Pregabalin-associated myoclonic encephalopathy without evidence of drug accumulation in a patient with acute renal failure

F. Courtois, D. Borrey[1], V. Haufroid[2], P. Hantson[2]

Department of Intensive Care Medicine, Cliniques St-Luc, Université catholique de Louvain, Brussels, [1]Department of Laboratory Medicine, Laboratory of Toxicology, AZ Sint-Jan AV Hospital, Brugge, [2]Louvain Centre for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium

ABSTRACT

Pregabalin, used for treating partial epilepsy and neuropathic pain, is usually well tolerated. Patients with impaired renal function are at risk to develop more serious adverse events. A 64-year-old woman was admitted in the Emergency Department for altered consciousness and abnormal movements. She recently started to take pregabalin (150 mg/day) for neuropathic pain. The drug was withdrawn 36 h before hospitalization following worsening of neurological symptoms. At physical examination, myoclonus was noted as main finding in the limbs and head, with encephalopathy. Laboratory investigations revealed acute renal failure with serum creatinine at 451.3 μmol/l. Urine output was preserved. After supportive care alone, myoclonus resolved after 24 h and consciousness was normal after 48 h. Renal function was also recovered. At the time of admission, the concentration of plasma pregabalin was 3.42 μg/ml, within therapeutic range. The calculated terminal elimination half-life was 11.5 h. Pregabalin-induced myoclonus may not be strictly related to drug accumulation in acute renal failure, with the possibility of a threshold phenomenon.

Key words: Encephalopathy, myoclonus, pharmacokinetics, pregabalin

Introduction

Treatment with pregabalin is usually well tolerated, with dizziness and somnolence being the most frequent adverse events after therapeutic doses. It is suggested that overdose causes only mild symptoms, but coma is possible after the ingestion of several grams of pregabalin.[1] Patients with chronic renal failure may develop more serious symptoms, particularly myoclonus and confusion, even with therapeutic doses, as pregabalin by renal elimination is reduced.[2-4] We report a patient who presented encephalopathy and myoclonus a few days after the intake of pregabalin 150 mg/day as treatment. Acute renal failure may have been a precipitating factor.

Address for correspondence:
Prof. Philippe Hantson, Department of Intensive Care,
Cliniques St-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium.
E-mail: philippe.hantson@uclouvain.be

Video available on www.indianjnephrol.org

Access this article online

Quick Response Code:

Website: www.indianjnephrol.org

DOI: 10.4103/0971-4065.125102

Case Report

A 64-year-old woman was admitted in the Emergency Department (ED) for altered consciousness and abnormal movements. Her medical history included arterial hypertension and type 2 diabetes mellitus. There was no history of epileptic seizures. She was treated since 1 year in the Hematology Department for a multiple myeloma complicated with chronic inflammatory demyelinating polyneuropathy (CIDP). Her current medications included clonazepam, amlodipine, L-thyroxin, metformin, repaglinide, spironolactone, furosemide, minoxidil, irbesartan, hydrochlorothiazide, acyclovir, pantoprazole, and fenofibrate. During the recent hospital stay, the patient started taking pregabalin (75 mg/day for 9 days and then 75 mg bid) to treat CIDP-related pain. At the time of discharge from the hospital, her serum creatinine concentration was 90.2 μmol/l. Five days later, when

admitted in the ED, the patient had already received a cumulative dose of 1,350 mg pregabalin for more than 14 days. The last dose of 75 mg had been ingested 36 h before the hospital admission. The medication was stopped by the patient following the symptoms of confusion, speech difficulties, visual hallucinations, and continuous limb and head movements.

When admitted in the ED, the Glasgow Coma Score was 11/15 (E3, V3, M5). Spontaneous myoclonus of the legs was observed, with involuntary movements of the arms and face, which were increased when the patient was stimulated (Video). She aroused but was unable to speak. The main findings of the laboratory investigations were an acute renal failure, with serum urea, 22.9 mmol/l (normal <8.3); serum creatinine, 451.3 μmol/l (normal <115); and hypercalcemia (total calcium: 3.1 μmol/l). The clearance of creatinine was reduced to 9 ml/min/m^2. Acute renal failure was multifactorial: Multiple myeloma, hypercalcemia, and drug interactions. There was no evidence for urinary tract obstruction.

The patient was transferred to the intensive care unit. Sedation with benzodiazepines was transiently required to insert venous and arterial catheters, and the intensity of the abnormal movements was decreased. It was not possible to perform an electroencephalogram due to incessant movements of the head. As urine output was maintained, and in the absence of severe metabolic disorders, hemodialysis was not required. Renal function rapidly recovered following fluid therapy. The neurological condition improved after 24 h of supportive care, with a resolution of myoclonus. Confusion and speech disorder persisted for 48 h, but ultimately the patient made a complete neurological recovery, with a total amnesia of the recent events. Pregabalin was not reintroduced. Renal function returned to previous values.

Later, the results of the toxicological analysis were obtained [Figure 1]. At the time of admission, the concentration of plasma pregabalin was 3.42 μg/ml (therapeutic range: 3-12). The terminal elimination half-life was 11.5 h and was calculated from five consecutive time points up to 31 h after admission. Based on these pharmacokinetic data and considering the delay of 36 h between last drug ingestion and hospital admission, a maximal plasma pregabalin concentration of 13.70 μg/ml could have been reached 12 h after the last drug administration (last theoretical trough concentration).

Discussion

Pregabalin modulates excitatory neurotransmitter release (glutamate, norepinephrine, and substance P) through the α-2 delta subunit of the voltage-gated calcium channel in the tissues of central nervous system. Its use has been approved for the treatment of partial epilepsy and chronic pain.

