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Case Report

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

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ABSTRACT

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 hepatically 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 proprionate 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

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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 m^2. 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, hydromorphone, sevelamer, lanthanum, epoetin, 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 diabetic peripheral neuropathic pain [9,10]. One mechanism suggested for the broad spectrum effects of gabapentin is voltage-sensitive calcium channel modulation [11].

Second, with normal renal function, the half-life of gabapentin ranges from 5 to 7 h [12]. In patients with ESRD on non-HD days, one study reported the gabapentin elimination half-life to be 132 h [12]. That study noted that 35% of a single gabapentin dose was removed after three sessions of HD, supporting the use of HD in the treatment of gabapentin toxicity [12].

Third, myoclonus is a known adverse effect associated with gabapentin with a prevalence as high as 12.5% which, depending on severity, may not interfere with AED therapy [13]. In the context of renal failure, myoclonus and neurotoxicity may require discontinuation of gabapentin [6]. Most reports demonstrate that serum concentrations greater than 15 μg/mL are associated with symptomatic toxicity [14]. In patients who have intact renal function, toxicities are uncommon as gabapentin is rapidly cleared based on its short half-life; however, gabapentin concentrations are significantly increased in patients with renal dysfunction, and in cases of symptomatic toxicity, dialysis should be instituted. Both intermittent and continuous forms of renal replacement therapy have been effectively utilized to treat gabapentin-induced neurotoxicity and myoclonic activity [7,15,16]. Although this report suggests the efficacy of PD in treating gabapentin-induced myoclonus and neurotoxicity, there are no published data regarding clearance of gabapentin with PD.

Fourth, pregabalin is an alternative AED with FDA/EMA approval for pain syndromes (central neuropathic pain, diabetic peripheral neuropathic pain, postherpetic neuralgia, and fibromyalgia) [17]. Pregabalin, which, like gabapentin, is a branched-chain amino acid AED that is cleared solely by renal excretion, is also noted to induce myoclonus [18,19]. As with gabapentin, dialysis has been utilized to treat pregabalin neurotoxicity and myoclonic activity [20,21].

Fifth, a threshold effect for the development of myoclonic activity with gabapentin and pregabalin has been previously reported [19,22]. This is consistent with the concept that adverse events for specific AEDs may require an individual threshold concentration which may be within the reference range [14,23,24].

Sixth, myoclonus has multiple etiologies [25]. Pertinent to these cases are azotemia and toxic effects of medications. Azotemia was present in both cases; however, in Case 2, the patient had chronic stable renal function 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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References

