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Encephalopathy and Hypotonia due to Baclofen Toxicity in a Patient with End-Stage Renal Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 57
Final Diagnosis: Baclofen toxicity
Symptoms: Encephalopathy • hypotonia
Medication: Baclofen
Clinical Procedure: Hemodialysis
Specialty: Critical Care

Objective: Unusual or unexpected effect of treatment

Background: Baclofen is a centrally acting gamma-aminobutyric acid agonist used for the symptomatic relief of skeletal muscle spasm and spasticity in traumatic spinal cord lesions, multiple sclerosis, cerebral palsy, and stroke. It is also used in the treatment of chronic hiccups and cocaine abuse. Baclofen-induced central nervous system depression is rare at the usual therapeutic doses. However, patients with impaired renal function are at a higher risk of developing baclofen toxicity, even at a lower dose.

Case Report: A 57-year-old woman with end-stage renal disease on hemodialysis was admitted to our emergency department with progressive confusion and a generalized decrease in muscular tone. There was no obvious metabolic or infectious etiology that could have explained her condition. A comprehensive laboratory and imaging workup was negative. A review of her medication showed that she had recently been prescribed baclofen for muscular spasm. She was diagnosed with baclofen toxicity and was treated with emergent hemodialysis, which improved her mental status and her decreased muscle tone. Repeated sessions of hemodialysis administered on her second and third days of admission ultimately produced sustained clinical improvement and a complete return to her baseline mental status. She was subsequently discharged home with instructions to stay off baclofen.

Conclusions: Baclofen toxicity is an under-diagnosed condition, especially in patients with renal dysfunction. Physicians should consider baclofen toxicity in patients with suboptimal kidney function on baclofen who present with altered mental status. Emergent hemodialysis and intensive care unit monitoring is recommended.

MeSH Keywords: Baclofen • Consciousness Disorders • Kidney Failure, Chronic • Muscle Hypotonia • Spasm

Abbreviations: GABA – gamma-aminobutyric acid; ESRD – end-stage renal disease; HD – hemodialysis; ICU – intensive care unit; GFR – glomerular filtration rate; CrCL – creatinine clearance; AUC – area under the curve; CNS – central nervous system

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/893222>



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Background

Baclofen is a centrally acting gamma-aminobutyric acid (GABA) agonist used for symptomatic relief of skeletal muscle spasm and spasticity in traumatic spinal cord lesions, multiple sclerosis, cerebral palsy, and stroke [1]. It is also used in the treatment of chronic hiccups and cocaine abuse [2], and has recently become popular as a recreational drug. Baclofen-induced central nervous system depression is rare at typical therapeutic doses. However, patients with impaired renal function are at a higher risk of developing baclofen toxicity, even at a lower dose, and baclofen effects can be prolonged in these patients [3,4]. This case report describes a patient with baclofen-induced encephalopathy and hypotonia. The authors describe the pathophysiology, clinical manifestations, and management of this condition, with a review of the literature.

Case Report

A 57-year-old woman presented to the emergency department of our hospital with an altered level of consciousness that started insidiously and progressively became worse over the course of one day. Her medical comorbidities included end-stage renal disease (ESRD) on hemodialysis (HD), hypertension, diabetes mellitus, hyperthyroidism, cervical spondylosis, and chronic lumbar osteoarthritis. Significant surgical history included an arteriovenous fistula placement 5 years previously and a Caesarian delivery. On initial evaluation, she was confused with decreased responsiveness to voice and verbal commands. Her level of consciousness fluctuated, and she showed an inability to concentrate. She did not have fever, headache, neck stiffness, photophobia, nausea, vomiting, seizures, head injury, loss of consciousness, diplopia, dysarthria, ataxia, weakness, numbness, or bowel or bladder complaints. She had not traveled recently and had no sick contacts. She did not smoke cigarettes or use illegal drugs. She did not miss her HD sessions. Her home medications included aspirin (81 mg once a day), simvastatin (20 mg once at night), metoprolol (25 mg twice a day), insulin aspart (24 units three times a day with meals), insulin glargine (36 units at bed time), methimazole (5 mg half tablet once a day), gabapentin (100 mg twice a day), and baclofen (10 mg twice a day).

