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Baclofen Toxicity in Kidney Disease

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Baclofen, a commonly prescribed muscle relaxant, is primarily excreted via the kidneys; toxicity is a potentially serious adverse outcome in patients with decreased kidney function. We describe a patient with end-stage kidney disease receiving hemodialysis who developed neurotoxicity and hemodynamic instability after receiving baclofen for muscle spasms. In this case, prompt recognition of baclofen toxicity and urgent hemodialysis were effective in reversing this toxicity. This case is used to examine the pharmacokinetics and pathophysiology of baclofen toxicity and discuss appropriate diagnosis and management of baclofen toxicity. We recommend reducing the baclofen dose in patients who have moderately reduced kidney function (estimated glomerular filtration rate, 30-60 mL/min/1.73 m^2) and avoiding use in patients with severely reduced kidney function (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or on renal replacement therapy.

Complete author and article information provided before references.

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Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Introduction

Baclofen, a γ-aminobutyric acid (GABA) agonist specific to the $GABA_B$ class, was first marketed in the United States in the 1970s to treat skeletal muscle spasticity secondary to spinal cord disease.[1] The modest cost[2] and low tolerance potential[3,4] of baclofen have made it an attractive option for a wide range of ailments, and it is frequently prescribed to patients as a muscle relaxant. Multiple studies have demonstrated the effectiveness of baclofen for several off-label uses, such as intractable hiccups,[5] trigeminal neuralgia,[6] acquired nystagmus,[7] gastroesophageal reflux,[8,9] and treatment of substance abuse, including alcohol and cocaine dependency.[10,11]

The precise mechanism of action of baclofen is not fully understood. It is thought to work through hyperpolarization of presynaptic motor neurons, inhibiting both monosynaptic and polysynaptic reflexes.[1] Unlike other muscle relaxants that are primarily metabolized by the liver,[12-14] baclofen is primarily excreted by the kidneys in its unchanged form.[15] For this reason, patients with diminished or absent kidney function are at risk for developing baclofen toxicity. During the past decade, multiple case reports have discussed patients with kidney disease experiencing baclofen toxicity.[16-25] We present another such case of baclofen toxicity in a patient with end-stage kidney disease and discuss the pharmacokinetics and pathophysiology of baclofen toxicity and its prevention and treatment.

Case Report

Clinical History and Initial Laboratory Data

A 58-year-old man with hypertension, chronic back spasms, and end-stage kidney disease secondary to perinuclear antineutrophil cytoplasmic antibody vasculitis who recently began thrice-weekly hemodialysis (HD) therapy via his tunneled right internal jugular catheter, was admitted for altered mental status. One week before the hospital admission, he presented to the emergency department seeking medical treatment for back spasms. Baclofen, 10 mg, every 8 hours was prescribed. During the next several days, the patient developed progressive confusion and was subsequently found at home after pulling out his HD catheter; he was disoriented and experiencing visual hallucinations.

On presentation, the patient was afebrile, heart rate was 105 beats/min, oxygen saturation was 90% on room air, and blood pressure was 98/67 mm Hg. His speech was reportedly tangential and he was unsure of the reason for his admission, but he was oriented to person and place, and neurologic examination findings were otherwise normal. His initial laboratory test results were not significant for a metabolic derangement or infection (Table 1). Additional home medications included amlodipine, 5 mg, daily; carvedilol, 50 mg, twice daily; atorvastatin, 40 mg, daily; pantoprazole, 40 mg, twice daily; and sevelamer carbonate, 800 mg, with meals. In addition, an electrocardiogram was normal. Serum urea nitrogen and serum creatinine concentrations were 62 mg/dL and 12.8 mg/dL, respectively, but he was asymptomatic 4 weeks prior with comparable laboratory results (serum urea nitrogen, 121 mg/dL; creatinine, 7.4 mg/dL). He was generally adherent to his HD prescription, and his last HD session was thought to be 5 days before presentation due to missing 1 scheduled session. His recent baclofen intake was suspected to be the most likely cause of the acute onset of altered mental status.

Table 1. Laboratory Data

Serum Chemistry	Value	Reference Range
Sodium, mmol/L	136	134-144
Potassium, mmol/L	4.8	3.5-5.4
Bicarbonate, mmol/L	21	22-32
SUN, mg/dL	62	8-23
Creatinine, mg/dL	12.8	0.6-1.4
Phosphate, mmol/L	6.8	2.4-4.7
Calcium, mmol/L	10.4	8.5-10.1
WBC, $\times 10^3/\mu L$	5.2	3.7-9.6
Hemoglobin, g/dL	11.3	12-17
Hematocrit, %	36.3	36-51
Platelets, $\times 10^3/\mu L$	253	123-309
AST, U/L	31	14-41
ALT, U/L	24	17-63
Total bilirubin, mg/dL	0.6	0.4-1.5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUN, serum urea nitrogen; WBC, white blood cells.

