Case Report

Baclofen-induced neurotoxicity in chronic kidney disease: Is there a safe dose?

Abstract

Most cases of Baclofen toxicity have been reported in patients with impaired kidney functions, within a few days to weeks after ingestion. We report three cases of Baclofen induced encephalopathy in chronic kidney disease patients; two developed encephalopathy within 6–8 h after ingestion of a single tablet and third on 4th day of consuming 2.5 mg twice daily dose. All three cases recovered fully following haemodialysis treatment.

Keywords: *Baclofen toxicity, dialysis, encephalopathy, renal failure*

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Introduction

Baclofen is a centrally acting muscle relaxant used both orally and intrathecally in the treatment of spasticity, muscle spasms, and intractable hiccups. It has also been misused as "fun drug" by adolescents.[1,2] Dosage for treatment of hiccups is 10–20 mg two to three times a day.[1-3] Chemically it is lipophilic analog of gamma-aminobutyric acid which crosses blood brain barrier. Eighty-five percent of the drug gets excreted unchanged in the urine; therefore, duration of action gets prolonged in patients with renal failure. Most of the cases of baclofen toxicity have been reported in dialysis-dependent patients, usually 2–3 days to 6 weeks following ingestion of the drug.[4] Here we report three cases of chronic kidney disease (CKD) stage 4–5D, two of them developed encephalopathy within 6–8 h of ingesting a single tablet and third developed acute pain abdomen and encephalopathy 4 days after consuming 2.5 mg BD dose.

Case 1

An 83-year-old male, known case of Type 2 diabetes mellitus, coronary artery disease, traumatic flaccid paraparesis and CKD stage 4 reported to emergency room (ER) with intractable hiccups. There was no preceding history of fever, gastroenteritis, jaundice or trauma. Treating doctor prescribed Baclofen 5 mg twice a day. Patient's attendant by mistake gave 20 mg tablet of Baclofen. Over next 7–8 h he was found to be drowsy with a blank stare and soon he became unresponsive to verbal commands. On arrival at ER, the patient was afebrile, and responsive to deep painful stimuli. His blood pressure was 140/90 mm Hg and Spo2 of 90%. His Glasgow coma scale was E2V2 M5, pupils were equal and reactive to light. There was no neck rigidity or focal neurologic deficit. Investigations revealed normal blood counts, blood glucose of 150 mg/dl, serum Na, K, and Ca were 135 meq/L, 4.2 meq/L and 8.7 mg/dl, respectively. His blood urea and creatinine were 87 mg and 4.4 mg/dl. CT scan of head did not show any abnormality. In view of history of Baclofen ingestion and development of altered sensorium within 8 h of ingestion, a diagnosis of baclofen toxicity was considered and he was given hemodialysis. His sensorium improved partially after the first dialysis and there was almost complete recovery of consciousness following second dialysis, given 12 h later. However, asterixis continued for an additional day. Patient was discharged after 2 days in good shape.

Case 2

An 84-year-old male, known case of diabetes mellitus, hypertension, end-stage renal disease (ESRD) on maintenance hemodialysis (MHD) for one year came to ER of hospital with intractable hiccups and nausea. Investigations revealed normal liver

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function tests (LFT) and ultrasonographic study (USG) of abdomen. He was started on tablet Baclofen 2.5 mg morning and evening for symptomatic relief; however, patient was found to be drowsy and unarousable the following morning. Patient was brought to the emergency and was admitted. Urgent CT brain was done to rule out stroke. Serum electrolyte, blood gases and serum ammonia were done to rule out any metabolic cause for encephalopathy and all were normal. On revisiting the history, patient's son admitted that he inadvertently gave 10 mg Baclofen tablet instead of giving 2.5 mg. Diagnosis of Baclofen neurotoxicity was made and patient was given 2 sessions of dialysis over the next 2 days. Patient came out of sedating effects of drugs and became responsive after 2 days and was discharged on 3rd day with full recovery of sensorium.

Case 3

A 46-year-old male, known case of diabetes mellitus, hypertension, and CKD-5D was on regular MHD at our centre for the last 4 months. He developed cervical lymphadenopathy which on biopsy was diagnosed to be tubercular. He was started on antitubercular therapy (ATT) with isoniazid, rifampicin, pyrazinamide and ethambutol. Two weeks after the start of ATT, the patient developed nausea, vomiting and bothersome hiccups. Liver function tests and USG abdomen study was normal. As there was no response in hiccups with Proton pump inhibitors, low dose Baclofen (2.5 mg BD) was started. Hiccups improved and routine dialysis was continued. 4 days later (after taking a cumulative dose of 20 mg) patient became drowsy, was talking irrelevantly, was disoriented in time and space and had severe upper abdominal and retrosternal pain. His metabolic profile, LFT, pancreatic profile, USG abdomen was normal. Baclofen toxicity was suspected and he was given three sittings of hemodialysis over 3 days. Patient's sensorium started improving after a day but he continued to have distressing constant upper epigastric and retrosternal discomfort. UGI endoscopy showed mild hiatus hernia. After 4 days (a day after complete improvement of sensorium), pain abdomen subsided and he was discharged in good shape.

