Research in Health Science
ISSN 2470-6205 (Print) ISSN 2470-6213 (Online)
Vol. 6, No. 3, 2021
www.scholink.org/ojs/index.php/rhs

Case Report

Pregabalin Neurotoxicity Associated with Triphasic Waves on Electroencephalogram. Conservative Management or Hemodialysis?

Harpreet Singh MD[1], Amanda R Kalupa MD[2], Chinmay Jani MD[3,4], Arashdeep Rupal MD[3,4], Alexander Walker MD[3,4], Harsh Patel[5] & Kurt Hu MD[1]

[1] Department of Pulmonary and Critical Care, Medical College of Wisconsin, Milwaukee, WI, USA

[2] Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[3] Department of Medicine, Mount Auburn Hospital/Beth Israel Lahey Health, Cambridge, MA, USA

[4] Harvard Medical School, Boston, MA, USA

[5] Department of Internal Medicine, Weiss Memorial Hospital, Chicago, Illinois, USA

[*] Corresponding Author: Harpreet Singh, MD., Medical College of Wisconsin, 8701 W Watertown Plank Road, Milwaukee, WI 53226. E-mail: hasingh@mcw.edu; Phone: 716-378-9697.

Received: June 30, 2021 Accepted: July 5, 2021 Online Published: July 22, 2021

doi:10.22158/rhs.v6n3p22 URL: http://dx.doi.org/10.22158/rhs.v6n3p22

Keywords:

Pregabalin, encephalopathy, myoclonus, triphasic waves, dialysis

Introduction:

Pregabalin is a lipophilic analogue of γ-aminobutyric acid. It is approved for the treatment of neuropathic pain, anxiety disorder, fibromyalgia, and as an adjunctive therapy for partial seizures (Calandre EP, Rico-Villademoros F, Slim, 2016; National Center for Biotechnology Information, 2021; Derry, Bell, Straube, Wiffen, Aldington, & Moore, 2019). Lately, pregabalin is also being prescribed for uremic pruritis (Khan, Wu, Goh, Lee, Alhafez, & Syed Sulaiman, 2016). Significant pregabalin toxicity associated with therapeutic use has been reported in chronic kidney disease (CKD) patients (Olaizola, Ellger, Young, Bosebeck, Evers, & Kellinghaus, 2006; Braga & Chidley, 2007; Huppertz, Feuerstein, & Schulze-Bonhage, 2001). Here, we report a case of pregabalin neurotoxicity presenting as acute severe encephalopathy, and facial myoclonus manifesting as triphasic waves on electroencephalogram (EEG) in a CKD IIIb-IV patient.

Case narration:

A 69-year-old woman was admitted to the intensive care unit with acute encephalopathy. Her medical history included HFrEF, CKD IIIb-IV, depression, and post traumatic distress disorder. Her psychotropic medications included pregabalin, quetiapine, and venlafaxine. Her family reported that she had become progressively short of breath for ten days leading up to her admission; therefore, her diuretic dose was increased. On presentation, she was arousable only to noxious stimulation. She had altered sensorium, unable to follow commands, and frequently falling asleep during the exam. Corneal reflexes and horizontal oculocephalic reflexes were present bilaterally. The pupils were equal, round, and reactive to light, and the pharyngeal reflex was present. There was spontaneous continuous myoclonus of the face. Muscle tone was normal. Plantar reflexes were equivocal bilaterally, and no clonus was observed on examination. The neck was supple.

Laboratory studies revealed an elevated serum creatinine of 3.86 mg/dL from a baseline creatinine of 2.3 mg/dL (normal: 0.60–1.30 mg/dL). Complete blood count and comprehensive metabolic panel at baseline. Her arterial blood gas showed a pH 7.49, pCO2 49 mmHg, bicarbonate 30 mmol/L. Additional laboratory studies showed blood ethanol level < 3 mg/dl, and blood ammonia level 19 umol/L. The urine toxicology screen was negative. Acetaminophen and salicylate were undetectable.

CT head revealed no acute abnormalities. Her EEG is shown here (Figure 1) and revealed continuous moderate generalized slowing of the background and abundant intermittent bi-anterior predominant, bi-synchronous triphasic waves that often occurred over several second runs at 1.5-2.2 Hz. Given the patient's worsening renal function associated with oliguria, there was a concern about pregabalin and venlafaxine toxicity. She was treated with intravenous fluids for the next 24 hours without any clinical improvement. The patient was then hemodialyzed for 3 hours leading to complete resolution of encephalopathy, facial myoclonic, and triphasic waves on EEG.

Discussion:

Pregabalin is an anti-epileptic, anxiolytic, and analgesic medication often used for neuropathic pain. Pregabalin binds selectively to the alpha2delta (A2D) subunits of presynaptic calcium channels in the central nervous system (Calandre EP, Rico-Villademoros F, Slim, 2016). This binding prevents calcium influx and blocks the calcium-dependent release of neurotransmitters, including serotonin, dopamine, norepinephrine, glutamate, and substance P (National Center for Biotechnology Information, 2021). This reduced excitability has efficacy in treating neuropathic pain (Derry, Bell, Straube, Wiffen, Aldington, & Moore, 2019). The most common adverse effects include dizziness, somnolence, myoclonus, blurred vision, peripheral edema, tremor, visual field loss, and rhabdomyolysis (Toth, 2014; Gunathilake, Boyce, &Knight, 2013).

