Baclofen toxicity in a patient with advanced chronic kidney disease

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Introduction

Baclofen is indicated for the symptomatic relief of spasticity and cramps associated with various central nervous system disorders, and is also widely prescribed off-label to treat musculoskeletal pain. Recommendations for dose adjustment in patients with renal impairment are limited to expert opinion, with no specific cut-offs provided by the manufacturer. This article describes a case of baclofen toxicity in a 62-year-old woman with advanced chronic kidney disease following therapeutic ingestion of baclofen. The patient exhibited several neurological features of toxicity, and was treated with emergent haemodialysis, making a full recovery after three haemodialysis sessions.

Case report

A 62-year-old woman presented to the emergency department with a 24-hour history of worsening lethargy associated with five bouts of vomiting. She had a background history of renal transplantation for end-stage kidney disease secondary to polycystic kidney disease, hypertension, depression and pancytopaenia under investigation. The patient had been discharged 2 weeks before this presentation following a prolonged admission with gastroenteritis and pre-renal acute kidney injury. She required temporary haemodialysis via a tunnelled central venous catheter, with gradual return of graft function back to her baseline estimated glomerular filtration rate of 18 ml/min/1.73 m^2.

Her regular medications included mycophenolate mofetil, tacrolimus, prednisolone, erythropoietin, calcium carbonate, 1-alpha-calcidol, sodium bicarbonate, amlodipine, atenolol, doxazosin, atorvastatin, omeprazole, amitriptyline and flupentixol. A collateral history from her husband revealed that she had been prescribed baclofen 10 mg twice daily for low back pain 2 days before the onset of symptoms, and had ingested a cumulative dose of 30 mg baclofen. She had no history of alcohol or substance misuse.

She was haemodynamically stable, afebrile and was maintaining oxygen saturations of 98% on room air. Her capillary glucose level was 5.8 mmol/litre. She was drowsy and non-communicative. She was opening her eyes to voice and was able to follow simple instructions, albeit with significant psychomotor delay. Her Glasgow coma score was 12 (E3, V3, M6). The rest of the physical examination was unremarkable.

Graft function was below her baseline with a serum creatinine level of 349 µmol/litre, estimated glomerular filtration rate of 12 ml/min/1.73 m^2 and urea level of 27 mmol/litre. Blood gases showed a metabolic acidosis with respiratory compensation, and a normal lactate level. Her pancytopaenia was stable, with a white cell count of 2.2x10^9/litre, haemoglobin level of 7.8 g/dl and platelet count of 65x10^9/litre. Her C-reactive protein level was 50 mg/litre. Liver enzymes, clotting, electrolytes, albumin, creatine kinase and ammonia levels were all within normal limits. Electrocardiogram showed sinus rhythm, with normal PR and QT intervals. Plain chest X-ray revealed a right lower zone consolidation. Brain computed tomography was normal.

Given the clinical findings and sequence of events, baclofen toxicity complicated by aspiration pneumonia was suspected. Intravenous fluids were started, and antibiotic cover with piperacillin/tazobactam was provided. Baclofen, amitriptyline and flupentixol were stopped, and urgent haemodialysis was organised. During haemodialysis, she became increasingly disoriented, had worsening psychomotor retardation, and her Glasgow coma score dropped to 10 (E3, V1, M6). Generalised rigidity developed, together with frequent and prominent upper limb myoclonic jerks. She was reviewed by a neurologist and intravenous levetiracetam was administered. The patient was subsequently transferred to intensive care for close monitoring.

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Case report (continued)

The following morning, she remained lethargic, but her rigidity had improved and the myoclonic jerks resolved. Endotracheal intubation was not necessary. An electroencephalogram showed a slow background with triphasic sharp wave components, consistent with a severe generalised metabolic encephalopathy. A further two haemodialysis sessions were carried out on the first and third days after admission, following which all neurological symptoms resolved. Serum baclofen levels taken before the third haemodialysis session were 417 ng/ml, declining to 57.3 ng/ml afterwards.

The patient was transferred to a general medical ward after 3 days in the intensive care unit. She regained her previous level of mobility with physiotherapy and was discharged home after 17 days in hospital.

Discussion

Baclofen, a synthetic derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), acts as an agonist at $GABA_B$ receptors, leading to a reduction in skeletal muscle tone (Leung et al, 2006). Within its therapeutic range (80–400 ng/ml), baclofen primarily acts on $GABA_B$ receptors at the spinal level. A toxic metabolic encephalopathy ensues if it accumulates in the brain (El-Husseini et al, 2011).

