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Baclofen-induced neurotoxicity in a dialysis patient managed with continuous venovenous hemodialysis: A case report and literature review

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Abstract:

Despite documented cases of baclofen toxicity in individuals with kidney disease, the drug is widely prescribed for various medical conditions, primarily spasticity, hiccups, and multiple sclerosis. Baclofen, a gamma-aminobutyric acid derivative, relies on renal excretion, rendering those with impaired kidney function susceptible to toxicity – a concern often underestimated by health-care providers. Adverse reactions, including single or double doses, are well documented in addition to multi-dose toxicity. This report discusses a case of baclofen-induced neurotoxicity in an end-stage renal disease patient undergoing dialysis, highlighting the subsequent management with continuous venovenous hemodialysis. In addition, it provides a comprehensive review of existing literature on baclofen toxicity in cases of renal insufficiency. Strikingly, the literature lacks clear guidelines regarding baclofen safety, dose adjustments, or renal function thresholds for contraindication. This contribution aims to augment understanding of this critical issue, emphasizing the need for heightened awareness and careful consideration of baclofen use in patients with kidney disease.

Keywords:

Baclofen toxicity, continuous venovenous hemodialysis, end-stage renal disease, neurotoxicity

Introduction

Baclofen, a Food and Drug Administration-approved centrally acting gamma-aminobutyric acid (GABA) agonist, is primarily prescribed for spasticity management in conditions such as multiple sclerosis, cerebral palsy, and spinal cord lesions.[1,2] It effectively mitigates symptoms such as flexor spasm, clonus, and pain.[1-3] Notably, baclofen's lipophilic nature facilitates efficient passage through the blood–brain barrier.[1] The therapeutic range is 0.1–0.4 mg/L, with a recommended initial oral dose of 5 mg three times daily for adults (maximum 80 mg/day). Exceeding 200 mg/day may cause severe toxicity.[1] Complications include central nervous system (CNS) and respiratory depression, with risks of anoxic brain injury, aspiration pneumonia, pressure ulcers, rhabdomyolysis, and hypothermia during prolonged periods without medical intervention.[1-3] Administering baclofen warrants particular caution in individuals with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD), due to its predominant renal metabolism, with approximately 80%–85% excretion through the kidneys.[4-6] In 41 baclofen toxicity cases, elderly dialysis-dependent individuals experienced neurotoxicity (doses 5–60 mg/day, median 20 mg/day) within 2–3 days

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to 16 weeks.[5] This article presents a rare case of baclofen-induced neurotoxicity in a 73-year-old patient, contributing valuable insights to the existing literature on this critical issue.

Case Report

A 73-year-old woman, escorted to the emergency department (ED) by the emergency medical services (EMS), presented with a gradual decrease in the level of consciousness. She had a medical history of hypertension, atrial fibrillation (managed with rate control medication), dyslipidemia, and ESRD (undergoing thrice-weekly hemodialysis [HD]). Her relatives reported a progressive deterioration in her mental status over the past 12 h, which prompted them to contact EMS. The patient had been partially dependent, needing assistance with mobility, eating, and using the toilet. Remarkably, her mental status and communication remained intact. Two days earlier, she had developed back pain and self-administered two 10 mg doses of baclofen, spaced 12 h apart, to alleviate her discomfort. There was no history of fever, gastroenteritis, jaundice, or falls. Two days before her presentation, she had successfully undergone her routine HD session and remained in a stable condition at home.

Upon examination in the ED, the patient exhibited a markedly decreased level of mental status, responding solely to painful stimuli. She showed stiffness, and dystonia affecting all limbs, along with a gradual decrease in both light and deep-tendon reflexes. Pupillary examination revealed equal and reactive bilateral pupils, and there was no evidence of neck rigidity. The remainder of the general and systemic examinations produced results within normal limits. Vital signs, neurological examination, and laboratory findings, detailed in Tables 1 and 2, did not suggest septic or metabolic encephalopathy. Noncontrast computed tomography of the brain revealed no acute abnormalities.

Given the history of baclofen ingestion and the onset of altered mental status within 48 h of ingestion and after consultation with the toxicologist, a diagnosis of baclofen toxicity was suspected. The patient was initiated on HD; nevertheless, after two HD sessions with a 12-h interval between them, there was only a slight improvement in her mental status. This prompted the initiation of continuous venovenous HD (CVVHD) with specific settings: a dialysate flow of 2000 mL, blood flow set at 120 mL, and maintaining a fluid balance of zero. We continued CVVHD for approximately 17.5 h, until a significant improvement in her mental status was noted. Her overall condition continued to improve the next day, leading to her discharge in a stable hemodynamic state after an additional day of observation.

We affirm that we have obtained written consent from the patient to disclose her clinical information in this journal report. The patient and her relatives acknowledge that the patient's name and initials will not be disclosed, and every effort will be made to protect her identity, although complete anonymity cannot be assured.

Discussion

Baclofen-induced neurotoxicity is an important consideration, particularly in patients with impaired renal function. This case underscores the potential dangers associated with baclofen use in individuals with ESRD and highlights the critical importance of early recognition and intervention in such cases. Baclofen, as a $GABA_B$ receptor agonist, has demonstrated efficacy in managing spasticity, making it an essential therapeutic agent for various neurological conditions.[1-3] However, its safety profile must be considered carefully, especially in individuals with renal impairment, as approximately 80%–85% of the drug is excreted through the kidneys.[4-6]

Around 50 baclofen toxicity cases are reported in CKD patients, mainly on dialysis.[5,7] Symptoms typically manifest 2–4 days post initiation.[6-8] The classic presentation of baclofen toxicity at large doses typically involves a spectrum of altered mental status, ranging from drowsiness to coma.[4,5,8] Other adverse effects mirror CNS inhibition, with standard doses causing drowsiness, lethargy, and nausea.[5-8] Rarely, hallucinations, delirium, and seizures occur. In this case, the patient's profound decrease in the level of consciousness and response only to painful stimuli indicated severe baclofen toxicity, following the exclusion of other potential causes such as septic, metabolic, or uremic encephalopathy, as well as an acute brain insult.