On examination, the patient was obese, with a height of 165 centimeters, weight of 110 kilograms and body mass index of 40.4. She was afebrile with a blood pressure of 140/85 mm Hg, a pulse rate of 78 per minute, a respiratory rate of 18 per minute, and a pulse oximetry oxygen saturation of 98% on ambient air. There were no signs of injury. There was no peculiar odor to her breath or her clothes. Her pupils were round, equal, and reactive to light. A neurologic examination was significant for a generalized decrease in muscular tone with normal

deep tendon reflexes and plantar reflexes. She was not alert or oriented to herself or her surroundings. Her Glasgow Coma Scale (GCS) was 11. There were no signs of meningeal irritation. The fundus showed no papilledema or hemorrhages. Lung auscultation revealed bilateral breath sounds with no adventitious sounds. Her abdomen was soft and non-tender with no palpable visceromegaly, and her bowel sounds were normal.

The patient's lab results on presentation and during hospitalization are summarized in Table 1. Of note, her arterial blood gas was normal. A computerized tomography scan of the brain without contrast and a chest X-ray were also normal. The electrocardiogram showed a normal sinus rhythm. A serum toxicology screen was negative.

In view of the absence of an obvious etiology for the patient's altered mental status, we carefully reviewed her history. This review revealed that the patient had presented to her primary care physician with complaints of muscular spasm 1 week prior to admission, for which she was prescribed baclofen, 10 mg twice daily (total dose of 140 mg in 1 week). This was the only new medication that had been added to her regimen. Considering this fact, our clinical suspicion was high for baclofen toxicity, and she was administered emergent HD for 4 hours in the emergency room. Her mental status improved, although she remained somnolent and confused. She was admitted to the intensive care unit (ICU) for monitoring, where she underwent a repeat session of HD for 3 hours on her second day of admission that produced sustained clinical improvement. On the third day of admission, a third session of HD was performed for 3.5 hours that yielded a complete return to baseline mental status (GCS 15). She was subsequently discharged home and instructed not to take baclofen.

Discussion

Baclofen is a lipophilic, gamma-aminobutyric acid (GABA) derivative that acts on GABA-B receptors in the spinal cord. At therapeutic doses, it exerts a long-lasting attenuating effect on muscle tone but has almost negligible effects on the central nervous system [1], despite readily penetrating the blood-brain barrier. Baclofen is effective in treating muscle spasticity, rigidity and pain. It has also been used in addiction medicine because it alters the reinforcing effects of abused substances [2]. Intrathecal baclofen therapy is also very effective in patients with refractory spasticity [3].

The daily dose of baclofen ranges from 5 to 60 mg, with a mean dose of 20 mg in patients with normal renal function. It is rapidly absorbed after oral intake, with a volume of distribution of 0.83 L/kg, 30% of which is bound to protein [4]. Its mean plasma elimination half-life is 3.5 hours [5]. About

Table 1. Laboratory parameters.

Laboratory tests	Prior to admission	Pre dialysis	After 2 nd dialysis	After 3 rd dialysis
Hemoglobin (g/dL)	12.4	11.8	11.8	12.1
Hematocrit (%)	39.5	36.6	36.2	37.8
WBC (k/ μ l)	7	6.8	7.1	7.2
Platelet (k/ μ l)	215	214	203	199
EGFR (mL/min/1.73 m ²)	5	4.5	7	21
Sodium (mEq/L)	138	135	136	138
Potassium (mEq/L)	5.2	4.3	3.7	3.2
Chloride (mEq/L)	96	96	92	94
CO ₂ (mg/dL)	28	26	29	28
Calcium (mg/dL)	9.7	9.9	9.3	9.7
Phosphorus (mg/dL)	3.9	3.4	3	3.3
Glucose (mg/dL)	96	120	98	102
BUN (mg/dl)	54	47	10	8
Creatinine (mg/dL)	9.1	9.7	3.4	2.5
ALT (units/L)	13	7	6	6
AST (units/L)	11	17	9	10
Total Protein (g/dL)	7.3	8	7.6	8
Albumin (g/dL)	3.8	3.4	3.3	3.6
Total bilirubin (mg/dL)	0.3	0.3	0.2	0.3
Lactic acid (mmoles/L)	2	1	0.9	0.8
Ammonia (μ moles/L)		15	10	

WBC – white blood cell; EGFR – epidermal growth factor receptor; BUN – blood urea nitrogen; ALT – alanine aminotransferase; AST – aspartate transaminase.