[1] Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. Epilepsy Behav 2011;21:1–11.
[2] Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? Epilepsia 2012;53(Suppl. 7):26–33.
[3] Anderson GD, Hakimian S. Pharmacokinetic of antiepileptic drugs in patients with hepatic or renal impairment. Clin Pharmacokinet Oct 13 2013. http://dx.doi.org/10.1007/s40262-013-01017-0.
[4] Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm 2003;9:559–68.
[5] Lai R, Sukbuntherng J, Luo W, Tovera J, Lassauzet ML, Cundy KC. Population pharmacokinetics and pharmacodynamics of gabapentin after administration of gabapentin enacarbil. J Clin Pharmacol 2013;53:29–40.
[6] Zhang C, Glenn DG, Bell WL, O'Donovan CA. Gabapentin-induced myoclonus in end-stage renal disease. Epilepsia 2005;46:156–8.
[7] Miller A, Price G. Gabapentin toxicity in renal failure: the importance of dose adjustment. Pain Med 2009;10:190–2.
[8] Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med 2006;166:1021–6.
[9] Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 2003;25:81–104.
[10] Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev March 16 2011;3:CD007938.
[11] Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca^{2+} channel $\alpha_2\delta$ ligands: novel modulators of neurotransmission. Trends Pharmacol Sci 2007;28:75–82.
[12] Wong MO, Eldon MA, Keane WF, Turck D, Bockbrader HN, Underwood BA, et al. Disposition of gabapentin in anuric subjects on hemodialysis. J Clin Pharmacol 1995;35:622–6.
[13] Asconape J, Diedrich A, DellaBadia J. Myoclonus associated with the use of gabapentin. Epilepsia 2000;44:479–81.
[14] Zand L, McKian KP, Qian Q. Gabapentin toxicity in patients with chronic kidney disease: a preventable cause of morbidity. Am J Med 2010;123:367–73.
[15] Hung TY, Seow VK, Chong CF, Wang TL, Chen CC. Gabapentin toxicity: an important cause of altered consciousness in patients with uraemia. BMJ Case Rep 2009. http://dx.doi.org/10.1136/bcr.11.2008.1268.
[16] Guddati AK, Zafar Z, Cheng JT, Mohan S. Treatment of gabapentin-induced myoclonus with continuous renal replacement therapy. Indian J Nephrol 2012;22:59–61.
[17] Finnerup NB, Jensen TS. Clinical use of pregabalin in the management of central neuropathic pain. Neuropsychiatr Dis Treat 2007;3:885–91.
[18] Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 2010;49:661–9.
[19] Huppertz HJ, Feuerstein TJ, Schulze-Bonhage A. Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. Epilepsia 2001;42:790–2.
[20] Healy DG, Ingle GT, Brown P. Pregabalin- and gabapentin-associated myoclonus in a patient with chronic renal failure. Mov Disord 2009;24:2028–9.
[21] Yoo L, Matalon D, Hoffman RS, Goldfarb DS. Treatment of pregabalin toxicity by hemodialysis in a patient with kidney failure. Am J Kidney Dis 2009;54:1127–30.
[22] Holtkamp M, Halle A, Meierkord H, Masuhr F. Gabapentin-induced severe myoclonus in a patient with impaired renal function. J Neurol 2006;253:382–3.
[23] Kaufman KR, Bisen V, Zimmerman A, Tobia A, Mani R, Wong S. Apparent dose-dependent levetiracetam-induced de novo major depression with suicidal behavior. Epilepsy Behav Case Rep 2013;1:110–2.
[24] Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs — best practice guidelines for therapeutic drug monitoring: a position paper for the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239–76.
[25] Borg M. Symptomatic myoclonus. Neurophysiol Clin 2006;36:309–18.
[26] Jung EY, Cho HS, Seo JW, Kim DW, Kim HJ, Chang SH, et al. Metformin-induced encephalopathy without lactic acidosis in a patient with contraindications for metformin. Hemodial Int 2009;13:172–5.
[27] Turedi S, Eraydin I, Gunduz A, Kalkan A. First time, low dose citalopram use-related serotonin syndrome. Neurotoxicology 2007;28:1272–4.
[28] Talarico G, Tosto G, Pietracupa S, Piacentini E, Canevelli M, Lenzi GL, et al. Serotonin toxicity: a short review of the literature and two case reports involving citalopram. Neurol Sci 2011;32:507–9.
[29] Mitcheli F, Cersosimo MG, Scorticati MC, Velez M, Gonzalez S. Myoclonus secondary to albuterol (salbutamol) instillation. Neurology 2000;54:2022–3.
[30] Wallace EL, Lingle K, Pierce D, Satko S. Amlodipine-induced myoclonus. Am J Med 2009;122:e7.
[31] Gopinath KG, Hewton C, Shibu PK. Myoclonus associated with concomitant ciprofloxacin and oxycodone in an older patient. Br J Clin Pharmacol 2013. http://dx.doi.org/10.1111/bcp.12213.
[32] Paramanandam G, Prommer E, Schwenke DC. Adverse effects in hospice patients with chronic kidney disease receiving hydromorphone. J Palliat Med 2011;14:1029–33.
[33] Bongue B, Laroche ML, Gutton S, Colvez A, Gueguen R, Moulin JJ, et al. Potentially inappropriate drug prescriptions in the elderly in France: a population-based study from the French National Insurance Healthcare system. Eur J Clin Pharmacol 2011;67:1291–9.
[34] Matanovic SM, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. Eur J Clin Pharmacol 2012;68:1123–38.
[35] Jones SA, Bhandari S. The prevalence of potentially inappropriate medication prescribing in elderly patients with chronic kidney disease. Postgrad Med J 2013;89:247–50.
[36] Bellingham GA, Peng PW. Duloxetine: a review of its pharmacology and use in chronic pain management. Reg Anesth Pain Med 2010;35:294–303.
[37] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.