Nepalese Medical Journal, (2018) Vol. 1, 53 - 55

Case Report

Baclofen Toxicity in a Chronic Kidney Disease Stage 5D Patient

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ABSTRACT

The toxicity of Baclofen is extremely unusual. However, its predominant renal clearance makes its vulnerable in patients with impaired renal function. Clinical manifestations may begin as early as 2-3 days after starting the drug, even with a smaller dosage.

A 73-year-old man with end-stage renal disease on maintenance hemodialysis was admitted to our emergency department with progressive confusion, hallucination and a generalized decrease in muscular tone. There was no significant metabolic or infectious etiology that could have clarified his condition. A thorough laboratory and imaging workup was negative too. A detailed history of his medication revealed that he had recently been prescribed baclofen for neck muscular spasm (10mg twice daily). He was then diagnosed with baclofen toxicity and was treated with intensive hemodialysis. During his admission, few sessions of hemodialysis on consecutive days, eventually produced expected clinical improvement and a complete return to his previous baseline mental status.
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Keywords: Adverse Reactions; Baclofen; Dialysis; Drug-Related; Renal; Side Effects

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Submitted: 20th January 2018
Accepted: 16th April 2018
Published: 1st June 2018

Sources of Support: None
Conflict of Interest: None

Citation: Singh SR, Dhakal M, Thapa S, Khakurel S. Baclofen Toxicity in a Chronic Kidney Disease. Nep Med J. 2018;1:53-5. DOI: 10.3126/nmj.v1i1.20403

INTRODUCTION

Baclofen, which is a centrally acting gamma-aminobutyric acid (GABA) agonist, is widely used not only for symptomatic relief of skeletal muscle spasm and spasticity but also for alcohol dependence, opiates and cocaine abuse and cigarette addiction these days.[1,2] Adverse effects of baclofen, manifesting central nervous system involvement are typically rare when orally prescribed in healthy adults. Since the drug is primarily excreted unchanged from kidneys[3], patients with impaired renal function are at a greater risk of developing baclofen toxicity. Adverse effects may be obvious even at a smaller dose in such cases.

The half-life of baclofen is known to be 2–6 hours for therapeutic oral doses in healthy adults and elderlies,[4,5] but half-life increases in patients with renal insufficiency.[6] Very less amount goes into hepatic metabolism.

Baclofen is usually detected in blood by gas chromatography-mass spectrometry and high performance liquid chromatography. Rapid methods used for toxicological screening are not available for detection of baclofen in blood. Therefore, awareness of the problem and a strong index of suspicion are required to reckon baclofen toxicity.

Baclofen has a low volume of distribution and a low protein binding, so its removal is significantly enhanced by hemodialysis (HD). Moreover, HD also appeared to shorten the period of toxic effects in patients with severely impaired renal function.[7] Meanwhile, some authors pointed that HD is not superior to continuous ambulatory peritoneal dialysis (CAPD) for decreasing the recovery time of baclofen-associated neurotoxicity.8 This case report reveals a patient with baclofen mediated encephalopathy and hallucination. The authors describe the pathophysiology, clinical manifestations, and management of this condition, with a review of the literature.

CASE REPORT

A 73-year-old male diabetic patient with End-stage Renal Disease (ESRD) on twice weekly hemodialysis was newly prescribed oral Baclofen 10 mg twice daily for spastic pain of neck. His routine medications included Metoprolol, Atorvastatin, Febuxostat, Methylcobalamin, Metolazone, Calcium with vitamin D, Aspirin, Pantoprazole, Multivitamin, Pregabalin, Inj. Human Insulin since 13 yrs. He has been taking baclofen since last 4 days. After 1 day, i.e. within 24 hours of intake of baclofen he started experiencing dizziness, confusion. His scheduled Dialysis was on the same day; he underwent dialysis for 3 hours 15 minutes. Post dialysis he again received baclofen on the same evening, since then he started experiencing dystonia, irregular jerky movement of upper and lower limb, muscle rigidity, slurred speech, confusion, visual hallucination, euphoria, somnolence and came to Emergency Department. On examination, his vitals were stable and Chest, Cardiovascular and Abdominal examination were normal. No signs of head trauma, meningeal irritation or any sensory/motor deficit were present. Immediate investigations were done which is listed in table.1, which were normal. His Arterial Blood Gas, Electrocardiogram CG and Chest X-Ray were normal. There was no other obvious cause for this condition except from intake of a new drug, i.e. baclofen. Considering this fact, we suspected it to be Baclofen toxicity and underwent immediate hemodialysis for 4 hours at the day of admission and 3 hours on the next day. Patient was symptomatically better.

DISCUSSION

Baclofen is a GABA (y-aminobutyric acid- an inhibitory transmitter in Central Nervous System) derivative, but it is not certain whether baclofen reduces muscle tone by GABA mimetic action, because bicuculline (a GABA antagonist) does not block its effects. Recently GABA receptors have been subdivided into GABA-A (bicuculline sensitive) and GABA-B (bicuculline insensitive) and it has been proposed that baclofen acts selectively through GABA-B receptors.

