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CASE REPORT

Altered Consciousness Following Head Injury in Advanced Renal Failure: Find the Culprit

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Conscious change following head injury needs a scrutiny of the "nontraumatic" cause to avoid inappropriate management and catastrophic complication. We described an 81-year-old diabetic woman with advanced chronic kidney disease (CKD) (estimated glomerular filtration rate: 6 ml/min/1.73 m^2) re-presented to Emergency Department with altered mentality and generalized muscular hypotonia 2 days after falling with a head injury. Her initial mentality was alert, and computed tomography of the brain was negative for organic lesions; she has been given oral baclofen 10 mg daily to control her associated spastic back pain. The repeated laboratory and imaging studies were still unrevealing. Her serum baclofen concentration was markedly elevated (1437 ng/ml). With emergent hemodialysis for two sessions, complete elimination of serum baclofen concentration was accompanied by full recovery of her consciousness. Nontraumatic causes, especially drug-induced neurotoxicity, must be kept in mind in traumatic patients with CKD and unexplained neurological feature.

Key words: Baclofen, encephalopathy, hemodialysis

INTRODUCTION

Conscious change after traumatic head injury can result from either direct traumatic or indirect nontraumatic causes. The traumatic causes include epidural hemorrhage, chronic subdural hemorrhage, severe brain swelling, and hydrocephalus, which can be rapidly confirmed by imaging studies. On the other hand, nontraumatic causes including toxins, drugs, metabolic abnormalities, infection, seizure, and psychogenic diseases should be cautiously assessed to avoid missing treatable or curable causes. In this study, we described an 81-year-old diabetic woman with advanced chronic kidney disease (CKD) and preceding head injury manifested progressive, conscious change caused by baclofen-induced neurotoxicity resolved by emergent hemodialysis (HD).

CASE REPORT

An 81-year-old woman presented to emergency department (ED) with comatose consciousness and generalized muscular hypotonia. She had a medical history of type 2 diabetes mellitus with advanced CKD (estimated glomerular filtration rate [GFR]: 6 ml/min/1.73 m^2) on regular medication including acarbose, amlodipine, valsartan, and furosemide. Two days ago, she was sent to ED with a headache and spastic back pain after falling in the bathroom. Her consciousness was alert, and the impression of a minor head injury with brain contusion was made by the unrevealing laboratory and imaging studies including computed tomography (CT) of the brain. She was given with medicine of acetaminophen 375 mg and baclofen 5 mg twice daily to treat her symptoms. Altered consciousness gradually developed and persisted for 12 h before arriving to ED again.

The vital signs were Glasgow Coma Scale E1M4V1, blood pressure 162/80 mmHg, heart rate 94/min, temperature 36.5°C, respiratory rate 18/min, and oxygen saturation 95–97% with 6 L/min of oxygen by nasal cannula. Further, pertinent neurological examinations demonstrated muscular hypotonia and generalized hyporeflexia. The laboratory tests

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showed serum sodium 135 mEq/L, potassium 5.2 mEq/L, chloride 103 mEq/L, serum urea nitrogen 73 mg/dL, creatinine 7 mg/dL, aspartate transaminase 23 U/L, alanine transaminase 24 U/L, glucose 118 mg/dL, albumin 3.9 g/dL, white blood cells 8,900/mm^3, hemoglobin 9.8 g/dL, and platelets 143,000/mm^3. The toxicological screens, electrocardiogram, and chest film were unremarkable. A repeated CT of the brain did not reveal any delayed organic lesion.

After the exclusion of traumatic causes, nontraumatic neurotoxicity caused by the accumulative baclofen was highly suspected due to the strong history of taking renally-eliminated baclofen, which may cause neurological symptoms in advanced CKD. A high serum baclofen concentration (1437 ng/ml) supported this diagnosis. With two sessions of emergent 4 h HD, the neurological symptom was completely reversed, and serum baclofen level was also undetectable [Figure 1]. Her hospital course was uneventful, but she was put on regular HD due to uremia.

DISCUSSION

This elderly and diabetic female with advanced CKD presented with unexplained coma 2 days following preceding head injury. The traumatic causes were excluded by brain imaging studies. She was established to have baclofen-induced encephalopathy based on the strong history of taking baclofen, elevated serum baclofen concentration, and resolution of neurological features with HD to eliminate baclofen accumulation. Drugs which were used and may potentially lead to neurotoxicity in traumatic patients with advanced CKD are shown in Table 1.

