalization. Comprehensive diagnostic studies and infectious work-up did not reveal an etiology. Upon further examination of history, acute kidney injury from chronic nonsteroidal use and complicated by vancomycin toxicity was suspected to cause acute baclofen toxicity. The patient underwent a single run of hemodialysis with resultant neurologic improvement and later laboratory-confirmed toxic baclofen levels.

Conclusion Clinicians should consider possible acute baclofen toxicity in patients with impaired renal function who present with neurologic depression. Respiratory failure and mechanical ventilation, with its associated intensive care costs and complications, may be avoided with prompt treatment using hemodialysis.

Keywords

- ▶ baclofen
- ▶ hemodialysis
- ▶ acute kidney injury
- ▶ toxicity

Introduction

Severe muscle spasticity is common in patients with cerebral palsy. As such, these patients are often prescribed chronic oral baclofen, a γ -aminobutyric acid derivative, for symptomatic relief and improved range of motion. However, baclofen is a potentially toxic drug with harmful side effects: obtundation, bradycardia with hyper- or hypotension, cardiac conduction abnormalities, and respiratory depression necessitating mechanical ventilation.^{1,2} It is a drug that is ~30% protein bound, with the remainder eliminated by renal excretion.^{3,4} Reports

in the literature describe inadvertent baclofen overdose in adult patients with chronic kidney disease and dialysis dependence who are prescribed short-term baclofen.^{5,6} In such cases, hemodialysis has been used successfully to assist with baclofen clearance in adults.^{6–8}

We present a case of a pediatric patient on chronic baclofen therapy who presented with altered mental status, initially attributed to severe dehydration and septic shock. Despite initial clinical improvement with antimicrobials and hemodynamic support, our patient suffered acute mental status deterioration prompting

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further investigation into an alternative and concurrent diagnosis. The possibility of acute baclofen toxicity was suspected after case reassessment revealed acute-on-chronic kidney injury, for which the patient improved after definitive treatment with hemodialysis. The significance of nonoliguric acute kidney injury (AKI) and baclofen toxicity is reviewed.

Case Report

A 16-year-old, 44-kg African American boy initially presented at an outside facility with fever and congestion. The patient's past medical history was significant for: developmental delay secondary to traumatic brain injury as a child, bilateral spastic cerebral palsy (Gross Motor Function Classification System level V), and epilepsy. Parents reported that the patient had been less active for the past few days, but he otherwise seemed fine and was tolerating his gastrostomy tube feeds and was urinating appropriately. Despite this history, the patient was noted at initial presentation to be hypotensive to 60s/30s mm Hg, but favorably responsive to fluid boluses. Laboratory work revealed a sodium (Na) concentration of 165 mmol/L, blood urea nitrogen (BUN) of 66 mg/dL, creatinine (Cr) of 1.3 mg/dL, and a white blood cell (WBC) count of 24,000/mL. Baseline Cr from a prior hospitalization 8 months prior was 0.2 to 0.4 mg/dL (normal 0.40–1.10 mg/dL). A chest X-ray demonstrated pneumonia, for which vancomycin and ceftazidime were started. Doses were not available from transport records. The patient was subsequently admitted to the outside hospital's intensive care unit for continued electrolyte management and rehydration.

After initial clinical improvement, the patient was transferred to the general floor for continued pneumonia treatment on hospital day (HD) #3. However, over the next 48 hours, the patient again experienced acute mental status depression and became unresponsive. The parents had endorsed that the patient is normally nonverbal, but that he does smile and give a "thumbs up" with interactions. A computed tomography of the brain showed no acute intracranial pathology. Repeat cultures from blood and urine were obtained and the patient was continued on vancomycin. Ceftazidime was discontinued and the patient was started on piperacillin and tazobactam for broader antimicrobial coverage. However, due to continued lack of neurologic improvement, the referring facility transferred the patient out on HD #8 to our tertiary care facility for suspected nonconvulsive status epilepticus and evaluation by a pediatric neurologist. Cr upon time of transfer was 1.8 mg/dL and urine output (UOP) 2.3 mL/kg/h.