While standard HD sessions can be effective, continuous modalities like CVVHD offer several advantages.[4,6-9] The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup discourages the use of extracorporeal therapy (ECTR) in conjunction with standard care for acute baclofen poisoning. Yet, they advocate considering ECTR for cases of therapeutic baclofen toxicity in individuals with kidney impairment, especially when accompanied by coma requiring mechanical ventilation.[10] Continuous therapies provide more consistent and prolonged clearance of the drug, potentially leading to a quicker improvement in the patient's clinical status. In this case, the decision to transition from HD to CVVHD was justified by the limited improvement observed after two sessions of HD in a day, and it ultimately contributed to the patient's recovery.

Conclusion

This case underscores the importance of heightened awareness among health-care providers regarding the

Table 1: Comprehensive overview of vital signs, neurological examination, and past medical history at presentation, interim, and discharge

Variables	At presentation	Interim	At discharge
Vital signs and neurological examination			
Systolic blood pressure (mmHg)	165	133	118
Heart rate (beats/min)	140 → 88*	92	78
Respiratory rate (/min)	20–24	18–20	18
Oxygen saturation (SpO_2%)	98–100[$]	98–100[$]	98–100[$]
Temperature (°C)	37.2	37.4	37.2
Random blood glucose levels (mg/dL)	4.9	5.3	5.8
Neurological examination	She was very drowsy and unresponsive verbally, but maintained her airway. She exhibited limb movement in response to painful stimuli, with pupils bilaterally equal and reactive to light	She was mildly drowsy but responsive, obeying simple verbal commands and moving all four limbs, with pupils bilaterally equal and reactive to light	She was drowsy but alert, oriented, and responsive to verbal commands, moving all four limbs. Pupils were bilaterally equal and reacted to light
Past medical background			
Essential hypertension	Tablet amlodipine 10 mg once daily		Tablet hydralazine 25 mg twice daily
Dyslipidemia	Tablet atorvastatin 20 mg once daily at night		
End-stage renal disease	Thrice weekly (Monday, Wednesday, and Saturday)		
Atrial fibrillation	Tablet bisoprolol 10 mg once daily		

[$]There were no drop in Oxygen saturation levels at presentaion, interim and at discharge (essential part of the vital signs and examination as the patient had low sensorium in the background of ESRD). *After receiving diltiazem

Table 2: Laboratory investigations, chest radiograph findings, and computed tomography scan of the brain at presentation, interim, and discharge

Variables	At presentation	Interim	At discharge
Hemoglobin (11.0–14.5; 10^{12}/L)	13.4	15.7	14.1
Platelet count (150–450; 10^9/L)	202	195	176
White cell count (2.4–9.5; 10^9/L)	5.5	6.3	6.5
Neutrophils (1.0–4.8; 10^9/L)	3.0	4.4	4.3
Lymphocytes (1.2–3.8; 10^9/L)	1.5	0.8	0.9
C-reactive protein (0–5 mg/L)	9	30	46
Sodium (135–145 mmol/L)	137	146	138
Potassium (3.5–5.1 mmol/L)	5.4	4.7	4.2
Creatinine (45–84 μmol/L)	589[?]	333	212
Urea (2.8–9.1 mmol/L	9.9	4.2	5.5
Estimated GFR-MDRD (mL/min/1.73 m^2)	6	11	11
Anion gap (5–13 mmol/L)	14	14	11
Bicarbonate (22–29 mmol/L)	26	24	23
Alanine aminotransferase (0–33 U/L)	7	9	8
Alkaline phosphatase (35–104 U/L)	103	79	77
Aspartate aminotransferase (0–32 U/L)	18	22	21
Bilirubin, total (0–17 μmol/L)	7	5	10
Protein, total (66–87 g/L)	77	65	60
Ammonia (11–51 μmol/L)	26	-	-
Creatine kinase (55–170 U/L)	72	-	-
Magnesium (0.66–0.99 mmol/L)	0.94	-	-

[?]Her predialysis baseline creatinine consistently fell within the range of 500–600 μmol/L. Her urine dipstick yielded negative results for nitrates and leukocytes, effectively ruling out a urinary tract infection. Her chest radiograph was suggestive of pulmonary edema, likely due to underlying CKD, along with no signs of infective infiltrates. Initial plain computed tomography (CT) scan of the brain ruled out any acute structural pathology causing her symptoms. Estimated GFR-MDRD: Glomerular Filtration Rate - Modification of Diet in Renal Disease

potential risks associated with baclofen use in patients with renal impairment. Furthermore, it emphasizes the significance of early recognition and intervention to achieve favorable outcomes in cases of baclofen toxicity. Future research may provide additional insights into optimizing the management of baclofen-induced neurotoxicity, potentially leading to improved outcomes and reduced morbidity in affected patients.

Authors' contribution statement using CRediT

NE: Conceptualization, data curation, methodology, resources, writing – original draft, writing – review, and editing. DH: Conceptualization, data curation, resources, writing – original

draft, writing – review, and editing. SA: Conceptualization, investigations, methodology, project administration, supervision, writing – review, and editing.

Conflicts of interest
None declared.

Consent to participate
The authors confirm that they have acquired all necessary patient consent forms, including consent from the patient's relatives, to share the patient's clinical information in this journal report. The patient and her relatives acknowledge that the patient's name and initials will not be disclosed, and every effort will be made to protect her identity, although complete anonymity cannot be assured.

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