Additional Investigations

The patient underwent computed tomography of the brain to evaluate for hemorrhage or stroke, which had negative results. He also had blood cultures, urinalysis, chest x-ray, and computed tomography to investigate infectious causes that may present with delirium; these results were normal. Urine toxicology screen was also performed on admission, which was negative.

Diagnosis

Altered mental status in a patient with end-stage kidney disease secondary to baclofen toxicity, accumulation of baclofen exacerbated by a missed HD session.

Clinical Follow-up

Baclofen treatment was discontinued, and the patient began immediate HD (Revaclear dialyzer with polysulfone membrane; Gambro Inc; 4.5 hours, 2-mEq/L potassium/2.5-mEq/L calcium bath, 400 mL/min blood flow, 800 mL/min dialysate flow, and no net ultrafiltration), with significant improvement in mental status after 1 session. His mental status rapidly returned to baseline, and he was discharged to home thereafter.

Discussion

This case illustrates an adverse outcome in a patient on HD taking oral baclofen at a dose typically given to a patient with normal kidney function. Baclofen is well absorbed by the gut, with oral bioavailability of 70% to 80%.[26] Approximately 15% of absorbed baclofen is metabolized by the liver through deamination,[3] and the other 60% to 80%[15,26,27] is excreted unchanged by the kidneys. The drug has a molecular weight of 213.7 g/mol,[28] is ~30% bound to serum protein,[3,15] and has an estimated volume of distribution of 0.83 L/kg.[29] Therapeutic blood levels are between 80 and 400 ng/mL, with doses of 25 to 40 mg resulting in a peak serum concentration of 500 to 600 ng/mL after 2 to 3 hours in healthy adults.[3,30,31] Drug concentrations > 800 ng/mL are associated with toxicity.[32] Symptoms of baclofen toxicity and overdose include encephalopathy, seizures, coma, areflexia, hypothermia, and respiratory and cardiovascular depression.[29,33,34] There have even been reported cases of baclofen toxicity mimicking brain death.[35,36]

Baclofen undergoes first-order elimination, has a half-life of 3 to 6.8 hours in patients with normal kidney function,[3,15,27,29,30] and has an average half-life of 7.8, 8.9, and 14.1 hours in patients with mild, moderate, and severe chronic kidney disease (CKD), respectively.[24] Total systemic clearance is 180 mL/min[26] and renal clearance is 103 to 151 mL/min.[26,27,32] Renal clearance is predominantly completed passively through glomerular filtration; however, coadministration with probenecid has been shown to reduce clearance, suggesting active secretion through the organic anion transport (OAT) pathway.[15,37] Animal models have shown that the drug effectively penetrates the blood-brain barrier, albeit reaching a 27-fold lower concentration in the central nervous system than blood serum levels.[37] However, clearance from the central nervous system is delayed compared with blood serum levels.[29,31] It should be mentioned that pharmacokinetics of baclofen differ widely between children and adults, partly due to the larger volume of distribution and likely faster elimination rates secondary to the higher estimated glomerular filtration rates (eGFRs) found in pediatric patients.[38]

The standard dosing regimen for oral baclofen in patients with normal kidney function is 5 mg 3 times daily, slowly titrated up by 15 mg daily every 3 days until optimal therapeutic effect is reached. This optimal effect is usually observed with total baclofen doses of 40 to 80 mg daily, and it is recommended that the daily dose not exceed 80 mg.[1] The manufacturer's label recommends caution when prescribing baclofen to patients with decreased kidney function, but it does not provide specific dose adjustments for such patients.[1] Although there have been many case reports discussing baclofen toxicity in patients with decreased kidney function,[16-25] until recently, there have not been dose adjustment guidelines for baclofen in this patient population. Vlavonou et al[24] recommended using the percent change in baclofen half-life and clearance among patients with normal kidney function relative to patients with mild, moderate, and severe CKD to guide dose and interval adjustments of the initial starting dose. They include that patients with severe CKD (creatinine clearance < 30 mL/min) not receiving dialysis can tolerate 5 mg of baclofen daily. However, there have been instances of patients with severe CKD on maintenance HD therapy taking 5 mg daily who developed neurotoxicity from this low dose.[17] Based on our experience, we recommend avoiding baclofen in all patients with eGFRs < 30 mL/min/1.73 m^2, independent of dialysis status. Of note, calculated eGFRs should not be used in patients on HD or peritoneal dialysis therapy because their

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