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CASE REPORT

Transient alteration of consciousness in spinal cord injury secondary to Baclofen use: a case report

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INTRODUCTION: Oral baclofen is commonly used for spasticity management, especially with neurogenic bladder in spinal cord injury (SCI). A less common side effect of baclofen is transient alterations of consciousness, which can easily be confused for altered mental status secondary to orthostatic hypotension in SCI.

CASE PRESENTATION: A 43-year-old man with an acute SCI secondary to an aortic dissection was found to have episodes of confusion after titrating oral baclofen from 5 mg three times per day to 10 mg three times per day at an acute rehabilitation facility. Orthostatic hypotension was initially suspected as the cause of transient alterations of consciousness; however, he was never found to be hypotensive during these episodes. His confusion resolved several days after discontinuation of baclofen.

DISCUSSION: Although, confusion and lightheadedness in SCI are commonly caused by orthostatic hypotension, it is important for physicians to be cognizant of baclofen's side effects, which increase in the setting of acute kidney injury (AKI). If an adverse effect is suspected, baclofen should be tapered while remaining observant for signs of baclofen withdrawal, which can be life-threatening. This case report is a reminder for clinicians to be aware of the uncommon adverse effects of baclofen when initiating therapy in SCI, especially in patients with AKI and neurogenic bladders.

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INTRODUCTION

Baclofen is a medication often used in the management of chronic spasticity. Common side effects include muscle weakness and sedation [1]. Less common adverse effects include confusion, hypotension, and seizures, amongst others [1]. Significant physiological variation exists in baclofen absorption, excretion, and dosage requirements for achieving desired effects [2–4]. Patients with decreased renal function are at increased risk for elevated baclofen plasma levels since baclofen is primarily cleared through the kidneys [5]. Symptoms from acute toxicity can occur in as early as 3 h after baclofen administration [6]. Immediately addressing toxicity results in better patient outcomes [7]. However, it is important to note that baclofen withdrawal in chronic use can be life threatening [8, 9].

In this case report, a 43-year-old man presented with acute chest pain and was found to have an aortic dissection. Emergent repair was performed with graft placement. Complications of his aortic dissection included a spinal cord infarct resulting in incomplete paraplegia: T2 American Spinal Injury Association Impairment Scale/ISCoS International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) grade C SCI.

He developed acute kidney injury (AKI) during his hospitalization. He was eventually discharged to a comprehensive inpatient acute rehabilitation facility and started on baclofen for spasticity. Shortly after starting the baclofen, the patient experienced mild dizziness. Eleven of the first fifteen days after starting baclofen, the patient had episodes of dizziness, lightheadedness and was noted to be more tangential and distractible. Routine cardiogenic and neurologic causes were ruled out. Baclofen was discontinued and episodes of confusion and lightheadedness resolved on the sixth day after discontinuation. This case serves as a reminder that baclofen, a spasticity medication commonly used in spinal cord injury (SCI), in the setting of AKI [6] can cause transient alteration of consciousness.

CASE PRESENTATION

A 43 year-old man with a history of human immunodeficiency virus (HIV), noncompliant with his medications, active polysubstance abuse including cocaine, perirectal abscess, orchiectomy years prior for testicular abscess, presented to a local hospital with severe chest pain. He was found to have an ascending aortic dissection and was transferred to a tertiary care center for emergent repair of his aortic dissection, unilateral anterograde cerebral perfusion and deep hypothermic circulatory arrest. Post-operatively, the patient was found to be paraplegic with bilateral pain and temperature sensation loss below the T-2 dermatome. An MRI of his spinal cord revealed a small right-sided C3 hemicord signal abnormality, concerning for an acute infarct, as well as acute infarcts spanning T7–T8 to T12–L1 (conus). A lumbar drain was temporarily placed to monitor perfusion pressures. An echocardiogram about two weeks