Pregabalin is well absorbed orally and has a bioavailability of >90%. It is excreted almost entirely unchanged in the urine (90%) and does not have any hepatic metabolism. To achieve comparable plasma drug concentrations in patients with creatinine clearance (CL_{cr}) values of < 60 ml/min, it is usually recommended that pregabalin doses be decreased by ~50% for each 50% decline in CL_{cr}

(Ben-Menachem, 2004). In individuals with normal kidney function, the drug has a serum half-life of 9 hours which increases to 49 hours when CL_{cr} drops below 15 ml/min. Hence, when CL_{cr} drops below 60 mL/min, reduced frequency of pregabalin administration should be considered (Randinitis, Posvar, Alvey, Sedman, Cook, & Bockbrader, 2003). In our patient, a significant decrease in her CL_{cr} and continued 75 mg twice daily dosing increased her serum level of pregabalin to induce acute encephalopathy, facial myoclonus, and triphasic EEG waves.

The pharmacokinetics of pregabalin makes it a dialyzable drug. It has a low volume of distribution, low molecular weight and is not protein bound. Hemodialysis reduces the half-life to 4 hours (Lee, Lee, Kim, Chang, & Park, 2011). Yoo et al. described a case of a hemodialysis-dependent end-stage renal failure patient who developed myoclonus that was thought to be related to pregabalin accumulation following an increase in the prescribed dose. Hemodialysis resulted in improvement of the clinical symptoms (Yoo, Matalon, Hoffman, & Goldfarb, 2009). Our patient was becoming progressively unresponsive. We favored hemodialysis over the potential risks of intubation. Immediately after dialysis patient's encephalopathy and myoclonus resolved completely. Fast recovery after dialysis supports pregabalin toxicity and argues against the venlafaxine toxicity as it is non-dialysable (Yeh et al., 2014).

Triphasic morphology EEG discharge waveforms have three principal phases: a positive, sharp transient preceded and followed by negative waves of relatively lower amplitude (Figure 1). These discharges are bilaterally synchronous, occurring at a frequency of 1.5 to 2.2 Hz and only rare reports have shown an association between these discharges and pregabalin toxicity (Anand & Kaplan, 2018). When triphasic waves are present in an individual with acute encephalopathy, it often indicates a more significant impairment, prolonged hospital course, and increased odds of mortality (Emmady & Murr 2021). Triphasic waves resemble certain EEG patterns associated with nonconvulsive status epilepticus. However, unlike nonconvulsive status epilepticus, the encephalopathy associated with triphasic waves does not improve or resolve with the administration of benzodiazepines (Fountain & Waldman, 2001). In our patient, the marked improvement in her EEG after dialysis suggests that her triphasic waves were related to pregabalin toxicity. Although serotonin syndrome has been described in association with triphasic waves, our patient had no hyperthermia, ankle clonus, dilated pupils, diaphoresis, or diarrhea to suggest this diagnosis.

After one week, pregabalin level was reported to be supratherapeutic at 12.3 mg/L (normal therapeutic 0.15 - 8 mg/L) (May, Rambeck, Neb, & Jürgens, 2007). Naranjo Score was 5, indicating a probable adverse drug reaction. This was not a definite case because we did not rechallenge her. Our patient had experienced a progressive decline in her CL_{cr} in the year prior to admission; however, her pregabalin dose had not been reduced. This case highlights that in patients with CKD, it is important to reduce dose and frequency of administration when further decline of creatinine clearance occurs. Additionally, this case underscores the potential role of dialysis in pregabalin toxicity to facilitate reversal of encephalopathy.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Anand, P., & Kaplan, P. W. (2018). Triphasic Waves and Encephalopathy in the Setting of Pregabalin Toxicity. *J Clin Neurophysiol*, *35*(6), 515-517. http://doi.org/10.1097/WNP.0000000000000511. PMID: 30222638.

Ben-Menachem, E. (2004). Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia*, *45 Suppl*(6), 13-18. http://doi.org/10.1111/j.0013-9580.2004.455003.x. PMID: 15315511.

Braga, A. J., & Chidley, K. (2007). Self-poisoning with lamotrigine and pregabalin. *Anaesthesia*, *62*, 524-527. https://doi.org/10.1111/j.1365-2044.2006.04913.x

Calandre, E. P., Rico-Villademoros, F., & Slim, M. (2016). Alpha$_2$delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. *Expert Rev Neurother*, *16*(11), 1263-1277. http://doi.org/10.1080/14737175.2016.1202764. Epub 2016 Jul 7. Erratum in: Expert Rev Neurother. 2016 Nov;16(11): iii. PMID: 27345098.

