Case Report

Myoclonus in renal failure: Two cases of gabapentin toxicity☆☆☆

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A B S T R A C T

Gabapentin, an AED approved for the adjunctive treatment of partial seizures with/without secondary generalization and for the treatment of postherpetic neuralgia, is frequently used off-label for the treatment of both psychiatric and pain disorders. Since gabapentin is cleared solely by renal excretion, dosing requires consideration of the patient’s renal function. Myoclonic activity may occur as a complication of gabapentin toxicity, especially with acute kidney injury or end-stage renal disease. We report 2 cases of myoclonic activity associated with gabapentin toxicity in the setting of renal disease which resolved with discontinuation of gabapentin and treatment with hemodialysis and peritoneal dialysis. As gabapentin has multiple indications and off-label uses, an understanding of myoclonus, neurotoxicity, and renal dosing is important to clinicians in multiple specialties.

1. Introduction

Antiepileptic drugs (AEDs) are used in the treatment of epilepsy, pain, and psychiatric disorders [1,2]. Hepatic and renal status may impact the efficacy and toxicity associated with AEDs which requires awareness by clinicians in multiple specialties and appropriate dose adjustments [3]. Gabapentin is an AED approved by the FDA for the adjunctive treatment of partial seizures with/without secondary generalization in children, adolescents, and adults and for the treatment of postherpetic neuralgia [4]; the prodrug gabapentin enacarbil is approved by the FDA for the treatment of restless leg syndrome [5]. Gabapentin is frequently used off-label for the treatment of both psychiatric and pain disorders [1,4]. Gabapentin is not heptically metabolized and is cleared solely by renal excretion; dosing requires consideration of the patient’s renal function, especially in the context of end-stage renal disease (ESRD) [3,6,7]. We report 2 cases of myoclonic activity associated with gabapentin toxicity in the setting of renal disease and address treatment with hemodialysis (HD) and peritoneal dialysis (PD).

2. Methods

Case analysis with PubMed literature review was employed.

3. Results

3.1. Case 1

A 78-year-old woman with congestive heart failure, history of thromboembolism, hypertension, diabetes mellitus, hyperlipidemia, asthma, diabetic peripheral neuropathy, and depression presented with tremors involving her upper extremities for 3 days prior to admission. The patient had no history of renal disease. Her admission medications included simvastatin, metformin, citalopram, gabapentin, fluticasone propionate inhaler, inhaled albuterol, lisinopril, furosemide, and metolazone. Physical examination noted severe bilateral upper extremity myoclonus with normal mental status and without other neurological symptoms. Abnormal laboratory results on admission included a sodium
level of 124 mEq/L, a potassium level of 7.2 mEq/L, a blood urea nitrogen (BUN) level of 91 mg/dL, a creatinine (Cr) level of 3.2 mg/dL, an elevated BUN/Cr ratio of 28.44, and an estimated glomerular filtration rate of 13 mL/min/1.73 m². Evaluation revealed acute kidney injury (AKI) secondary to a recently increased furosemide total dose of 60 mg daily and lisinopril 5 mg daily with hyperkalemia and azotemia. Prior to admission, the patient had been chronically treated with gabapentin 900 mg total daily dose for neuropathic pain. With discontinuation of gabapentin and initiation of HD, marked improvement in her myoclonus occurred. The patient received 2 sessions of HD and was discharged with normal renal function, a BUN level of 20 mg/dL and a Cr level of 1.1 mg/dL, and resolved myoclonus. Gabapentin was held on discharge.

3.2. Case 2

A 55-year-old man with ESRD on PD, anemia, diabetes mellitus, hypertension, neuropathic pain, hyperlipidemia, hepatitis C, peripheral vascular disease with recently amputated gangrenous toe on long-term vancomycin and piperacillin/tazobactam, and acute pain syndrome presented for evaluation of bilateral upper extremity tremors, altered mental status, hypotension, and worsening leg infection. Following initiation of gabapentin 600 mg total daily dose for neuropathic pain 3 days prior to admission, the patient developed severe arm tremors with the inability to hold objects, lethargy, and intermittent episodes of confusion. His other admission medications included clopidogrel, amlodipine, hydralazine, metoprolol, clonidine, atorvastatin, oxycodone, hydrophosphate, sevelamer, lanthanum, eproten, and insulin glargine. Physical examination confirmed bilateral upper extremity myoclonus. Abnormal renal function on admission, with a BUN level of 49 mg/dL and a Cr level of 12.7 mg/dL, was comparable to outpatient renal function during the prior three months, with a BUN level of 50–52 mg/dL and a Cr level of 10.4–11.1 mg/dL, when the patient did not have myoclonus. The patient’s PD treatment was increased from 4 to 6 exchanges daily. With increased dialysis and discontinuation of gabapentin, myoclonus and altered mental status resolved within four days.

4. Discussion

These unique cases raise a series of important points specifically related to these patients that should be considered in the general treatment of patients with gabapentin and other AEDs that require renal clearance.

First, a recent study of off-label prescriptions found the overall rate to be 21%; however, AEDs as a class are higher at 46%, and gabapentin, in particular, has the highest rate of all drugs with 83% prescribed off-label [1,4,8]. Research supports the off-label use of gabapentin to treat neuropathic pain with the development of myoclonus only after initiation of gabapentin. Case reports implicate metformin, citalopram, albuterol, amlodipine, oxycodone, and hydromorphone as potential etiologies for myoclonus [26–32]. In both cases, the patients had been stable on these and other admission medications prior to the AKI in Case 1 and the addition of gabapentin in Case 2.

Seventh, potentially inappropriate medications (PIMs) are frequently prescribed in both geriatric patients and patients with chronic kidney disease [33–35]. In patients at risk for AKI or with ESRD on dialysis, these cases suggest that gabapentin is a relative PIM unless there is renal dosing with close monitoring of efficacy and adverse effects. Pregabalin would also be a relative PIM. In such instances, duloxetine, a serotonin norepinephrine reuptake inhibitor antidepressant with FDA approval for diabetic peripheral neuropathic pain and fibromyalgia, may be an effective treatment option [36].

Eighth, each case had multiple potential risk factors for the development of myoclonus. In the context of additive risk factors, the probability of gabapentin inducing myoclonus was determined by Naranjo’s Adverse Reaction Probability Scale in Case 1 as possible and in Case 2 as probable [37].

There are specific limitations to this paper. As a case report (N = 2), the findings cannot be generalized. Both cases were complicated by the presence of medical comorbid conditions and specific medications that have been implicated as potential etiologies for myoclonus. Gabapentin drug monitoring was not performed such that the threshold concentration associated with developing and resolving myoclonus in each case could not be specified. Neither case had neuroimaging or EEGs. For ethical reasons, neither patient was rechallenged (Case 1 — maintaining gabapentin with increased total daily dose of furosemide and addition of lisinopril; Case 2 — addition of gabapentin); further, the impact of renal dosing was not assessed in either case. Both patients were lost to clinical follow-up.

5. Conclusions

Myoclonic activity may occur as a complication of gabapentin toxicity, especially in the setting of renal dysfunction. In the cases reported, both HD and PD were effective in treating myoclonic activity in acute and chronic renal dysfunction. Gabapentin requires renal dosing in patients with chronic kidney disease and in patients at risk for developing AKI. In cases of symptomatic gabapentin-induced toxicity, dialysis should be instituted. As gabapentin has multiple indications and off-label uses, an understanding of myoclonus, neurotoxicity, and renal dosing is important to clinicians in multiple specialties. Further clinical education is required.
Conflict of interest statement

There are no conflicts of interest to declare.

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