WORLD JOURNAL OF GASTROENTEROLOGY, HEPATOLOGY AND ENDOSCOPY

A Case Report On Baclofen Induced Acute Encephalopathy in Esrd Patient

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Article Information

Article Type: Case Report
Journal Type: Open Access
Volume: 3 Issue: 6
Manuscript ID: WJGHE-3-144
Publisher: Science World Publishing

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Citation:
S Haja Sherief. (2021). A Case Report On Baclofen Induced Acute Encephalopathy in Esrd Patient. J Gastroenterol Hepatol Endosc. 3(6); 1-4

Received Date: 18 Oct 2021
Accepted Date: 02 Nov 2021
Published Date: 06 Nov 2021

ABSTRACT

Baclofen is a commonly prescribed muscle relaxant, also used for hiccups and muscle spasm. It is usually administered orally or delivered intrathecal. Baclofen is extensively eliminated through kidneys as unchanged drug, hence renal compromised patients are more prone to risk of accumulation and toxicity. Neurological manifestations are highly prevalent in such patients. Here we delineate a case report on baclofen induced encephalopathy in end stage renal disease (ESRD) patient, which was resolved with the help of prompt hemodialysis.

KEYWORDS: Baclofen, Hiccups Encephalopathy, ESRD, Neurotoxicity, Seizure, Hemodialysis

INTRODUCTION

Baclofen is a beta- (p-chlorophenyl) derivative of gamma amino butyric acid (GABA). It acts mainly on $GABA_B$ receptors to inhibit synaptic motor neurons resulting in centrally acting anti-spasmodic or anti-convulsant response [1]. Activation of these receptors by baclofen results in increased K^+ conductance leading to hyperpolarization which reduces calcium influx and thereby depletes release of excitatory transmitters in brain and spinal cord [2]. Baclofen is Food and Drug Administration (FDA) approved for flexor spasms, clonus, concomitant pain, common sequelae of spinal cord lesions and multiple sclerosis [3]. Gastro esophageal reflux disease (GERD), alcohol related anxiety, trigeminal neuralgia, hiccups are the off label indications of baclofen [4, 5]. In Hiccups, $GABA_B$ receptor stimulation reduces dopamine release in the central nervous system (CNS), and this could interrupt hiccup's reflex arc [6]. Baclofen is rapidly and extensively absorbed from gastrointestinal (GI) tract following oral administration. Peak plasma concentrations are observed 2-3 hours post ingestion. Baclofen is excreted primarily unchanged by the kidneys. Elimination half-life is 2-6 hours, which extends in renal impaired patients, resulting in drug accumulation [7]. Being lipophilic in nature, the drug can easily penetrate blood brain barrier precipitating neurological manifestations, especially in ESRD patients. These adverse effects are reversible with immediate hemodialysis

because of the low molecular weight, lipophilic nature and low protein binding of the drug [8, 9].

Several cases have been reported on neurotoxic effects of baclofen in renal patients. Here, we report a case of baclofen induced acute encephalopathy in ESRD patient which was reversed with drug withdrawal and hemodialysis.

CASE PRESENTATION

A 67 year old male patient with a past medical history of end stage renal disease on hemodialysis was presented to emergency department with acute onset of altered sensorium. He had a medical history of tuberculosis, on anti-tubercular therapy (ATT) since 2 weeks, minor coronary artery disease (CAD) for which he had undergone coronary angiogram 12 years back. He also had a history of prostatomegaly (status post transurethral resection of prostate a year ago), old ischemic stroke (two years ago), type 2 Diabetes mellitus(DM), proliferative diabetic retinopathy, peripheral diabetic neuropathy, systemic hypertension, dyslipidemia and anemia.

The patient had a recent admission to the hospital with the concern of persistent hiccups for which he was administered with tablet baclofen 10mg two times daily and injection perinorm 10 mg IV stat. Following which the complaints of hiccups ceased, but later on he developed generalized tiredness, unsteadiness in gait, drowsiness, decreased food intake, restlessness and oxygen desaturation (85%). Noticing the patient condition deterioration, he was shifted to the medical ICU. The next day he had an altered sensorium and developed focal seizure subsequently. With high suspicion for isoniazid or baclofen induced encephalopathy, their further administration was halted. Electroencephalogram showed status epilepticus for which tablet clobazam was commenced as per neurological advice and the seizure was settled.