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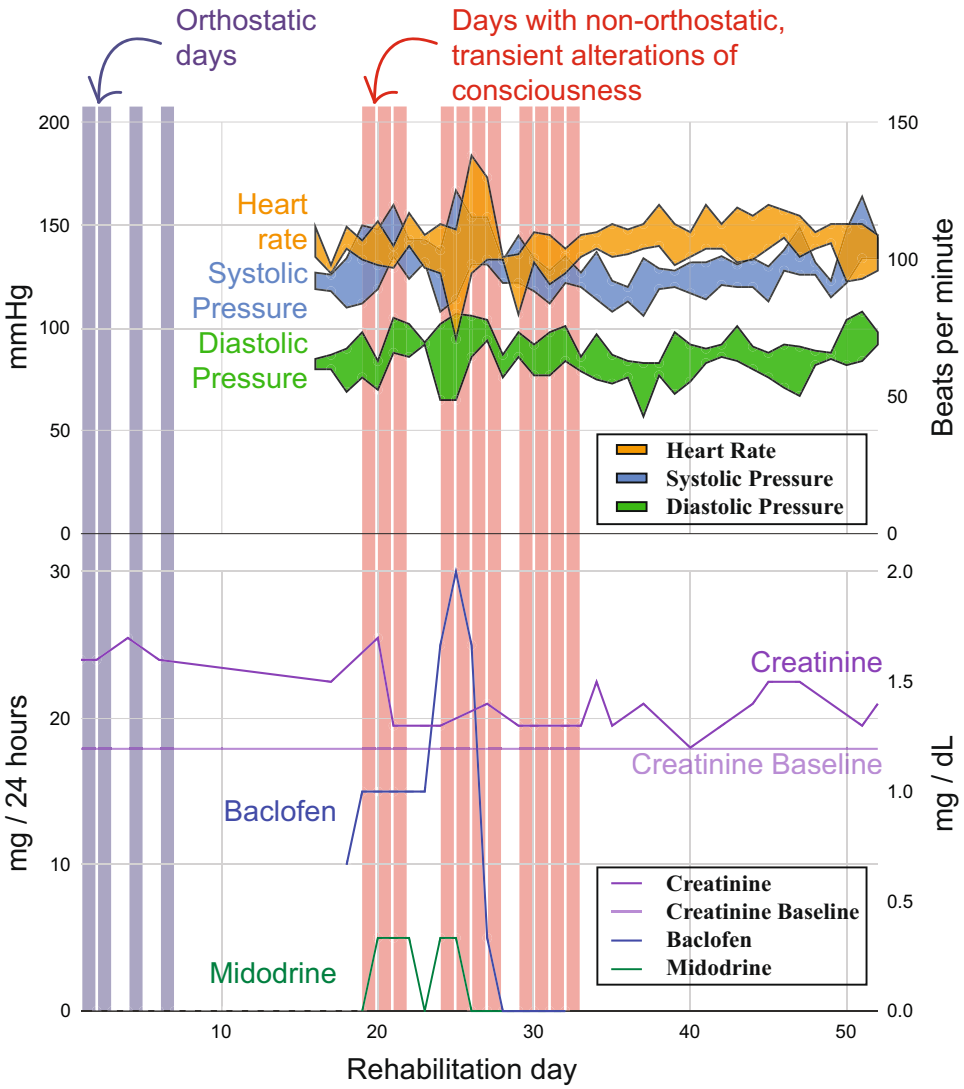

Fig. 1 Laboratory values during rehabilitation. Values are plotted during inpatient rehabilitation. Upper and lower bounds of daily heart rate, systolic and diastolic blood pressure are plotted. Days with at least one episode of non-orthostatic, transient alteration of consciousness and separately days with orthostasis are shown. The patient was never found to be hypothermic (not shown).

later revealed an ejection fraction of 45–50%, mild aortic regurgitation, mild mitral regurgitation, trace tricuspid regurgitation, trace pulmonic regurgitation and mild aortic root dilation. Highly active antiretroviral therapy (HAART) was restarted. Initially he was placed on trimethoprim/sulfamethoxazole for pneumocystis jiroveci prophylaxis but was converted to atovaquone after he was found to be hyperkalemic. His perirectal abscess was drained and cultures revealed pseudomonas and methicillin resistant staphylococcus aureus, for which he was started on an antibiotic regiment that included vancomycin.

The patient's hospital course was further complicated by acute kidney injury (AKI; Fig. 1 Creatinine maximum 3.1 mg/dL, lab normal upper limit 1.2 mg/dL; patient baseline 1.2 mg/dL) with electrolyte abnormalities secondary to a combination of contrast nephropathy, renal hypoperfusion during surgery, and vancomycin toxicity. He was also found to have a urinary tract infection (UTI) with possible renal obstruction observed on computed tomography but lacked signs or symptoms; additional antibiotics were not warranted for UTI treatment since he was already on sufficient coverage for his perirectal abscess. He was transferred to an acute rehabilitation facility about three weeks after his initial presentation. Five days later he was found to have variable systolic blood pressures ranging from 60 to 190 mmHg. An echocardiography revealed abnormal aortic root and ascending aorta dilation, with an intramural hematoma of the ascending aorta. Duplex ultrasound of his right calf revealed a deep vein thrombosis. He was transferred back to the tertiary hospital where CT angiography of his chest, abdomen, and pelvis with and without contrast revealed a stable dissection without any graft leak and thus did not require further surgical intervention. Duplex ultrasonography of his carotids revealed vertebral artery dilation but with normal carotid flow. Neurosurgery recommended no further intervention as it was unlikely to be contributing to his symptoms. His hypotension improved with intravenous fluid hydration as well as cessation of carvedilol. He was started on midodrine for low blood pressures. One week later he was discharged back to the acute rehabilitation facility for comprehensive inpatient rehabilitation of his activities of daily living as well as gait and motor deficits secondary to his SCI.

