


Baclofen Toxicity in Children With Acute Kidney Injury: Case Reports and Review of the Literature

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Abstract

Baclofen is a medication used for tone management in cerebral palsy. Although it acts mainly at the spinal cord level, it can cause central nervous system adverse reactions at higher doses. Baclofen is mainly eliminated by renal excretion and there have been reports on adverse events when used in adults with renal impairment; however, there are no consensus guidelines as to the dose adjustments required due to renal impairment. The authors describe 2 children with acute kidney injury (AKI) and systemic side effects with initiation of oral baclofen, which was started for treatment of dystonia/spasticity in the recovery phase of their kidney injury. Following the initiation of the drug, they both had decreased level of consciousness and respiratory difficulties, which warranted discontinuation of the drug. These cases highlight the need for reduced initial dose, slow titration, and close monitoring when initiating baclofen treatment in children with AKI.

Keywords

traumatic brain injury, rehabilitation, dystonia, children, spasticity, kidney injury, baclofen

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Baclofen is a medication used for tone management in adults and children. Although its exact mechanism of action is not fully known, it acts as a GABA_B receptors agonist in the central nervous system (CNS), leading to neuronal inhibition and muscle relaxation.¹ As a moderately lipophilic drug, baclofen penetrates the blood–brain barrier and can cause CNS adverse reactions at high doses.^{2,3} Baclofen is mainly eliminated by renal excretion,^{3,4} and there have been reports on adverse events when used in adults with renal impairment.⁵⁻⁷ Although there are suggestions to modify dose with chronic kidney disease (CKD),^{6,7} no consensus guidelines exist as to the dose adjustments required.

To the best of our knowledge, systemic baclofen adverse effects in children with renal dysfunction have not been previously described. The authors describe 2 children with acute kidney injury (AKI) and systemic side effects with baclofen initiation.

Case Descriptions

The 2 children had an acute systemic disorder with severe AKI and CNS involvement, causing altered level of consciousness

(LOC) and increased tone. Both children were started on oral baclofen for tone management in the recovery phase of their kidney injury, with an intention for gradual dose increase. Systemic responses warranted discontinuation of the drug.

Patient I

A 2½-year-old boy with an unremarkable medical history was admitted with a diagnosis of hemolytic uremic syndrome and

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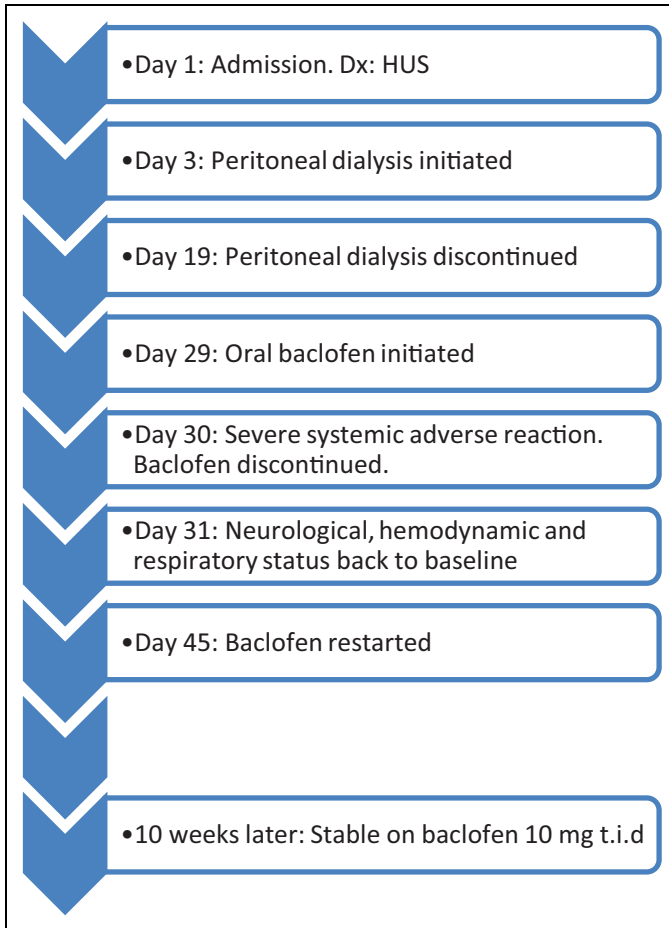


Figure 1. Patient 1 time line.

AKI (Figure 1). Rapid renal function decline warranted peritoneal dialysis (PD) at day 3 of admission.

Concurrently, he developed signs of brain injury, with a minimally conscious state, dystonia, and dysautonomia, with intermittent tachycardia and hypertension. Brain magnetic resonance imaging (MRI) at day 15 demonstrated extensive cerebral disease, with innumerable white matter and basal ganglia ischemic and hemorrhagic infarcts.