Discussion

Baclofen, a centrally acting muscle relaxant is used for the treatment of spasticity, muscle spasms and intractable hiccups. The recommended dose for treatment of spasticity is 5 mg thrice a day to a maximum of 80 mg a day and for hiccups 10–20 mg three times a day.[3,4] Eighty-five percent of the drug is cleared unchanged in urine and rest is metabolised by liver. Aging, uremia and concomitant central nervous system pathology increases the risk of toxic effects.[4] Drug has a half-life of 4.5-6.8 h in healthy subjects which gets prolonged in kidney failure patients, hence most cases of Baclofen toxicity are reported in dialysis patients.[3,4] Drug is moderately lipophilic and crosses blood–brain barrier. Cerebrospinal fluid concentration is 8.4 times lesser than plasma. In CKD patients drug gets sequestrated in brain and patients with toxicity usually have blood levels in therapeutic range of 80–400 ng/ml only. Literature is silent on dose modification in patients with renal impairment. Vlavonou R *et al*. studied pharmacokinetics of Baclofen in patients with mild (50-80 ml/min), moderate (30–50 ml/min) and severe renal failure (<30 ml/min) and suggested dose reduction by 2/3rd, ½, and 1/3rd, respectively, for mild, moderate and severe renal failure.[5] Neurotoxicity symptoms include sedation, drowsiness, encephalopathy, seizures, ataxia, vertigo and respiratory depression. Renal failure patients generally present with altered sensorium and non-renal patients can have seizures, respiratory depression and coma. There are reports of drug being taken as fun drug by adolescents with resultant seizures or respiratory depression, requiring mechanical ventilation for days.[1,2] Abdominal pain/cramps is not common but has been reported in few patients. Pathogenesis of abdominal pain/cramps is possibly GABA mediated cholinergic effect and it generally clears along with neurotoxicity.[3]

So far around 50 cases of Baclofen toxicity have been reported in CKD patients, mostly in dialysis-dependent patients. A review of 41 reported cases of Baclofen toxicity, showed that those who developed toxicity were generally elderly and mostly dialysis dependent.[4] Neurotoxicity has been reported in those taking 5-60 mg of Baclofen/day (median dose 20 mg/day) from as early as 2–3 days to as long as 16 weeks after starting the drug.[3] Khazneh E *et al*.[6] reported encephalopathy in a patient 12 h after ingestion of single 25 mg tablet of Baclofen, which required 5 sessions of dialysis for full recovery. Radhakrishnan *et al*.[7] reported a dialysis patient who developed toxicity following single tablet of 10 mg. Hadjiyannacos D *et al*.[8] suggested that rather than 5 mg BD, possibly 2.5 mg BD is safe dose in dialysis patients.

Our one patient had encephalopathy following ingestion of 20 mg and other after ingesting 10 mg tablet. In India Baclofen tablets are marketed only in strength of 5, 10 and 20 mg and in syrup form (1 mg/ml); so to take 2.5 mg dose, one has to break the tablet, as was done by our 3rd patient. However, he also developed encephalopathy and acute pain abdomen with a cumulative dose of 20 mg, which he consumed during the interdialytic period. We feel that even a single dose of 10 mg or low dose of 2.5 mg BD is not safe in dialysis patients. One has to keep in mind that no toxicity has been reported with less than 10 mg consumption of Baclofen, hence we feel if there is no alternative, drug can be given in a dose of 2.5 mg SOS, with a cumulative dose not exceeding 10 mg.

With a molecular weight of 213 daltons, low volume of distribution and only 30% protein binding, the drug is dialyzable. Stopping the further use of the drug and

enhanced clearance of drug with hemodialysis hastens recovery. Van-Cint Wu *et al.* reported pharmokinetics of Baclofen in a patient with Baclofen toxicity. They found that 4 h of hemodialysis cleared the drug by 79% and shortened the half-life from 15.5 hr to 2.06 h.[9] Patients on regular dialysis develop encephalopathy as drug gets sequestrated in CSF and repeated sessions may be required for clearance of drug. Continuous ambulatory peritoneal dialysis and hemodiafiltration have also been successfully used as treatment modality.[10] In absence of any specific antidote hemodialysis has been used in BBclofen toxicity even in patients with normal renal functions.[7,11] Algorithms have been published suggesting supportive therapy in those with only mild toxicity and dialysis therapy for those with impaired renal function and severe symptoms.[12]

Conclusions

Our cases emphasise that Baclofen can prove dangerous not only in dialysis-dependent but also in CKD patients. Even a single tablet of 10 mg or low dose of 2.5 mg BD with a cumulative dose approaching 20 mg can result in encephalopathy, hence it is prudent to avoid the drug in CKD patients and look for an alternative drug.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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