The primary site of action of baclofen is considered to be in the spinal cord where it depresses both polysynaptic and monosynaptic reflexes. As such, it does produce muscle weakness. Baclofen is well absorbed orally and is primarily excreted unchanged in urine with a t1/2 of 3-4 hours.[3]

Side effects of baclofen are: Transient Drowsiness (10-63%), dizziness (5-15%), confusion (1-11%), insomnia, euphoria, hallucinations, slurred speech.

Table 1A: Vital Signs

Blood Pressure (mmHg)	140/70
Pulse (per min)	84
Temperature (□C)	96.5
SPO2 (%)	97 % in room air

Table 1B: Hematological Parameters

Hemoglobin (gm/dl)	**8.0**
WBC (per cumm)	**8900**
Neutrophils (%)	75
Lymphocyte (%)	24
Eosinophils (%)	01
Platelets (per cumm)	**240,000**

Table 1C: Biochemical Parameters

Blood Sugar Random (mg/dl)	223
Serum Urea (mg/dl)	142
Serum Creatinine (mg/dl)	8.6
Sodium (mmol/L)	141
Potassium (mmol/L)	5.2
Serum Calcium (mg/dl)	7.8
Phosphorous (mg/dl)	5.8
Liver Function tests	
Serum Total Protein (gm/dl)	5.7
Serum Albumin (gm/dl)	3.0
Serum Bilirubin	
SGPT (IU/L)	15
SGOT (IU/L)	12
Lipid Profile	
Cholesterol (mg/dl)	149
HDL Cholesterol (mg/dl)	43
LDL Cholesterol (mg/dl)	78
Triglyceride (mg/dl)	137

Table 1D: Arterial Blood Gas Parameters

pH	7.49
PO2 (mmHg)	87
PCO2 (mmHg)	34.4
HCO3 (mEq/L)	27.2

Baclofen is a centrally acting GABA agonist which is prescribed as therapy for spasticity in spinal cord region. In this case, Patient was prescribed 10mg d twice daily for neck spasm. Ingested baclofen is absorbed rapidly and completely, there after 69-89% are excreted without changing in urine and 15% are metabolized by the liver to its inactive deaminated product, B-(p-chlorophenyl)-Y-hydroxybutyric acid. The half-life is between 2 hours and 6 hours in healthy subjects, but increases in ESRD and an accumulation phenomenon can occur.[3]

The therapeutic dosage range of baclofen is between 15 and 60mg/day. Using this dosage range, symptoms generally develop only after long term treatment. But in our patient and the review of literature, most patient with severely impaired renal function

rapidly develop toxicity with very low doses of baclofen.[7] Seyfert et.al[9] suggested baclofen administration should not exceed 5mg/d in dialysis patient. Our patient received a daily dose of 20mg, and developed toxic symptoms immediately after first day of treatment.

Acute baclofen intoxication usually present with four major clinical manifestation: encephalopathy, respiratory depression, muscular hypotonia and generalized hypoflexia[7]. One study, reported clinical effects of baclofen: hyporeflexia 100%, hypotonia 100%, required ventilation 92%, bradycardia 50%, seizure 42%, myoclonic jerking 42%, hypotension 33%, tachycardia 33%, hypertension 25%, cardiac conduction 85%10. However, in our patient, encephalopathy and hypotonia along with bradycardia was more evident. Concentration of baclofen in cerebrospinal fluid have been described to be 8.4 times lower than those simultaneously present in plasma.[11] It has a volume distribution of 0.83 L/kg in adult [12] and 2.58 L/kg in children.[13] The appropriate serum level of baclofen in a patient with the severely impaired renal function remains unclear. Several authors have suggested that patients with renal failure are more susceptible to baclofen toxicity.[7]

Also, several observations of a baclofen associated encephalopathy have been reported in patient with ESRD.[14] This was also seen in our patient. Patient with the severely impaired renal function generally develop baclofen intoxication soon after the initiation of therapy.[15]

Most ESRD patient experience marked improvement in clinical toxicity following hemodialysis compared with patient who did not receive hemodialysis.[7] Baclofen is moderately lipophilic and 30% drug is protein bound. It has a molecular weight of 213 Da and a volume distribution of 0.83 L/kg or 2.58 l/kg.[12] Given these properties, hemodialysis should be able to clear baclofen.[7] Although efficacy may not be optimal, there have been demonstrations depicting that hemodialysis are effective in removing baclofen from the body. The similar scenario was seen with our patient whose general condition, consciousness and neurological symptoms improved after hemodialysis. While it was seen in our case that hemodialysis lessens the toxic symptoms of baclofen. This report is however just a follow of one patient and the conclusion remains preliminary because drug dosage, age, body size, sample size and underlying condition which can vary and produce different results. However, numerous studies have found hemodialysis reduce the toxicity of baclofen. Another limitation of this report is that the serum and plasma concentration were not measured in pre and post hemodialysis sessions. However, the patient was landed in our center after the drug ingestion confirmed by history taking on multiple occasions and other investigations. We, therefore conclude that the use of baclofen in any patient with severely impaired renal function carries an unnecessarily high risk and an alternative form of drug therapy should be used in this group of patient. If a patient in ESRD develops baclofen toxicity, hemodialysis may be appropriate treatment to alleviate clinical symptoms and shorten the recovery time.

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