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CASE REPORT

Baclofen-induced Encephalopathy in Patients with End-stage Kidney Disease – A Case Series

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Abstract:

Introduction/Background:

Baclofen is a centrally acting GABA B receptor agonist, widely used for the treatment of neurological diseases ranging from hiccups to multiple sclerosis. As the drug is renally excreted, intoxication can rapidly develop in those patients with a reduced glomerular filtration rate. A strong index of clinical suspicion is essential to correctly diagnose the condition.

Case Presentation:

We report a case series of patients with advanced kidney disease and baclofen-induced encephalopathy that settled with discontinuation of the drug and hemodialysis sessions.

Conclusion:

We report this cluster of patients with baclofen toxicity to highlight the common occurrence of neurotoxicity after its use in patients with end-stage renal disease and its resolution after cessation of the drug and hemodialysis sessions.

Keywords: Baclofen, Encephalopathy, Hemodialysis, ESKD, Kidney Disease, Neurotoxicity.

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1. BACKGROUND

Baclofen is a centrally acting GABA B receptor agonist, used extensively for the treatment of neurological diseases ranging from hiccups to multiple sclerosis. As the drug is renally excreted, intoxication can develop rapidly in patients with reduced glomerular filtration rate, resulting in an extended drug half-life with more crossing of the blood-brain barrier. The generalized depression of the central nervous system becomes more evident, producing fatigue, syncope, ataxia, psychological disturbances, hypotension, cardiovascular and respiratory depression [1, 2]. Patients with a reduced glomerular filtration rate can experience toxic adverse effects at the initial dosage of 5 mg within the first few days [3]. Here, we report a case series (three patients) of baclofen-induced encephalopathy in patients with end-stage kidney disease.

1.1. Case 1

A 62-year old male had presented to the emergency department with hiccups. His medical history was relevant for CKD stage 5 secondary to diabetic nephropathy on conservative management and hypertension on three antihypertensive medications. Upon examination, his Glasgow coma score (GCS) was E4V3M6, vitally stable, pupils equal, and reactive. The patient was not cooperative for a thorough central nervous system examination as he was agitated. His investigations revealed blood urea: 172 mg/dl, serum creatinine of 10.2mg/dl, serum sodium 137mmol/L, potassium 4.4mmol/L, serum ammonia of 30µmol/L, with low-risk inflammatory markers. CT brain showed features of small vessel disease with no acute changes. The medical team reviewed the patient and excluded any medical cause for altered sensorium. He was started on intravenous hydration and the option of dialysis was discussed, which he didn't wish to consider. He had earlier been prescribed baclofen 10mg once daily for occasional hiccups, earlier. As per the escort, he took it for two days (total of 20mg) preceding his presentation to the ED with hiccups and worsening renal parameters. After 24 hours of admission, the patient started to become drowsy with irrelevant speech and agitation. Vital signs were stable and central nervous system

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examination did not reveal any focal neurologic deficits. After ruling out all other possible causes of drowsiness, baclofen toxicity was presumed to be the cause. Baclofen was discontinued, given the possibility of baclofen toxicity. He also received three sessions of hemodialysis over three consecutive days, after which he recovered. Sensorium returned to normal and he was discharged in a stable state.

1.2. Case 2

A 63 year old lady, who is a known case of End-stage renal disease on hemodialysis, Type 2 diabetes mellitus, and hypertension, presented to the ED with complaints of increased sleepiness, drowsiness, and difficulty with concentration. She was seen four days earlier in the neurology outpatient clinic where she had been prescribed Gabapentin 400mg once daily for neuropathy, and on the following day, she presented to the ED where she was given 20mg of baclofen (total intake of 80mg over 4 days) for muscle spasticity. Within a span of 72 hours, she presented to the ED with drowsiness, sleepiness, and amnesia. CT brain did not reveal any acute insult.

Her laboratory investigations showed low-risk inflammatory markers, serum creatinine of 4.8mg/dl, Urea: 77 mg/dl Na: 138 mmol/L K:6.1 mmol/L, HCO3: 20.3 mmol/L and serum ammonia of 44umol/L. Her venous blood gas was within normal limits. Possible causes of drowsiness were evaluated and ruled out. She was diagnosed to have baclofen toxicity in the setting of severe chronic kidney disease. She was admitted under the care of the nephrology team and received daily hemodialysis over three consecutive days, after which she showed clinical improvement and returned to her baseline neurological status. She was counseled regarding the avoidance of Baclofen.