As renal function gradually improved, PD was stopped at approximately 3 weeks after admission. He was then started on oral baclofen to treat dystonia. At that time, he weighed 15.5 kg, serum creatinine was 54 $\mu\text{mol/L}$, and estimated glomerular filtration rate (eGFR) 64 mL/min/1.73 m^2 (71% normal).

Baclofen initial dose was 5 mg 3 times a day (tid). At that point, he has already been treated with gabapentin for 2 weeks.

After the second dose of baclofen, he developed periodic breathing that resolved spontaneously. Two hours after his fourth dose, he developed bradypnea of 6 to 8 bpm and bradycardia. Blood pressure and O_2 saturation were within normal limits. There was further decrease in his LOC, with no response to painful stimuli.

Baclofen was discontinued, he received intravenous fluids but did not require ventilation or hemodynamic support. Within

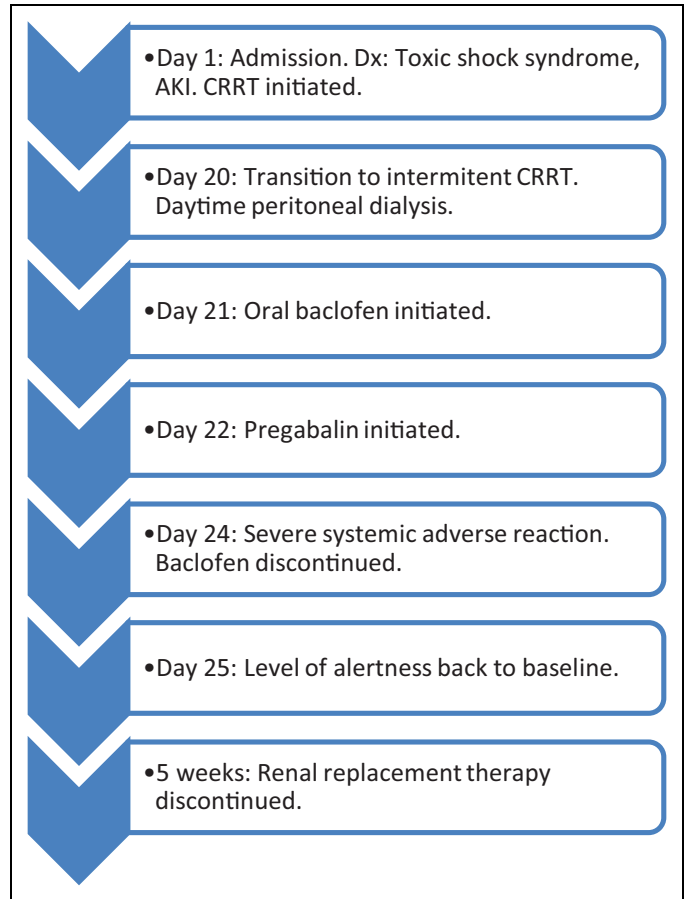


Figure 2. Patient 2 time line.

12 hours, his hemodynamic, neurologic, and respiratory status were back to his baseline.

Two weeks later, low-dose baclofen was restarted (2.5 mg daily). The dose was gradually increased to a dose of 10 mg tid. There were no side effects noticed and there was an improvement in dystonic episodes frequency, severity, and length.

Patient 2

A 9-year-old, previously healthy girl, was admitted to hospital due to group A streptococcus toxic shock syndrome and severe AKI, requiring immediate continuous renal replacement therapy (CRRT; Figure 2). She was transitioned to overnight CRRT and daytime PD after approximately 3 weeks. She gradually regained renal function and dialysis was discontinued at approximately 5 weeks after admission.

At admission, she presented with seizures and decreased LOC, which improved after 7 days. Brain MRI demonstrated left frontoparietal and right paracentral subdural hemorrhages, with sulcal Fluid-attenuated inversion recovery (FLAIR) hyperintensity.

Three weeks into admission, while still on overnight CRRT, oral baclofen was started for generalized spasticity, at a dose of 2.5 mg twice daily. Two days later, she was also treated with pregabalin 25 mg daily for neuropathic pain. Neurologically, at

this stage, she was opening her eyes spontaneously and to command and followed simple directions.

On the fourth day of baclofen treatment, after receiving a total of 8 doses (20 mg) and 2 doses (50 mg) of pregabalin, she developed generalized decreased tone with upper airway obstruction, increased work of breathing, and decreased LOC with no response to painful stimuli. She required nasopharyngeal airway insertion to protect her airway. Blood pressure and heart rate were slightly increased (150/105 mm Hg, and 90-150 bpm, respectively).

This episode started 2 and 12 hours after the last dose of baclofen and pregabalin, respectively, while still on intermittent dialysis (serum creatinine 82 $\mu\text{mol/L}$, eGFR 86 mL/min/1.73 m²).