Initially he was making good progress in rehabilitation despite mild, intermittent episodes of orthostatic hypotension (inpatient rehabilitation days 1, 2, 4 and 6; Fig. 1). On inpatient day 19, he was started on baclofen 5 mg by mouth twice daily for his spasticity. The day after starting baclofen, he complained of

dizziness while sitting, but was documented to have normotensive systolic pressures. The next day, he was noted to be "very tangible and distractible with frequent need for redirection" during therapy. His baclofen dose was escalated to 10 mg by mouth three times a day (see Fig. 1 for timing of dosing). The patient continued to have episodes of transient alterations of consciousness described by observers as confusion, lightheadedness and dizziness (noted to have multiple episodes on 11 separate days as documented by various support staff; see Fig. 1). In fact, they were described by his physical and occupational therapists as "brief syncopal episodes", where the patient was unresponsive for a period lasting approximately one minute. The patient never bit his tongue or lost bowel/bladder continence (incomplete SCI). Given the patient's extensive cardiac history, his blood pressure and heart rate were monitored closely during his therapy sessions. During these episodes of transient alterations of consciousness, the patient was never found to be hypotensive; however he was tried on midodrine as needed (Fig. 1), but it did not help prevent these episodes so it was discontinued. The patient's temperature was not taken specifically during these episodes, but over the course of his baclofen therapy he was never found to be hypothermic.

Cardiac and neurologic diagnostics were performed to further rule out syncope as the source of these episodes. Cardiology workup was unremarkable, EKG revealed mild tachycardia with severe left ventricular hypertrophy. His echocardiogram was unchanged. Cardiology advised to increase his hydration. Neurological syncope workup was unremarkable, including a normal computed tomography of his head, with no evidence of mass, intracranial hemorrhage or hydrocephalus. Since cardiac and neurological etiologies couldn't explain these episodes of transient alterations of consciousness, it was decided to wean the patient off of baclofen therapy, since his episodes began only after initiating the medication. Baclofen was tapered down over the next three days (Fig. 1), episodes resolved after his fourth day of stopping the medication and he has not had any further episodes.

The patient was interviewed several months after these events. Without prompting, he described the episodes as dizziness and lightheadedness. He stated that he did not remember changes in vision, despite several healthcare providers documenting it at the time. He could tell when a transient alteration of consciousness episode was coming on as he felt lightheaded. After sitting down for approximately 10 min or changing position, he felt better. The patient has previously experienced orthostatic hypotension and when asked to compare the two, he distinguished these episodes from orthostatic hypotension by the lack of feeling any warmth, flushing, or diaphoresis. He has not had any episodes since his baclofen was discontinued. The remainder of his inpatient stay went well and he was safely discharged home, using a manual wheelchair. His neurological status at time of discharge was T2 ISNCSCI grade C SCI. He was discharged to outpatient occupational and physical therapy and was initially followed by urology, psychology and spinal cord physicians.

DISCUSSION

We present a 43 year-old man with an acute ischemic SCI secondary to hypoperfusion during an emergent aortic dissection repair, resulting in T2 ISNCSCI grade C SCI. He had a history of polysubstance abuse including cocaine which likely contributed to his aortic dissection. HAART was restarted and a perirectal abscess was drained. He was started on an antibiotic regimen including vancomycin for a perirectal abscess. He developed an AKI, likely secondary to a combination of contrast nephropathy, renal hypoperfusion during emergent surgery and vancomycin toxicity.

The patient was discharged to a comprehensive inpatient rehabilitation facility about three weeks after his procedure. He was initially noted to have orthostatic episodes. Almost two weeks later, he was also started on baclofen for spasticity secondary to his spinal cord injury. The day after starting baclofen therapy, he had an episode of normotensive dizziness. The next day, he was noted to be more distractible during therapy. He experienced more episodes of transient alterations of consciousness, some being described by therapists as near syncopal events. These events consisted primarily of confusion and lightheadedness that usually resolved within minutes. He also reported blurry vision during some episodes. Each time an event occurred during therapy, his vital signs were checked immediately and he was assessed by the physician. While orthostasis is the more common cause of syncope in the SCI population, the patient was either normotensive or hypertensive, both before and after each event, making orthostasis an unlikely cause. Routine cardiogenic and neurogenic causes of altered mental status were ruled out through extensive diagnostic workups.