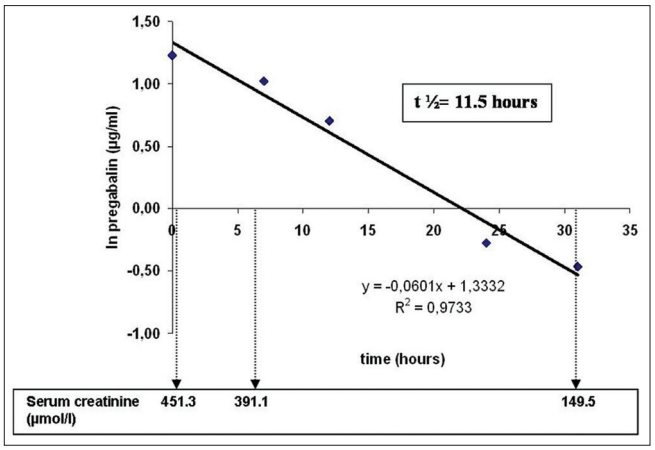

Figure 1: Pregabalin plasma concentration (ln μg/ml) over time and relationship with serum creatinine. Pharmacokinetic analysis was performed on five data points from admission (36 h after the last drug administration)

Pregabalin is not bound to plasma proteins. Approximately, 90% of an oral dose of pregabalin is eliminated unchanged in urine. In patients with renal impairment, dose adjustments are required.[2,4] The mean elimination half-life is 6.3 h in patients with normal renal function.[5] The determination technique of pregabalin plasma concentration is not routinely available; therapeutic range is usually 2.8-8.2 μg/ml.[6]

Myoclonus, usually transient, may be observed after the first doses of pregabalin, even in patients without a history of seizures or renal dysfunction.[7] It seems more frequent when pregabalin is added to other antiepileptic agents.[8] Although the association between gabapentin and myoclonus is well characterized, few reports have described myoclonus and altered consciousness after pregabalin therapy in patients with chronically altered renal function.[3,4,9] Only anecdotal data correlated pregabalin level with toxicity. Pregabalin was measured during its use in adults with partial seizures and normal kidney function. Levels with doses of 150 and 600 mg/d were 0.29-2.84 and 0.87-14.2 μg/ml, respectively.[10]

A 47-year-old man with chronic renal failure developed confusion, hallucination, and myoclonus after 2 days of treatment at the dose of 75 mg bid.[3] Partial resolution was observed after 42 h, but complete recovery only after 90 h and 16 peritoneal dialysates. However, no blood concentrations were available for pharmacokinetic analysis, and the role of excessive plasma concentration remained speculative. In a 30-year-old woman on

long-term hemodialysis, the inadvertent increase in pregabalin dose led to significant myoclonus of the arms and legs.[4] Pre-dialysis serum showed a pregabalin concentration of 13 μg/ml. After a 2-h hemodialysis, myoclonus resolved with a post-dialysis pregabalin concentration at 6.5 μg/ml.

In the present observation, the causality assessment was based on the Naranjo algorithm, with a score of five (probable adverse drug reaction). It was also supported by the published experience of altered pharmacokinetics and increased neurotoxicity in case of chronic renal impairment.[11] Drug – drug interaction between pregabalin and the patient's medications was unlikely. In contrast to previous observations, our patient was still symptomatic with a low pregabalin plasma concentration.[4] We cannot exclude that acute renal failure may have lowered the myoclonus threshold.[7,12] Finally, a genetic susceptibility remains possible including, for instance, the α-2 delta subunit of the voltage-gated calcium channel. This observation suggests that the risk to develop myoclonus could, in some patients, be related to a threshold phenomenon rather than linear dose dependency; these patients may be managed by supportive measures alone.[1,8]

References

1. Wood DM, Berry DJ, Glover G, Eastwood J, Dargan PI. Significant pregabalin toxicity managed with supportive care alone. J Med Toxicol 2010;6:435-7.
2. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003;43:277-83.
3. Healy DG, Ingle GT, Brown P. Pregabalin-and gabapentin-associated myoclonus in a patient with chronic renal failure. Mov Disord 2009;24:2028-9.
4. 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.
5. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, *et al*. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 2010;50:941-50.
6. Berry D, Millington C. Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. Ther Drug Monit 2005;27:451-6.
7. Hellwig S, Amtage F. Pregabalin-induced cortical negative myoclonus in a patient with neuropathic pain. Epilepsy Behav 2008;13:418-20.
8. Huppertz HJ, Feuerstein TJ, Schulze-Bonhage A. Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. Epilepsia 2001;42:790-2.
9. Prieto-Pérez L, Montastruc J, García-Ruiz PJ. Myoclonias secondary to gabapentin in a patient with chronic renal failure. Rev Neurol 2011;52:512.
10. Arroyo S, Anhut H, Kugler AR, Lee CM, Knapp LE, Garofalo EA, *et al*. Pregabalin add-on treatment: A randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 2004;45:20-7.
11. 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.
12. Muscatt S, Rothwell J, Obeso J, Leigh N, Jenner P, Marsden CD. Urea-induced stimulus-sensitive myoclonus in the rat. Adv Neurol 1986;43:553-63.

How to cite this article: Courtois F, Borrey D, Haufroid V, Hantson P. Pregabalin-associated myoclonic encephalopathy without evidence of drug accumulation in a patient with acute renal failure. Indian J Nephrol 2014;24:48-50.

Source of Support: Nil, **Conflict of Interest:** None declared.