

## 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<sup>2</sup>) and avoiding use in patients with severely reduced kidney function (estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>) or on renal replacement therapy.

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**INDEX WORDS:** Baclofen; drug toxicity; decreased kidney function; end-stage kidney disease (ESKD); hemodialysis; pharmacokinetics; renal clearance; muscle relaxant; drug dosing; creatinine clearance.

## INTRODUCTION

Baclofen, a  $\gamma$ -aminobutyric acid (GABA) agonist specific to the GABA<sub>B</sub> class, was first marketed in the United States in the 1970s to treat skeletal muscle spasticity secondary to spinal cord disease.<sup>1</sup> The modest cost<sup>2</sup> and low tolerance potential<sup>3,4</sup> 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,<sup>5</sup> trigeminal neuralgia,<sup>6</sup> acquired nystagmus,<sup>7</sup> gastroesophageal reflux,<sup>8,9</sup> and treatment of substance abuse, including alcohol and cocaine dependency.<sup>10,11</sup>

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.<sup>1</sup> Unlike other muscle relaxants that are primarily metabolized by the liver,<sup>12-14</sup> baclofen is primarily excreted by the kidneys in its unchanged form.<sup>15</sup> 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.<sup>16-25</sup> 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;

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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, $\times 10^3$ /cmm	5.2	3.7-9.6
Hemoglobin, g/dL	11.3	12-17
Hematocrit, %	36.3	36-51
Platelets, $\times 10^3$ /cmm	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.

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.

### 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%.<sup>26</sup> Approximately 15% of absorbed baclofen is metabolized by the liver through deamination,<sup>3</sup> and the other 60% to 80%<sup>15,26,27</sup> is excreted

unchanged by the kidneys. The drug has a molecular weight of 213.7 g/mol,<sup>28</sup> is ~30% bound to serum protein,<sup>3,15</sup> and has an estimated volume of distribution of 0.83 L/kg.<sup>29</sup> 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.<sup>3,30,31</sup> Drug concentrations > 800 ng/mL are associated with toxicity.<sup>32</sup> Symptoms of baclofen toxicity and overdose include encephalopathy, seizures, coma, areflexia, hypothermia, and respiratory and cardiovascular depression.<sup>29,33,34</sup> There have even been reported cases of baclofen toxicity mimicking brain death.<sup>35,36</sup>

Baclofen undergoes first-order elimination, has a half-life of 3 to 6.8 hours in patients with normal kidney function,<sup>3,15,27,29,30</sup> 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.<sup>24</sup> Total systemic clearance is 180 mL/min<sup>26</sup> and renal clearance is 103 to 151 mL/min.<sup>26,27,32</sup> 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.<sup>15,37</sup> 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.<sup>37</sup> However, clearance from the central nervous system is delayed compared with blood serum levels.<sup>29,31</sup> 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.<sup>38</sup>

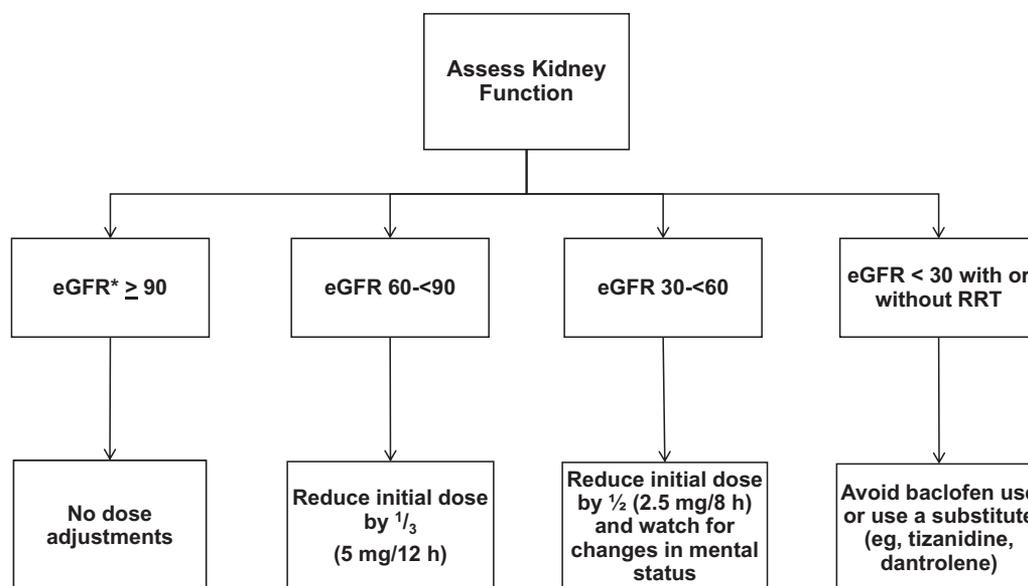
The standard dosing regimen for oral baclofen in patients with normal kidney function is 5 mg 3 times daily, slowly titrated up by 15 mg daily every 3 days until optimal therapeutic effect is reached. This optimal effect is usually observed with total baclofen doses of 40 to 80 mg daily, and it is recommended that the daily dose not exceed 80 mg.<sup>1</sup> 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.<sup>1</sup> Although there have been many case reports discussing baclofen toxicity in patients with decreased kidney function,<sup>16-25</sup> until recently, there have not been dose adjustment guidelines for baclofen in this patient population. Vlavonou et al<sup>24</sup> 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.<sup>17</sup> Based on our experience, we recommend avoiding baclofen in all patients with eGFRs < 30 mL/min/1.73 m<sup>2</sup>, independent of dialysis status. Of note, calculated eGFRs should not be used in patients on HD or peritoneal dialysis therapy because their eGFRs should be assumed to be <10 mL/min/1.73 m<sup>2</sup>. We have created a schematic with recommendations for the initial starting dose of baclofen based on a patient's baseline eGFR (Fig 1).

