SAGE Open Medical Case Reports
Volume 11: 1–4

DOI: 10.1177/2050313X231200966
journals.sagepub.com/home/sco
Sage

Baclofen-induced myoclonus in patients with renal impairment: A case series

Manudi Nushara Vidanapathirana[1], Thamalee Palliyaguruge[1] and Eranga Wijewickrama[2]

Abstract

Baclofen is a derivative of gamma amino butyric acid and is used for control of pain and muscular spasms. It is primarily excreted via the kidneys. In patients with impaired renal functions, the half-life of baclofen is prolonged and symptoms of toxicity can occur with normal doses. Commonly reported symptoms of baclofen toxicity are somnolence, altered mentation, seizures and respiratory depression. Myoclonus secondary to baclofen toxicity is scarcely reported. This case series describes two patients with chronic kidney disease (CKD) who were prescribed regular doses of baclofen for analgesia, and subsequently developed generalized myoclonus. The symptoms resolved with omission of baclofen and haemodialysis. There is currently no consensus on dose modification of baclofen in renal impairment for prevention of adverse neurological events. However, considering the surmounting evidence for low threshold of baclofen toxicity in CKD, dose adjustment protocols or consensus on contraindication need to be established.

Keywords

Baclofen, myoclonus, chronic kidney disease, renal impairment, neurotoxicity

Date received: 7 June 2023; accepted: 18 August 2023

Introduction

Baclofen is a synthetic derivative of gamma amino butyric acid (GABA) which is used for control of pain, muscle spasms, intractable hiccups and abnormal movements such as palatal myoclonus.[1,2] It has a half-life of 4.5–6.8 h and is primarily excreted via the kidneys.[1] The kidneys excrete between 70% and 85%–90% of the drug unchanged.[1,3] In patients with impaired renal function, baclofen can have a longer half-life due to reduced elimination.[1]

Baclofen crosses the blood brain barrier due to its lipophilic nature, and in patients with chronic kidney disease (CKD), it gets sequestered in the central nervous system.[1] As a result of this, its effects on the central nervous system outlast the decrease in serum baclofen level. The common symptoms of baclofen toxicity are altered level of consciousness, encephalopathy, seizures, ataxia, vertigo and respiratory depression.[4] Several case reports of encephalopathy secondary to baclofen toxicity are found in literature. However, myoclonus in baclofen toxicity is a rarely reported adverse effect, especially with preserved mentation.[5] Myoclonus, by definition is a hyperkinetic movement that is characterized by brief, shock-like, involuntary movements due to muscular contractions or inhibitions.[6] It could be physiological or pathological.[6] Causes of pathological myoclonus are metabolic derangements, degenerative changes in basal ganglia, drugs/toxins and viral encephalopathies.[6,7] Metabolic derangements known to cause myoclonus are hyponatremia, hypomagnesemia, hypocalcaemia, hypoxia, hypercapnia, hypo/hyperglycaemia, uraemia and liver failure.[6,7] Drugs known to cause myoclonus are levodopa, antihistamines, antiepileptic drugs, opioids, tricyclic antidepressants and selective serotonin receptor inhibitors.[6,7] Due to the rarity of baclofen-induced myoclonus, it is necessary to exclude these more common causes of myoclonus before attributing the myoclonus to be baclofen induced.

Baclofen, unlike most other muscle relaxants which are metabolized in the liver, is excreted unchanged by the kidneys.[8] There is currently, no consensus on dose modification

[1]Professorial Medical Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka
[2]University of Colombo, Sri Lanka

Corresponding Author:
Manudi Nushara Vidanapathirana, Professorial Medical Unit, National Hospital of Sri Lanka, No.124/1 Madiwela Road, Embuldeniya, Nugegoda, Colombo 01000, Sri Lanka.
Email: manudi.vidanapathirana@gmail.com

of baclofen in patients with renal failure, despite it being renally excreted, and being known to potentiate adverse neurological effects at low doses in this population. Clinicians can therefore have a low suspicion for identifying baclofen as a possible cause of myoclonus in patients who present with it in the setting of kidney disease, or worse yet, may prescribe it unknowingly due to a lack of knowledge and guidance on its prescription in renal failure.