Both medications were discontinued, and within 10 hours, her level of alertness, respiratory, and hemodynamic status returned to her baseline.

Discussion

The authors described 2 children treated with baclofen for hypertonia, who developed serious side effects due to their compromised kidney function. They both presented with severe AKI requiring renal replacement therapy and had respiratory and CNS depression after the initiation of baclofen. At the time of initiation and the described episodes, while both patients were recovering from their AKI, both still had evidence of kidney injury and decreased clearance.

Baclofen is absorbed in the gastrointestinal system and peak serum concentrations are achieved approximately 2 hours post-ingestion.²⁻⁴ While about 15% of the drug undergoes liver metabolism, 65% to 85% is eliminated by renal excretion, with an elimination half-life of 2 to 4 hours.²⁻⁴ Hence, patients with decreased kidney function are at risk of toxicity.

Baclofen toxicity has previously been described with overdose in adults^{8,9} and children,¹⁰⁻¹² as well as in adults with renal dysfunction.⁵⁻⁷ The main adverse events described were CNS depression and decreased LOC, hypotonia, respiratory depression, bradycardia, hypertension, or hypotension. Some of these patients recovered spontaneously, while others required clearance of the drug by dialysis.

The suggested starting dose for baclofen in children is 5 mg tid with a titration to a maximum dose of 1.5 to 2 mg/kg/d or 80 mg daily.^{13,14} Although caution in patients with impaired renal function is suggested by the manufacturer,¹⁵ no consensus dose adjustments guidelines exist. Recently, 2 articles suggested an algorithm for dose modification in these cases. Vlavonou et al⁷ assessed oral baclofen pharmacokinetics in patients with CKD. They divided their cohort into 4 groups based on creatinine clearance: >80 mL/min, 50 to 80 mL/min (mild CKD), 30 to 50 mL/min (moderate CKD), and <30 mL/min (severe CKD). Based on their results, they suggested decreasing the total daily baclofen dose by 1/3, 1/2, and 2/3 in patients with mild, moderate, and severe CKD, respectively.

Based on clinical experience and reports of neurotoxicity in patients with severe CKD on maintenance hemodialysis

therapy taking low-dose baclofen, Wolf et al⁶ recommend avoiding baclofen in all patients with eGFR < 30 mL/min/1.73 m², whether on renal replacement therapy or not. According to their algorithm for dose adjustments in CKD, the initial dose should be as follows: for eGFR \geq 90 mL/min/1.73 m², no adjustments; for eGFR 60 to 90 mL/min/1.73 m², reduce dose by 1/3; for eGFR 30 to 60 mL/min/1.73 m², reduce dose by 1/2; and for eGFR < 30 mL/min/1.73 m², avoid baclofen use.

These algorithms were created for patients with CKD and can differ from those for patients with acute and evolving kidney injury. In addition, baclofen dosing recommendations in children are based on body weight and extrapolated from adult dosing. The pharmacokinetics of baclofen in children can differ widely from that in adults.^{13,14} This suggests the need for future pharmacokinetic studies in children and in those with AKI.

Baclofen was started for patient 1 described here, while his renal function was only mildly declined. As he had significant dystonia, the aim was to reach a therapeutic dose quickly. Since he was admitted in hospital and closely monitored, he was started on the full recommended initial dose,^{13,14} with the assumption that although it can cause some temporary sedation, there would not be significant hemodynamic side effects.

Patient 2 was also treated with pregabalin at the time of the described episode. Although pregabalin can have contributed to this event, the last pregabalin dose was given 12 hours prior to the described episode. The episodes in both patients started 2 hours after the last dose of baclofen, which matches baclofen's expected peak serum concentration time.²⁻⁴ Therefore, although other medications can have contributed to these events, it appears that baclofen played the key role.

To the best of our knowledge, this is the first report of systemic adverse effects in children treated with baclofen at therapeutic doses with renal dysfunction. As there are no data regarding suggested dose adjustments in the pediatric population with renal impairment, the authors suggest caution when initiating baclofen treatment in these cases, using a reduced initial dose and slowly titrating while monitoring for systemic side effects. Close monitoring in the appropriate health care setting should also be considered.

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Authors Contributions

RM contributed to conception and design; acquisition, analysis, and interpretation; and drafted manuscript. NL contributed to conception; acquisition and interpretation; and critically revised manuscript. EA, EVR, and DM contributed to acquisition and critically revised manuscript. All authors gave final approval and agrees to be accountable for all aspects of work ensuring integrity and accuracy.


Declaration of Conflicting Interests

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Ethical Approval

The children's parents gave written informed consent that the cases could be published anonymously. The interventions described were part of the children's treatment according to accepted practice. Hence, ethical approval from the regional committee for medical and health research ethics was not needed.

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