Baclofen, γ-aminobutyric acid derivative, is usually used to treat skeletal spasticity or refractory hiccups in a therapeutic serum range 80–400 ng/ml. It is mainly excreted in unchanged form by the kidneys (69–85%) with a half-life of 4.5–6.8 h. Of note, baclofen is prone to be uptake in the central nervous system once accumulated, leading to neurotoxicity or encephalopathy. This has been reported with the minimally accumulative baclofen 10 mg in CKD patients not yet on dialysis.[1-3] Our patient

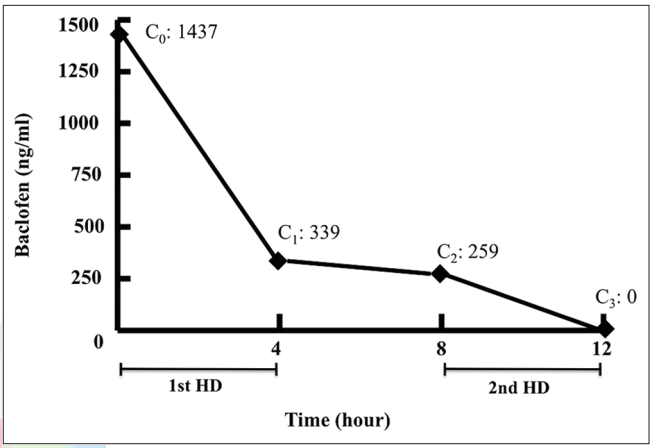

Figure 1: A serial serum baclofen concentration treated hemodialysis. C0: Initial concentration, C1: Concentration at the end of the first hemodialysis, C2: Concentration at the beginning of the second hemodialysis, C3: Concentration at the end of the second hemodialysis

Table 1: Drugs commonly used for head injury inducing encephalopathy

	Mechanism	Dosage in advanced CKD GFR (<10 ml/min/1.73 m^2)	Encephalopathy	Treatment	References
Anticonvulsants					
Carbamazepine	Blocker of voltage-gated sodium channels	75% of dose	Drowsiness to coma	HD or/and HP, plasma-pheresis, PE	7
Valproic acid	Blocker of voltage-gated sodium channels and T-type calcium channels, GABA transaminase inhibitor	75% of dose	Drowsiness to coma	HD or/and HP, naloxone	8,9
Opioids					
Morphine	Bind to opiate receptors	50% of dose	Drowsiness to coma, miosis	HD, naloxone	10
Tramadol	Bind to opiate receptors	<50-100 mg q12 h	Drowsiness to coma	HD, naloxone	11
Meperidine	Bind to opiate receptors	Avoid	Mydriasis, delirium, nervousness, tremors, myoclonus, seizure	HD	12
Muscle relaxants					
Baclofen	Activate GABA receptor	Avoid	Drowsiness to coma	HD	1-3
Orphenadrine	Inhibit central cholinergic effects, atropine-like effect	Use with great caution	Confusion to coma, excitement, hallucinations, seizures	Physostigmine	13
Chlorzoxazone	Centrally acting muscle relaxant	Use with great caution	Drowsiness to coma, excitement, restlessness	Flumazenil	14

CKD = Chronic kidney disease; HD = Hemodialysis; HP = Hemoperfusion; PE = Plasma exchange; GABA = Gamma-aminobutyric acid

developed neurotoxicity with a serum level up to 1437 ng/mL just after the administration of baclofen 10 mg/days for 1 day, supporting that its accumulative effect can occur in a very short period in advanced CKD. Some cumulative mechanisms secondary to renal failure are responsible for baclofen-induced neurotoxicity. First, baclofen accumulation phenomenon can occur because its renal elimination decline.[4] Second, there is mounting evidence that renal impairment impacts the hepatic cytochrome P450 activity and acetylation, inducing the diminishing of hepatic drug metabolism on nonrenal clearance and bioavailability.[5] Third, P-glycoprotein inhibition due to renal failure in blood-brain barrier may induce drug accumulation in the brain.[6] Furthermore, aging reduces drug distribution and increases plasma concentration when most of the reported baclofen-induced neurotoxicity occurred in the elders.[1]

Given the small molecular weight (213 Da) and low protein binding (30%) of baclofen, high-flux HD can remove 37% active baclofen for 4 h-HD and effectively reduce the half-life to 2.06–3.7 h based on one-compartment model with the equation: $C = C_0 e^{-Kt}$ (C: Baclofen serum concentration, K: Elimination rate constant, t: Time).[2,3] In our patient, the half-life of serum baclofen with HD was 2.1 h but increased up to 10.2 h during the non-HD period.

CKD with high prevalence 8–16% is recognized as worldwide public health issue,[15] and these patients are at high risk for drug accumulation and toxicity. Drug-induced encephalopathy is often misinterpreted as other causes and should be kept in mind with CKD and unexplained neurological feature. Our case reiterates the importance of a scrutiny for the "nontraumatic" cause in any traumatic patient with advanced CKD and unexplained neurological symptoms to avoid inappropriate management and catastrophic complication. In Table 1, we suggest drug dosing adjustments and avoid the use of baclofen in the patient with estimated GFR < 10 ml/min/1.73 m^2.

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Conflicts of interest

There are no conflicts of interest.

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