1.3. Case 3

A 67-year-old male, known to have hypertension, type 2 diabetes, and chronic kidney disease stage-5 on maintenance hemodialysis, presented to his regular hemodialysis session, where he was noted by the nurse to be in a state of disorientation, and the caregiver also reported to have noticed abnormal behavior for the preceding two days. While reviewing the patient's file, it was noted that he had made an outpatient visit to the emergency department two days prior to this episode, where he had been prescribed baclofen 10mg twice daily for intractable hiccups, which he took for 2 days (total of 40mg of baclofen). CT brain was done and the scan revealed a left frontoparietal small chronic subdural hematoma, but with no significant mass effect or midline shift. He was then reviewed by the neurosurgery team, who opted for no active intervention. Lab investigations showed: Serum creatinine: 7.5 mg/dl, urea 67 mg/dl, Na: 133mmol/L K: 4 mmol/L, HCO3: 19.5mmol/L, ammonia: 28µmol/L. Hemoglobin:9.5 g/dL WBC:13,100/cc Platelets: 371000/cc. C reactive protein was 270 mg/dL and Procalcitonin was 1.66 ng/ml. He was also diagnosed to have right leg cellulitis and received IV Co-amoxiclav. Baclofen was discontinued, and he received two sessions of hemodialysis on consecutive days. He showed rapid clinical improvement and no residual alterations in the sensorium. He was advised to refrain from using baclofen in the future.

2. DISCUSSION

Baclofen (4-amino-3-[-4-chlorophenyl]-butanoic acid) is a natural derivative, centrally acting GABA B receptor agonist. The mechanism of action is not well understood, but in therapeutic doses, it works at the level of the spinal cord, reducing muscle tone and reducing spasticity. It is frequently prescribed as an antispasmodic agent. The daily therapeutic dose ranges between 5 and 60 mg [4, 5] Adverse effects on the nervous system due to baclofen toxicity have been observed among people with normal kidney function, including transient drowsiness, sedation, dizziness, confusion, muscle weakness, and respiratory depression [6].

Baclofen is absorbed into the gastrointestinal tract, and its half-life is mainly dependent on the kidneys as the primary mechanism of excretion [7]. The kidneys eliminate eighty-five percent of an oral dose, and its clearance is proportional to creatinine clearance. Accumulation of Baclofen, even in normal doses precipitating encephalopathy can occur in patients with impaired renal function [5]. Half-life of baclofen is significantly increased in patients with past history of renal failure and the recommended dose, or even low doses as little as 5 mg daily, or a cumulative dose of 10 mg, could result in its accumulation and severe drug intoxication with neurological side effects in patients with renal dysfunction [8].

Consistent with the clinical presentation of the patients in this case series, the known manifestations of baclofen toxicity in the literature include dizziness, nausea, vomiting, altered speech, akinetic mutism, respiratory depression, altered mental status, ataxia, dystonia, and coma. Baclofen-associated encephalopathy has been described in literature in patients with varying degrees of renal dysfunction. The spectrum of affected patients includes those with normal kidney function to acute kidney injury to end-stage kidney disease (ESKD) [4]. In a case report published in 1994, Aisen ML *et al*. described a patient that developed baclofen-associated encephalopathy with an estimated Glomerular Filtration Rate (eGFR) of 55-60 mL/min and creatinine of 0.8 mg/dl [9]. Kumar A *et al*. reported various degrees of baclofen-induced encephalopathy in adult patients with advanced renal failure or on renal replacement therapy [8]. In our case series, patients received baclofen in doses ranging from 20 mg to 80 mg per day. All patients showed resolution of neurologic symptoms within a span of 24 to 96 hours from discontinuation of the drug, in addition to the commencement of renal replacement therapy.

The management of baclofen-induced encephalopathy in patients with renal dysfunction includes monitoring of baclofen-induced respiratory depression, supportive care, and the elimination of baclofen from the body system through renal replacement therapy. Wu VC *et al*. showed that hemodialysis was effective in the treatment of baclofen-induced encephalopathy as it decreased baclofen half-life from 15 hours to 2 hours. Moreover, up to 79% of the serum baclofen was eliminated during one hemodialysis session [10]. In 2011, Diaz LS *et al*. reported the use of hemodialysis successfully in treating baclofen toxicity in a patient with normal renal function who had consumed 200 mg of extended-release baclofen [11]. Similarly, the EXTRIP workgroup (2021) recommended extracorporeal treatments (hemodialysis or

hemoperfusion) to be used for kidney disease patients with toxicity from therapeutic baclofen dosage, especially in the presence of coma that necessitated mechanical ventilation [12]. The number of hemodialysis sessions required for clinical improvement is varied. Some case reports showed improvement after just one session, whereas others needed up to five sessions for complete recovery [4]. In our case series of three patients, the first patient showed improvement after three days of hemodialysis sessions, the second patient improved after just one session of hemodialysis, and the third patient showed improvement after two sessions of hemodialysis. In the literature, continuous ambulatory peritoneal dialysis (CAPD) has been used efficiently in managing baclofen toxicity in renal failure patients, albeit with a longer time to recovery [5].

In our case series, all three patients had been prescribed baclofen from the emergency department. This calls for increasing the awareness among emergency physicians regarding the necessary caution with regard to its prescription for patients with kidney disease and the neurological adverse events of this drug being more pronounced in those with advanced kidney disease.