Upon admission to our pediatric intensive care unit (PICU), the patient's vitals were: heart rate (HR), 67 beats per minute (bpm); blood pressure, 102/73 mm Hg; respiratory rate (RR), 11 breaths per minute; saturations, 94% on room air; and temperature, 37.4°C (99.3°F). Pertinent exam findings included: bilateral 4-mm minimally reactive pupils, absent response to painful stimuli, intact cough and gag reflexes, diffuse rhonchi with regular respirations, and a soft abdomen with normoactive bowel sounds. Significant laboratory results upon PICU

admission were: Na, 149 mmol/L; BUN, 12 mg/dL; Cr, 1.87 mg/dL; ammonia < 9 µmol/L (normal 10–64 µmol/L); WBC count, 11,000 cells/mL; and a prevancomycin dose level of 39.6 µg/mL (normal 10–20 µg/mL). The patient had normal liver enzymes, lipase, lactate, and blood gas. UOP had been 1.6 to 2 mL/kg/h during interfacility transport.

The neurology team empirically recommended levetiracetam 15 mg/kg intravenously (IV) twice daily and long-term electroencephalography (EEG) for monitoring. No seizures were noted on admission, but the EEG did note an abnormal background most likely consistent with known history of remote infarct and likely reflective of his baseline. A brain magnetic resonance imaging (MRI) was also obtained and showed no acute pathology. Clinically, our patient continued to have HRs of 40 to 60 bpm and RRs of 6 to 10 breaths per minute, but he remained normotensive with good perfusion. A lumbar puncture was unsuccessfully performed by our interventional radiologists, due to the presence of heterotopic bone over the dorsal surface of the lumbosacral spine. Nonetheless, the patient was continued on broad-spectrum coverage with linezolid 600 mg IV every 12 hours, ciprofloxacin 10 mg/kg IV every 24 hours (renal dose), and piperacillin and tazobactam 60 mg/kg IV every 6 hours (renal dose).

Upon further examination of detailed history from the father, the patient had been receiving enteral naproxen 375 mg, prescribed initially for pain relief related to hip surgery, twice daily for the 2 months leading up to hospitalization. In addition, review of the patient's prior hospital course from the referring facility had also revealed continued vancomycin dosing without renal insufficiency adjustment, as well as continuation of his home baclofen 7.5 mg twice daily for the duration of his 7 days before transfer. The presence of renal insufficiency with a Cr of 1.87 mg/dL was suspected to have been precipitated by acute tubular injury, secondary to chronic nonsteroidal drug use at home, and acutely worsened due to prerenal dehydration and vancomycin toxicity-induced renal injury. Given this presentation and the unexplained mental status deterioration in the setting of known nonoliguric AKI, the possibility of baclofen toxicity was then considered in this patient. After discussing the potential benefits and risks, the family agreed to proceed with hemodialysis (HD).

A temporary 11.5-French double lumen dialysis catheter was placed in the right internal jugular vein using Seldinger technique. We dialyzed the patient for 240 minutes on a Gambro Phoenix dialysis machine with the following prescription: Xenium 150 dialyzer (Baxter), adult tubing, blood flow 150 mL/min, dialysate flow 500 mL/min, potassium bath 3 Eq/L, and calcium bath 3 mEq/L. Serum baclofen levels were obtained prior to HD and then hourly during the treatment. Resulted levels were not immediately available for review, as this test is only processed at designated specialized laboratories.