With a small molecular weight, low volume of distribution, and relatively low protein binding, baclofen is suitable for dialytic clearance. HD has been shown to effectively remove baclofen in patients with end-stage kidney disease, with one report of 79% serum clearance after 4 hours of HD, resulting in a half-life reduction from 15.5 to 2.06 hours.<sup>20</sup> In another patient with acute kidney injury, 37% of serum baclofen was recovered in dialysate following 4 hours of HD, and the half-life was reduced from 12.6 to 3.7 hours.<sup>21</sup> Although no clearance studies of baclofen using continuous ambulatory peritoneal dialysis (CAPD) have been performed, a small case study of baclofen toxicity compared CAPD to HD. This study determined that neurologic recovery in

baclofen toxicity was similar in CAPD and HD.<sup>19</sup> Therefore, the decision to use HD in a patient with baclofen toxicity currently receiving CAPD should be guided by available resources because CAPD should effectively remove baclofen. Serum baclofen concentrations can be obtained using liquid chromatography and tandem mass spectrometry. However, in many instances, these are send-out tests and results can take at least 2 days to return. Because many patients with baclofen toxicity are threatened by acute and potentially life-threatening effects, it is not safe to delay decisions awaiting serum baclofen concentrations. We suggest making clinical decisions based on patient symptoms and clinical suspicion instead of drug concentrations.

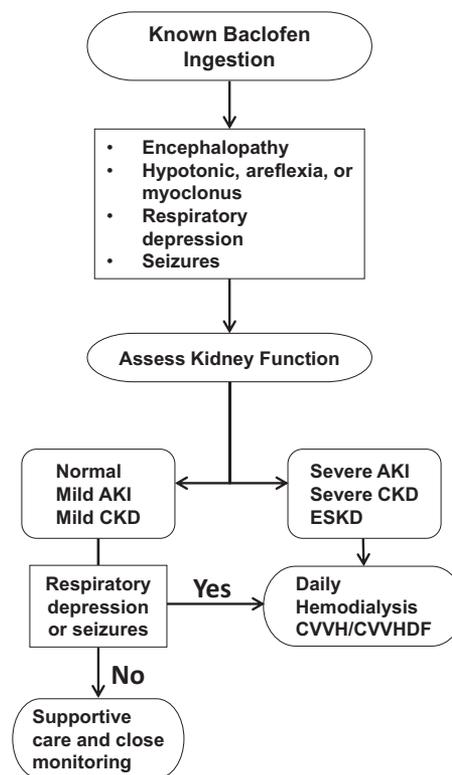
Careful monitoring of patients' kidney function should be performed in any patient on baclofen therapy, even those with normal baseline kidney function. There has been one reported case of a patient on long-term therapy who started coadministration of ibuprofen, leading to acute kidney injury and baclofen toxicity.<sup>39</sup> Another patient who began long-term baclofen therapy at normal baseline kidney function began to develop asymptomatic toxicity (hypotension) and was found to have subclinical CKD.<sup>40</sup> HD has been shown to be effective in removing baclofen and improving neurologic status in patients with normal kidney function in cases of overdose, reducing the half-life from 15.7 to 3.1 hours.<sup>41</sup> However, there is debate as to whether extracorporeal treatment should be used in patients