Confusion and lightheadedness in SCI patients is commonly attributed to orthostatic hypotension [10]; however, a less common cause of transient alterations of consciousness is an adverse reaction to oral baclofen [1], which can mimic symptoms of orthostatic hypotension. This case serves as a reminder that the differential for altered mental status in SCI should include baclofen toxicity. Baclofen is a GABA receptor agonist [11], and is often used in the management of spasticity [12]. Additionally, baclofen is also utilized as a treatment for alcohol cravings in dependent persons [13]. Side effects of baclofen include hypotension, bradycardia, changes in vision, hypothermia, mental status changes, abnormal EEG patterns and myoclonus [2]. Oral baclofen is enterally absorbed and plasma concentrations peak between 2 and 3 h after ingestion [1]. Approximately 70% of clearance occurs renally and the half-life ranges from 2 to 6 hours [1]. It is important to note that significant inter-patient variability exists in pharmacokinetic measures including absorption and excretion [3], as well as blood and cerebrospinal fluid (CSF) levels to achieve therapeutic response [4]. Baclofen's brain penetration has been attributed as a mechanism for inter-patient response variability [3]. Glomerular filtration rate appears to be the dominant transport mechanism for removal [2].

Patients with renal dysfunction are at increased risk for baclofen toxicity [5]. Baclofen dosage should be reduced in moderate renal dysfunction and should not be used in severe dysfunction [5]. Acute baclofen neurotoxicity can typically be observed between 3 h to four days after initiation of baclofen therapy [6]. Although acute intoxication typically has a faster symptom onset with more severe clinical encephalopathic manifestations, individuals who receive immediate attention to address baclofen toxicity can still achieve benign outcomes [7]. One study found that some patients with stable medication regimens had an accumulation of baclofen in blood plasma over time [14]. The authors suggested that this was likely due to impaired renal clearance, indicating that those with neurogenic bladder and renal insufficiency are at higher risk of baclofen accumulation. This study also noted that different patients required varied blood concentrations to achieve anti-spasticity effects; plasma concentrations are often 10 fold that of CSF concentrations [4] and are not a reliable measure of brain penetration [3]. With regards to kidney function, SCI patients might have generally decreased glomerular filtration rates [15], putting them at higher risk for baclofen accumulation. There are several case reports associated with rapid baclofen toxicity in patients with renal dysfunction [5, 6, 16, 17] and even the development of confusion and disorientation following baclofen initiation in an SCI patient with concurrent AKI secondary to nonsteroidal anti-inflammatory use [18]. In severe cases of acute toxicity, treatment is supportive, with priority towards that of airway protection and maintenance of respiration, often in the intensive care unit [19]. Activated charcoal can be administered in acute oral overdose [20]. In cases of severe baclofen toxicity with associated renal dysfunction, hemodialysis has been shown to be effective [5, 21]

Our patient was on a relatively low dose, as the maximum FDA-approved dose of oral baclofen is 20 mg four times per day for a total of 80 mg daily [1]. It is recommended that discontinuation of high doses of baclofen occur as a taper across several weeks [22], as abrupt cessation of oral or intrathecal baclofen can result in life-threatening withdrawal [8, 9]. Withdrawal signs and symptoms include weakness, fevers, sedation, altered mental status, respiratory insufficiency, autonomic instability, increased spasticity, dyskinesia, delirium, hallucinations, psychosis and seizures [8, 9, 23–26]. Patients on long term baclofen therapy are at particular risk for withdrawal during perioperative medication discontinuation [27]. Treatment involves restarting previously tolerated baclofen dosages while providing supportive care in an intensive care setting if necessary [22, 28]. Benzodiazepines and antiepileptics can be used for agitation and seizure management [23]. In the case of severe withdrawal, a patient's original baclofen dosage and frequency should be restarted and then tapered by 5–10 mg per week until reaching a target dose [29]. In the case of intrathecal baclofen withdrawal, immediate restoration of medication infusion as well as supportive care with low dose benzodiazepines or propofol can be used to mitigate adverse effects in an intensive care unit [30]. Dantrolene, flumazenil and cyproheptadine have also been proposed as treatments for intrathecal withdrawal [31–33].

Baclofen is often used in SCI for spasticity management. Side effects include hypotension, bradycardia, changes in vision, hypothermia, and mental status changes. This case report emphasizes the need for clinicians to be aware of the uncommon adverse effects of baclofen when initiating therapy in SCI patients, especially those with AKI and neurogenic bladders. If a patient is suspected for baclofen side effects, baclofen should be tapered; if the patient is on high doses, that taper should occur over several weeks. Abrupt baclofen discontinuation risks life-threatening withdrawal; symptoms of withdrawal include altered mental status, respiratory insufficiency, autonomic instability, and seizures. If withdrawal is suspected the original tolerated dose should be restarted, followed by a taper over several weeks.

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COMPETING INTERESTS

The authors declare no competing interests.

INFORMED CONSENT

Patient gave verbal informed consent on 8/25/2020.

ADDITIONAL INFORMATION

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