After a 4-hour run, the patient's vitals improved with HRs of 80 to 90 bpm and RRs of 18 to 20 breaths per minute. Family reported that the patient seemed more awake, specifically noting that he was now opening his eyes and attempting to track familiar voices. Serum baclofen results confirmed a toxic level pre-HD of 0.60 mcg/mL (normal 0.08–0.4 mcg/mL) and levels post-HD of 0.15 to 0.20 mcg/

Fig. 1 Baclofen level predialysis and trend during dialysis.

mL (►Fig. 1).⁹ The patient did not require any further HD runs, as his clinical status remained improved in the subsequent days and his home baclofen dose was adjusted. He completed a course of empiric antibiotics for pneumonia and possible meningitis, given his initial presentation and the inability to obtain cerebral spinal fluid (CSF) for definitive culture. The patient was eventually discharged to home with resolution of his AKI (Cr normalized to 0.21 mg/dL) and parents' reported return of neurologic baseline.

Discussion

Baclofen is a commonly prescribed drug for muscle spasticity. It is completely absorbed following ingestion, with ~30% of the drug being protein bound. Because the drug crosses the blood–brain barrier, baclofen does exhibit central nervous system effects that may be undesirable. Reports exist in the literature describing baclofen toxicity and obtundation following overdose or when administered to patients with impaired kidney function.^{5,8}

However, baclofen toxicity is a clinical diagnosis that requires a high index of suspicion, as baclofen levels are not readily available to guide initial diagnosis and treatment. Additionally, as in the case of our patient, suspicion in a neurologically impaired individual at baseline may be difficult. Young and Delwaide reported normal baclofen levels to be 80 to 400 ng/mL (0.08–0.4 mcg/mL).⁹ However, this report does not consider the potential difference in pharmacokinetics for a patient who is on chronic baclofen therapy.^{2–6,10} It is unclear if depot lipophilic stores of drug or the chronic saturation of plasma protein and tissue-binding sites is the mechanism responsible for the reported toxicities in this patient population. Moreover, patients with severe chronic renal disease have been reported to have increased susceptibility to baclofen toxicity, despite levels that are within defined “range.”^{4–6} Current labeling for baclofen does not specify minimal renal function before warning the potential for toxicity. Thus, further research into baclofen's pharmacodynamics in the patient with renal insufficiency on chronic baclofen is also needed.

Treatment of baclofen intoxication is mainly supportive. However, awaiting renal clearance in the setting of acute or

chronic renal insufficiency may mean prolonged periods of neurologic and respiratory depression, necessarily resulting in mechanical ventilation with potential ventilator-associated pneumonia risk, prolonged PICU stay, and higher hospital charges. Because our patient demonstrated the ability to protect his airway and dialysis was used emergently for acute reversal of symptoms, he did not require intubation. Multiple reports of respiratory failure do exist with baclofen toxicity. Specifically, Perry et al cited a duration of mechanical ventilation between 24 and 61 hours in a previously healthy group of 14 teenagers who experimented in baclofen ingestion.¹

Reversal of baclofen toxicity in the acute setting has proven to be challenging. Previous attempts to empirically treat baclofen toxicity with flumazenil, a benzodiazepine receptor antagonist, have shown conflicting results.^{11,12} Moreover, in terms of avoiding intubation, there has been no proven benefit in the administration of charcoal to decrease absorption.^{1,13} There is, however, literature supporting the use of hemodialysis to clear baclofen toxicity in adults.^{6–8} Theoretically, baclofen is efficiently removed by hemodialysis, secondary to low protein binding and volumes of distribution in adults (0.83 L/kg) and children (2.58 L/kg).^{14,15} To our knowledge, this is the first report in the literature of using hemodialysis to treat baclofen toxicity in a pediatric patient.

In conclusion, acute hemodialysis resulted in the rapid reversal of neurologic depression, normalization of serum baclofen levels, and avoidance of intubation in a pediatric patient with baclofen intoxication. The baclofen toxidrome must be considered in patients who present with AKI and altered mental status. In the case of our patient, an infectious neurologic process to explain his mental decline was not clearly identified by MRI and there were limitations to obtaining CSF for culture. However, the improved neurologic exam immediately after HD supported our suspicion, later verified by the elevated pre-HD serum baclofen level. Hemodialysis may be a modality that offers definitive treatment for baclofen toxicity while potentially reducing PICU stay and its associated complications in pediatric patients.

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