The vital signs were the following, blood pressure 140/90mm Hg, pulse rate 78/min, temperature 98.4°F, and pulse oximetry 85% on room air. There was no focal neurological deficit. Laboratory tests showed the following: sodium 135mEq/L, potassium 4.13mEq/L, calcium 10.5 mg/dl, phosphorous 7.22mg/dl, magnesium 2.22mg/dl, urea 115.1mg/dl, creatinine 9.01mg/dl, CRP 157.9mg/L, troponin I 2.45µg/L. His liver function tests showed, aspartate transaminase 45U/L, alanine transaminase 21U/L, alkaline phosphatase 93U/L, total bilirubin 1.1mg/dl, direct bilirubin 0.7mg/dl, indirect bilirubin 0.4mg/dl, total protein 7.4g/dl, albumin 2.5g/dl, globulin 4.9g/dl, albumin/globulin ratio 0.51. The white blood cell count was 9.9mg/dL, hemoglobin 11.1mg/dL and platelet 336mg/dL, remaining examinations were consistent with his known comorbidities including a left radio cephalic fistula. A computed tomography and magnetic resonance imaging of brain didn't show any significant findings for hemorrhage or infarction. Electro encephalogram showed status epilepticus. Given his clinical presentation, confirmation from the pharmacy that he had been prescribed with baclofen and absence of other evident etiologies, baclofen induced neurotoxicity was confirmed, additional baclofen administration was retained. Isoniazid was restarted two days before discharge which he tolerated well. Immediate hemodialysis was done and the patient's sensorium reverted eventually. The patient got symptomatically better and was discharged with an advice to continue maintenance hemodialysis.

DISCUSSION

Baclofen is a $GABA_B$ mimetic agent used as a centrally acting muscle relaxant [10]. The therapeutic dose ranges between 5-120mg per day [11]. Recent studies has demonstrated the effective use of baclofen in the treatment of persistent hiccups [12]. GI system is the main absorption site for baclofen and reaches its peak concentrations within two hours post ingestion approximately. Therapeutic range of baclofen observed in normal subjects is approximately 80-400ng/ml, but the serum concentration level of baclofen in ESRD is vaguely known [13]. About 15% of the drug metabolism occurs in the liver, while 65-85% is excreted unchanged by the kidneys with a half-life of 2-4 hours. On this account, patients with renal impairment are at high risk of accumulation and toxicity, even when given with normal doses [14].

Since baclofen is a moderately lipophilic agent and approximately binds 30% to serum protein, it slowly passes the blood brain barrier exhibiting neurotoxicity [15]. In the CNS, the removal of baclofen is slow, leading to the persistence of the CNS symptoms irrespective of the plasma baclofen concentration [16]. The most commonly observed CNS manifestation is seizure. The mechanism of seizures induced by baclofen include the inactivation of both postsynaptic and presynaptic inhibitory interneurons, which shifts the neuronal balance towards excitation and lowers the seizure threshold. Baclofen induced changes in intrinsic membrane properties has also been observed as another mechanism for baclofen-associated seizures [17, 18].

The most commonly observed symptoms of baclofen neurotoxicity include confusion, somnolence, nausea/vomiting, myoclonus, hypotonia, coma, seizures, and autonomic dysfunction. EEG features include generalized slowing, burst suppression, triphasic waves, rhythmic high-amplitude delta waves, and non-convulsive status epilepticus [19]. In this case report our patient had an EEG finding of status epilepticus.

Emad Khazneh *et al*, remarked on their case report that the development of symptoms usually starts within 2-3 days post-ingestion of baclofen but for ESRD patients onset of symptoms has also been documented as early as 24 hours [20]. However, our case developed a state of altered sensorium and unsteady within gait 24 hours after baclofen administration. The reliable treatment for

baclofen induced neurotoxicity in ESRD patients is hemodialysis aided with supportive therapy and close monitoring for possible respiratory compromise [21 -43]. In this case, hemodialysis was instituted after immediate cessation of baclofen therapy to which the subject responded well presenting significant neurologic improvement.

To demonstrate the likelihood of adverse drug reaction (ADR) in our subject, the following criteria were satisfied among the components of the Naranjo algorithm[22]:

1. Previous conclusive reports on this reaction
2. Appearance of the reaction after the suspected drug was given
3. Clinical improvement upon drug discontinuation
4. Review of potential alternative causes
5. Confirmation of the adverse event by objective evidence

A score of 7 indicates a probable adverse drug reaction according to Naranjo causality assessment. Thus it's evident that baclofen even in low or normal doses in renal impaired patients, can cause undesirable effects in the CNS. Therefore a close monitoring has to be ensured in case of ESRD patients ingesting baclofen. More specific guidelines on prescribing this drug would likely further alleviate incidence of ADR.

CONCLUSION

CKD has been recognized as a leading public health problem worldwide, the dose adjustments for such patients is of crucial importance. Baclofen even in normal concentrations could lead to serious or fatal neuro-complications in renal insufficiency. Therefore prompt diagnosis and withdrawal of the drug is advisable in case of altered mental status with history of baclofen ingestion in renal patients. Hemodialysis is the initial choice to revert the obnoxious effect. We recommend dose reduction or use of alternative drugs in risk prone patients.

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