**Figure 1.** A stepwise approach to safely prescribe baclofen to patients with decreased kidney function. \*Many drug-dosing recommendations are determined in studies based on creatinine clearance calculated using the Cockcroft-Gault formula. Here we list estimated glomerular filtration rate (eGFR; mL/min/1.73 m<sup>2</sup>) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, which is similar to the MDRD (Modification of Diet in Renal Disease) Study equation but with better accuracy at higher GFRs.<sup>52,53</sup> Of note, providers should be vigilant of mental status changes in all patients because side effects can occur at any dose and level of kidney function. Abbreviation: RRT, renal replacement therapy.

with normal kidney function,<sup>42-44</sup> with some reasoning that baclofen elimination half-life with extracorporeal therapy is similar to the patient's native kidney elimination rate.<sup>33,45</sup> It should also be noted that in patients on long-term baclofen therapy, caution should be taken with management because baclofen withdrawal syndrome can occur after abrupt discontinuation. Signs and symptoms of withdrawal include tremor, rigidity, fever, seizures, tachycardia, or altered mental status.<sup>1,46,47</sup> Although there is not a universal recommendation, case reports suggest that in patients with normal kidney function, the original dose can be resumed followed by a slow taper (reduction of 5-10 mg/wk).<sup>48,49</sup> We have adapted a treatment algorithm from Roberts et al<sup>25</sup> to suggest treatment of baclofen toxicity in patients with kidney disease and those with normal kidney function, who should be transitioned to dialysis therapy if they develop encephalopathy, hypotonia, respiratory depression, or seizures (Fig 2).

Another point of discussion involves the proper prescribing indications of baclofen when patients present with muscle spasm. Muscle relaxants are classified into 2 main categories: antispasitics, such as baclofen, tizanidine, and dantrolene are used to alleviate spasticity secondary to an upper motor neuron disorder, whereas antispasmodics such as cyclobenzaprine are indicated for spasms associated with acute musculoskeletal disorders such as back or neck pain.<sup>50</sup> Examining the multiple case reports discussing baclofen toxicity in patients with decreased kidney function, providers often prescribed baclofen to treat spasmodic disorders,<sup>16,22,23,25</sup> for which baclofen is not indicated<sup>1</sup> and has not been proven effective.<sup>51</sup> Hence, if a patient presents with muscle spasms secondary to a musculoskeletal disorder, the provider should consider an antispasmodic such as cyclobenzaprine, which is metabolized primarily by the liver.<sup>14</sup> Alternatively, benzodiazepines such as diazepam act as antispasmodics, but carry risks such as dependency and withdrawal.<sup>4</sup> If an antispasmodic agent such as baclofen is indicated and the patient has decreased kidney function, the provider should consider prescribing another antispasmodic medication, such as tizanidine or dantrolene. Although tizanidine, an  $\alpha_2$ -adrenergic agonist, undergoes substantial hepatic metabolism, a portion is excreted by the kidneys; therefore, the manufacturer recommends dose adjustment in patients with creatinine clearances < 25 mL/min.<sup>13</sup> Dantrolene functions at the level of the sarcoplasmic reticulum, preventing release of calcium ions, and does not require dosage adjustments in patients with decreased kidney function, but carries a risk for severe hepatotoxicity.<sup>12</sup>



**Figure 2.** A stepwise approach to managing baclofen toxicity. Adapted from Roberts et al<sup>25</sup> with permission of Wiley Periodicals, Inc. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; ESKD, end-stage kidney disease.

In summary, careful assessment of risk versus benefit is required when considering the use of baclofen for patients with acute kidney injury, non-dialysis-dependent CKD, or end-stage kidney disease on maintenance renal replacement therapy. There is a need for provider education on the possible dangers of prescribing baclofen in this patient population, as well as prompt diagnosis and management of baclofen toxicity. The key teaching points of this review are summarized in Box 1.

#### Box 1. Key Teaching Points

- Pharmacokinetics:
  - 70%-80% oral bioavailability
  - Half-life is 3-6.8 h in those with no decrease in kidney function
  - 15% metabolized through the hepatic system
  - Up to 80% of baclofen excreted unchanged by the kidneys
- Dose adjustment is necessary even in mild CKD
- Dialysis is often indicated during baclofen use in cases of significant CKD, AKI, and ESRD

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease.

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