This case series describes two patients with CKD who developed generalized myoclonus secondary to baclofen toxicity. It will highlight the ability of baclofen to cause myoclonus in patients with renal failure with potentially low exposures and thereby call attention to the need for establishing a consensus for the prescription of baclofen in renal failure and the need for inclusion of the relevant package warnings.

Case 1

A 72-year-old man with diabetes mellitus and CKD stage 4 sought medical attention for the management of an ischiorectal abscess. To alleviate the pelvic pain resulting from the abscess and its surgical drainage, he was prescribed 10 mg of baclofen three times daily. Approximately 12 h following the first dose, after being exposed to 20 mg of baclofen, he started developing bilateral myoclonic movements involving both upper and lower limbs. Each episode lasted anywhere from 30 s to 4 min each. Notably, the patient remained conscious during the myoclonic jerks. However, approximately 24 h later, he developed drowsiness along with disorientation. Asterixis was also noted during this period.

The patient did not exhibit any fever, neck stiffness or focal neurological signs. Limbs were globally hypotonic. Pupils were bilateral (2 mm) in size and were reactive to light.

The patient's capillary blood sugar was measured to be 150 mg/dL. Further investigations revealed a serum creatinine level of 2.4 mg/dL, consistent with his known baseline kidney function. Blood urea level was elevated at 70 mg/dL. Liver function tests and serum calcium and magnesium concentrations were all within the normal range. A venous blood gas revealed normal partial pressures of oxygen and carbon dioxide. A non-contrast CT (NCCT) scan of the brain did not reveal any structural abnormalities. However, an electroencephalogram (EEG) showed diffuse slow cortical activity, indicating moderate cortical dysfunction. Cerebrospinal fluid's full report was normal. He was also not identified as being on any other drugs known to cause myoclonus.

Baclofen was discontinued, and the patient underwent a single session of haemodialysis. The haemodialysis lasted for 2.5 h with a basal flow rate of 250 ml per minute with no ultra-filtrate.

Around 12 h after the completion of the dialysis procedure, which corresponded to 24 h after the last dose of baclofen, the myoclonus gradually subsided. The patient was seen 1 month subsequent to this incident, and was not noted to have lasting neurological effects.

Case 2

A 50-year-old man with diabetes mellitus and end stage kidney disease on regular haemodialysis, was prescribed 10 mg of baclofen three times daily by his general practitioner for a mechanical neck pain.

Two days after the first dose, after being exposed to 60 mg of baclofen, he developed bilateral myoclonic movements, with involvement of all four limbs. He did not develop drowsiness or disorientation and the conscious level was preserved. The patient developed the myoclonic movements 1 day after his regular haemodialysis session and 2 days before his next due dialysis.

On examination, there was no fever, neck stiffness or focal neurological signs. Asterixis was absent.

Metabolic panel inclusive of capillary blood sugar, liver function tests and serum calcium and magnesium were all within the normal range. Partial pressures of oxygen and carbon dioxide too were normal. Renal function tests revealed a serum creatinine of 9 mg/dL. A NCCT scan of the brain revealed no abnormalities, and an EEG showed diffuse slowing of cortical activity.

Baclofen was withdrawn, and the patient underwent a haemodialysis. The haemodialysis lasted for 4 h with a basal flow rate of 300 ml/min. His symptoms improved within 24 h of haemodialysis. The patient was also reviewed 1 month subsequent to this incident, and was not noted to have lasting neurological effects.

Discussion

Baclofen is a synthetic derivative of GABA, with renal excretion and sequestration in the central nervous system.[1] These two properties explain the occurrence of CNS symptoms such as somnolence and seizures in the event of baclofen toxicity in patients with CKD.

Baclofen toxicity has been described in patients with CKD in case reports and case series. The common symptoms of baclofen toxicity are drowsiness, altered level of consciousness, seizures and respiratory depression.[4] Several case reports and case series describe the occurrence of encephalopathy secondary to baclofen toxicity in patients with CKD. There is a single case report of a patient developing myoclonic status epilepticus as a consequence of baclofen overdose. To the best of our knowledge, myoclonus without any alteration in the conscious level, has not been previously reported or described as a consequence of baclofen toxicity in patients with CKD. This case series represents the first documented instances of myoclonus with preserved conscious level, occurring as a result of baclofen toxicity in this patient population.