15% of baclofen is metabolized by the liver into its inactive, deaminated metabolite, and 69–85% is excreted unchanged in the urine [6]. The main determinant of urinary excretion is glomerular filtration rate (GFR), and there is a high correlation between creatinine clearance (CrCL) and baclofen clearance.

Baclofen accumulation and neurotoxicity may occur with therapeutic doses in patients with impaired renal function [6]. As GFR or CrCL decreases, the elimination of baclofen is compromised, leading to an increased area under the curve (AUC) that may potentially affect the safety profile. Although the concentration of baclofen in the brain is lower than in serum, it is eliminated more slowly from the central nervous system (CNS) than from serum. Entry of baclofen into the CNS is largely a function of its moderate lipid solubility. However, an active transport system may account for the greater clearance of baclofen from the CNS. In the CNS, baclofen decreases excitatory

neurotransmitter output and enhances the effects of 1-glutamate and substance P, both of which are involved in the pain pathway. It can also enhance the release of the endogenous opioid methionine-enkephalin. In cases of overdose, plasma and CNS levels of baclofen are poorly correlated [7].

Manifestations of baclofen toxicity include delirium, seizures, excessive salivation, dizziness, nausea, vomiting, somnolence, hypotonia and coma. Tachycardia and hypertension are considerably more common, especially at high doses, but bradycardia and hypotension can also occur with either high or low doses [8]. Hyporeflexia or areflexia, hypothermia, rhabdomyolysis, cardiac conduction abnormalities and abnormal EEG pattern with non-convulsive status have all been reported in patients with acute baclofen toxicity [9]. Prolonged tachycardia can also occur as a result of sympathetic hyperactivity following a period of depression, especially while recovering from

toxicity [1]. In addition, akinetic mutism can occur through interruption of the thalamocortical limbic pathway [10], a consequence of toxicity that can mimic brain death [11].

Gabapentin acts synergistically with baclofen and can significantly potentiate baclofen-induced motor impairment and side effects [12]. Our patient had not missed any HD sessions prior to admission, but was taking gabapentin, which likely exacerbated the effect of baclofen. Medications that affect renal function can also potentiate baclofen toxicity. Therefore, clinicians should be vigilant in identifying the potential risk of renal dysfunction when prescribing baclofen [13].

Co-ingestion with alcohol, hydrocodone, zolpidem, mirtazapine, buprenorphine or cannabis can also potentiate the effects of baclofen. Notably, the use of higher doses of baclofen in conjunction with CNS depressants can have a pronounced synergistic effect with major functional consequences, including flaccid paralysis [14]. Neurotoxicity can be pronounced in those patients, as was evident in our case.

Treatment for baclofen toxicity is supportive. HD is the most common treatment modality as it shortens the baclofen half-life [4]. Early diagnosis, early initiation of hemodialysis and reduction of serum concentrations of baclofen can lead to early recovery from toxicity [6]. The recovery time can be as short as 2 hours in patients who receive HD. Our patient required two additional sessions of hemodialysis to achieve complete clinical recovery. Delayed diffusion across the blood–brain barrier could account for the lag in clinical recovery after HD. In one

small study, patients who were intoxicated with high doses of baclofen (>200 mg) more frequently required ICU admission (85%) or mechanical ventilation (54%), and had longer hospital stays [8]. Because withdrawal symptoms have been described during recovery [15], patients should be monitored in an ICU.

Conclusions

To the best of our knowledge, there have been 22 published reports involving 44 patients in the English-language literature that describe baclofen toxicity in patients with impaired renal function [5,16]. The risk of baclofen toxicity is higher in patients with ESRD, even at lower doses, and its administration should be avoided in patients with a GFR <30 mL/min/1.73 m² [16]. Physicians should consider baclofen toxicity in patients who present with an altered mental status and show a history of taking baclofen with suboptimal kidney function. Concomitant use of baclofen with other CNS depressants should be avoided, as it increases the risk of toxicity.

Conflict of interest

The authors of the manuscript have no conflicts of interest to declare.

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