Baclofen-associated neurotoxicity may present in a spectrum of both inhibitory and paradoxical disinhibitory clinical features (Romito et al, 2021). The former manifestations include drowsiness, delirium, hyporeflexia, hypotonia, respiratory depression and an absence of brainstem reflexes resembling brain death. Paradoxical myoclonus, non-convulsive status epilepticus and tonic–clonic seizures have been well documented. Muscle rigidity, as in this case, has been less commonly reported. Patients with impaired kidney function are at high risk of developing adverse reactions to therapeutic doses of baclofen (Vlavonou et al, 2014).

Up to 85% of baclofen is excreted unchanged via the kidneys, with only around 15% inactivated by deamination in the liver (Wu et al, 2005). Consequently, the plasma elimination half-life of baclofen (3–6 hours in individuals with normal renal function) may be prolonged to 20–80 hours in those with advanced kidney disease (Ghannoum et al, 2021). Baclofen crosses the blood–brain barrier slowly, so poor elimination increases the likelihood of baclofen crossing the blood–brain barrier and accumulating to cause toxicity (Meillier et al, 2015).

Baclofen has a low molecular weight (213 Da), a low volume of distribution (0.83 litre/kg), and a low degree of plasma protein binding (only 30% of baclofen is protein-bound) (Wolf et al, 2018). These physicochemical properties make enhanced elimination by haemodialysis an effective management option (Brvar et al, 2007). A pharmacokinetic study showed that a 4-hour session of haemodialysis can remove 79% of serum baclofen (Wu et al, 2005).

The Extracorporeal Treatments in Poisoning workgroup guidelines on the treatment of baclofen poisoning suggest that haemodialysis is carried out when severe toxicity from therapeutic baclofen use occurs in patients with renal impairment (Ghannoum et al, 2021). This led to complete resolution of this patient's symptoms after three sessions of haemodialysis.

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References

Brvar M, Vrtovec M, Kovac D et al. Haemodialysis clearance of baclofen. Eur J Clin Pharmacol. 2007;63(12):1143–1146. https://doi.org/10.1007/s00228-007-0371-8

El-Husseini A, Sabucedo A, Lamarche J, Courville C, Peguero A. Baclofen toxicity in patients with advanced nephropathy: proposal for new labeling. Am J Nephrol. 2011;34(6):491–495. https://doi.org/10.1159/000333247

Ghannoum M, Berling I, Lavergne V et al. Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning. Kidney Int. 2021;100(4):720–736. https://doi.org/10.1016/j.kint.2021.07.014

Learning points

- Impaired renal function can lead to baclofen accumulation and toxicity.
- Baclofen use should be avoided in patients with an estimated glomerular filtration rate less than 30 ml/min/1.73m^2.
- Neurotoxicity can present in a mixture of inhibitory and paradoxical disinhibitory clinical features.
- The physicochemical properties of baclofen mean that haemodialysis is an effective management option.
- The Extracorporeal Treatments in Poisoning workgroup recommendations are useful to guide decision making in cases of baclofen toxicity.

Leung NY, Whyte IM, Isbister GK. Baclofen overdose: defining the spectrum of toxicity. Emerg Med Australas. 2006;18(1):77–82. https://doi.org/10.1111/j.1742-6723.2006.00805.x

Meillier A, Heller C, Patel S. Baclofen-induced encephalopathy in end stage renal disease. Case Rep Med. 2015;2015:1–3. https://doi.org/10.1155/2015/203936

Romito JW, Turner ER, Rosener JA et al. Baclofen therapeutics, toxicity, and withdrawal: a narrative review. SAGE Open Med. 2021;9:20503121211022197. https://doi.org/10.1177/20503121211022197

Vlavonou R, Perreault MM, Barrière O et al. Pharmacokinetic characterization of baclofen in patients with chronic kidney disease: dose adjustment recommendations. J Clin Pharmacol. 2014;54(5):584–592. https://doi.org/10.1002/jcph.247

Wolf E, Kothari NR, Roberts JK, Sparks MA. Baclofen toxicity in kidney disease. Am J Kidney Dis. 2018;71(2):275–280. https://doi.org/10.1053/j.ajkd.2017.07.005

Wu VC, Lin SL, Lin SM, Fang CC. Treatment of baclofen overdose by haemodialysis: a pharmacokinetic study. Nephrol Dial Transplant. 2005;20(2):441–443. https://doi.org/10.1093/ndt/gfh297