Baclofen generally has an inhibitory effect on abnormal movements and muscle contraction.[4] This is due to its agonist action on GABA receptors, which increases membrane conductance of potassium and thereby promotes cell membrane polarization.[4] This in turn increases the threshold for development on action potentials and inhibits central neurons.

Paradoxically, in supra-therapeutic doses, it has been reported to lower seizure threshold and cause myoclonic movements.[8] The mechanism is unclear, but it has been postulated that baclofen can cause myoclonic status epilepticus by inactivating inhibitory interneurons in both pre- and post synapses, thereby lowering the threshold for seizures.[8]

The dose of baclofen linked with adverse neurological effects is a cumulative dose of 10–20 mg, and the time for developing adverse neurological effects with baclofen is therefore largely dependent on when this cumulative dose is reached.[1,9,10] However, an alternate hypothesis suggests that there is a large, disproportionate accumulation of baclofen in the central nervous system of uremic patients, and neurological toxicity in this population can occur even at therapeutic doses of baclofen.[11] A study done among 360 patients with renal impairment, who were prescribed baclofen, had a median period of 3 days before presenting to hospital with encephalopathy.[10] Granted, the two patients described in this case series developed neurological symptoms before the lapse of said median period, but that could be due to the shorter time required to cause the central nervous system changes, leading to the less severe symptom of myoclonus compared to the more severe presentation of encephalopathy.

Management options of baclofen toxicity in CKD is supportive care with observation for respiratory compromise and extracorporeal treatment.[2] Baclofen can be eliminated through haemodialysis due to its low molecular weight, reduced protein binding and low volume of distribution.[1] As a result, it is possible to reduce the half-life of baclofen through haemodialysis. A 4-h haemodialysis is capable of eliminating 79% of the drug and thereby reducing the half-life from 15.5 h to 2.06 h.[1] The first patient, being dialysis-naïve, received a 2.5-h dialysis. This was retrospectively deemed sufficient for him, considering that he was exposed to only 20 mg of the drug and the symptoms completely disappeared following dialysis. The second patient who was exposed to a much higher dose, received a 4-h dialysis, and also showed good resolution of symptoms. It can even be hypothesized, according to the review by Salim et al., that in addition to eliminating the drug, haemodialysis, by way of reducing uraemia, reduces the disproportionate accumulation of baclofen in the central nervous system of patients with renal impairment and thereby controls symptoms.[11]

As baclofen has been reported to have several adverse neurological effects in patients with CKD, it is important to use it with caution in these patients. Its use in renal impairment is not definitively contraindicated, but there is no consensus on dose modification in CKD patients, in spite of increased risk of toxicity. Furthermore, due to the potential presentation of baclofen toxicity as myoclonic movements without any changes in the conscious level, a heightened level of suspicion is imperative, particularly in patients with CKD.

A study by Vlavonou et al, which analysed the pharmacokinetics of baclofen, recommended dose reductions of 2/3, 1/2 and 1/3 for mild, moderate and severe renal failure.[3] Severity of renal failure was categorized according to estimated glomerular filtration rate (mild – 50–80 ml/min, moderate – 30–50 ml/min, severe – $<$30 ml/min). Another study by Varma et al.[1] suggests 2.5 mg of baclofen be given as needed without exceeding a cumulative dose of 10 mg, on the basis that no adverse events have been reported with dosing under 10 mg. Both of the patients presented in the case series were exposed to more than 10 mg of baclofen. Despite these isolated recommendations, a review on the topic by Hayati et al.,[2] failed to identify the agreed-upon guidelines for the prescription of baclofen in CKD patients.

The varied suggestions on dose modification of baclofen in renal impairment, only highlights the need for expert consensus in this regard.

This case series brings to light two important points for nephrologists and physicians: baclofen as a cause of myoclonus with preserved conscious level in patients with renal impairment and the lack of guidance on the prescription of baclofen in renal failure.

Conclusion

Baclofen has an increased risk of adverse neurological effects in patients with renal impairment. Expert consensus on dose modification or contraindication of baclofen in renal impairment is necessary.

Acknowledgements

None.

Authors' contributions

M.N.V. Conceptualization and writing the main article. T.P. Writing the article. E.W. Editing the article.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Consent for publication

Informed written consent for publication was obtained from the patients. (The authors are able to provide proof if required).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Manudi Nushara Vidanapathirana https://orcid.org/0000-0002-0725-1238

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