There is still debate in the literature regarding the correct dosage of baclofen that can be administered in patients with impaired kidney function [4]. Despite several case reports of baclofen-induced toxicity in patients with renal dysfunction, clear guidelines have still not been formulated regarding the level of kidney function below which the drug should not be administered. In general, nephrologists advise avoiding baclofen in patients with advanced renal insufficiency, and if given, should be monitored closely for toxicity [5]. In our second patient, the concomitant use of Gabapentin could have added to the neurotoxicity of baclofen in a patient on hemodialysis.

In a case report by Roberts *et al*., it was clearly advised to avoid baclofen use among patients with end-stage renal disease and those with a glomerular filtration rate of less than 60 ml/minute [13]. In this series, the cases represent baclofen-induced toxic encephalopathy due to inappropriate dosing of baclofen that was eventually resolved with discontinuation of the drug and hemodialysis sessions. Thus, special consideration is needed for the safe prescription of this renally excreted medication, and further guidelines are needed to avoid the occurrence of this side effect. Through this publication, we aim to highlight the neurological manifestations of baclofen toxicity that can be more pronounced in patients with renal impairment, especially in those with end-stage kidney disease.

CONCLUSION

Physicians must avoid or exercise caution in prescribing baclofen in patients with end-stage renal disease. Alternative drugs must be preferred in this setting.

PATIENT PERSPECTIVE

All patients in the case report were educated regarding avoiding baclofen in the future. Two of the patients are no longer on hemodialysis with us currently.

LIST OF ABBREVIATIONS

ESKD = End-Stage Kidney Disease

CAPD = Continuous Ambulatory Peritoneal Dialysis

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

The consent form is not obtained as patients are not identified by their images or names or even nationality. Moreover, some of these patients are no longer with us on hemodialysis.

STANDARDS OF REPORTING

CARE guideline has been followed.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available within the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. Drug Saf 2004; 27(11): 799-818. [http://dx.doi.org/10.2165/00002018-200427110-00004] [PMID: 15350152]

[2] Young RR, Delwaide PJ. Drug therapy: Spasticity (first of two parts). N Engl J Med 1981; 304(1): 28-33. [PMID: 6448959]

[3] Chou CL, Chen CA, Lin SH, Huang HH. Baclofen-induced neurotoxicity in chronic renal failure patients with intractable hiccups. South Med J 2006; 99(11): 1308-9. [http://dx.doi.org/10.1097/01.smj.0000247632.84949.27] [PMID: 17195438]

[4] Khazneh E, Shamlawi A, Jebrin K, Hamdan Z, Sawalmeh O. Single-dose baclofen-induced neurotoxicity in a patient with end stage renal disease: case report. BMC Nephrol 2018; 19(1): 352. [http://dx.doi.org/10.1186/s12882-018-1167-z] [PMID: 30537935]

[5] Radhakrishnan H. Baclofen-induced neurotoxicity in a patient with end-stage renal disease. Saudi J Kidney Dis Transpl 2016; 27(3): 595-7. [http://dx.doi.org/10.4103/1319-2442.182437] [PMID: 27215257]

[6] Beladi Mousavi SS, Mousavi MB, Motemednia F. Baclofen-induced encephalopathy in patient with end stage renal disease: Two case reports. Indian J Nephrol 2012; 22(3): 210-2. [http://dx.doi.org/10.4103/0971-4065.98762] [PMID: 23087558]

[7] Meillier A, Heller C, Patel S. Baclofen-induced encephalopathy in end stage renal disease. Case Rep Med 2015; 2015: 1-3. [http://dx.doi.org/10.1155/2015/203936] [PMID: 26294912]

[8] Kumar A, Khrime D, Bansal N, Agarwal S, Sharma U. Baclofen induced encephalopathy in patients with chronic kidney disease. J Clin Diagn Res 2020; 14(9): R01-02.
[http://dx.doi.org/10.7860/JCDR/2020/44729.13998]

[9] Aisen ML, Dietz M, McDowell F, Kutt H. Baclofen toxicity in a patient with subclinical renal insufficiency. Arch Phys Med Rehabil 1994; 75(1): 109-11.
[http://dx.doi.org/10.1016/0003-9993(94)90347-6] [PMID: 8291951]

[10] Wu VC, Lin SL, Lin SM, Fang CC. Treatment of baclofen overdose by haemodialysis: A pharmacokinetic study. Nephrol Dial Transplant 2005; 20(2): 441-3.
[http://dx.doi.org/10.1093/ndt/gfh297] [PMID: 15615812]

[11] Dias LS, Vivek G, Manthappa M, Acharya RV. Role of hemodialysis in baclofen overdose with normal renal function. Indian J Pharmacol 2011; 43(6): 722-3.
[PMID: 22144783]

[12] Ghannoum M, Berling I, Lavergne V, *et al.* Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning. Kidney Int 2021; 100(4): 720-36.
[http://dx.doi.org/10.1016/j.kint.2021.07.014] [PMID: 34358487]

[13] Roberts JK, Westphal S, Sparks MA. Iatrogenic baclofen neurotoxicity in ESRD: Recognition and management. Semin Dial 2015; 28(5): 525-9.
[http://dx.doi.org/10.1111/sdi.12400] [PMID: 26096760]