Derry, S., Bell, R. F., Straube, S., Wiffen, P. J., Aldington, D., & Moore, R. A. (2019). Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev.*, *1*(1), CD007076. http://doi.org/10.1002/14651858.CD007076.pub3. PMID: 30673120; PMCID: PMC6353204.

Emmady, P. D., & Murr, N. (2021). EEG Triphasic Waves. 2020 Dec 12. In *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 32491611.

Fountain, N. B., & Waldman, W. A. (2001). Effects of benzodiazepines on triphasic waves: Implications for nonconvulsive status epilepticus. *J Clin Neurophysiol*, *18*, 345-352. https://doi.org/10.1097/00004691-200107000-00006

Gunathilake, R., Boyce, L. E., & Knight, A. T. (2013). Pregabalin-associated rhabdomyolysis. *Med J Aust.*, *199*(9), 624-625. http://doi.org/10.5694/mja13.10769. PMID: 24182230.

Huppertz, H. J., Feuerstein, T. J., & Schulze-Bonhage, A. (2001). Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. *Epilepsia*, *42*, 790-792. https://doi.org/10.1046/j.1528-1157.2001.44000.x

Hustey, F. M. (1999). Acute quetiapine poisoning. *J Emerg Med.*, *17*(6), 995-997. http://doi.org/10.1016/s0736-4679(99)00128-6. Erratum in: J Emerg Med 2000 Apr;18(3):403. PMID: 10595886.

Janet Webb, BSc(Pharm), MSc. (2007). Venlafaxine: Troubling toxicity in overdose. *BCMJ*, *49*(1), January, February, 10 - BCCDC.

Kaplan, P. W., & Sutter, R. (2015). Affair with triphasic waves-their striking presence, mysterious significance, and cryptic origins: What are they? *J Clin Neurophysiol*, *32*, 401-405. https://doi.org/10.1097/WNP.0000000000000151

Khan, T. M., Wu, D. B., Goh, B. H., Lee, L. H., Alhafez, A. A., & Syed Sulaiman, S. A. (2016). An Observational Longitudinal Study Investigating the Effectiveness of 75 mg Pregabalin Post-Hemodialysis among Uremic Pruritus Patients. *Sci Rep*, *6*, 36555. http://doi.org/10.1038/srep36555. PMID: 27824127; PMCID: PMC5099892.

Lee, D. W., Lee, H. J., Kim, H. J., Chang, S. H., & Park, D. J. (2011). Two cases of pregabalin neurotoxicity in chronic kidney disease patients. *NDT Plus*, *4*(2), 138. http://doi.org/10.1093/ndtplus/sfq219. PMID: 25984138; PMCID: PMC4421577.

May, T. W., Rambeck, B., Neb, R., & Jürgens, U. (2007). Serum concentrations of pregabalin in patients with epilepsy: The influence of dose, age, and comedication. *Ther Drug Monit*, *29*(6), 789-794. http://doi.org/10.1097/FTD.0b013e31815d0cd5. PMID: 18043477.

National Center for Biotechnology Information. (2021). *PubChem Compound Summary for CID 5486971, Pregabalin*. Retrieved May 30, 2021, from https://pubchem.ncbi.nlm.nih.gov/compound/Pregabalin

Olaizola I., Ellger T., Young P., Bosebeck F., Evers S., & Kellinghaus C. (2006). Pregabalin-associated acute psychosis and epileptiform EEG-changes. *Seizure*, *15*, 208-210. https://doi.org/10.1016/j.seizure.2006.02.004

Randinitis, E. J., Posvar, E. L., Alvey, C. W., Sedman, A. J., Cook, J. A., & Bockbrader, H. N. (2003). Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol.*, *43*(3), 277-283. http://doi.org/10.1177/0091270003251119. PMID: 12638396.

Toth, C. (2014). Pregabalin: Latest safety evidence and clinical implications for the management of neuropathic pain. *Ther Adv Drug Saf.*, *5*(1), 38-56. http://doi.org/10.1177/2042098613505614. PMID: 25083261; PMCID: PMC4110876.

Yeh, C. Y., Chen, C. K., Hsu, H. J., Wu, I. W., Sun, C. Y., Chou, C. C., … Wang, L. J. (2014). Prescription of psychotropic drugs in patients with chronic renal failure on hemodialysis. *Ren Fail.*, *36*(10), 1545-1549. http://doi.org/10.3109/0886022X.2014.949762. Epub 2014 Aug 26. PMID: 25154717.

Yoo, L., Matalon, D., Hoffman, R. S., & Goldfarb, D. S. (2009). Treatment of pregabalin toxicity by hemodialysis in a patient with kidney failure. *Am J Kidney Dis.*, *54*(6), 1127-1130. http://doi.org/10.1053/j.ajkd.2009.04.014. Epub 2009 Jun 3. PMID: 19493601.

Abbreviations:

AKI: Acute Kidney Injury.

CKD: Chronic Kidney Disease.

CL_{cr}: Creatinine Clearance.

Figure legend

Figure 1 showing intermittent bi-anterior predominant, bi-synchronous triphasic waves running at runs at 1.5-2.2 Hz.

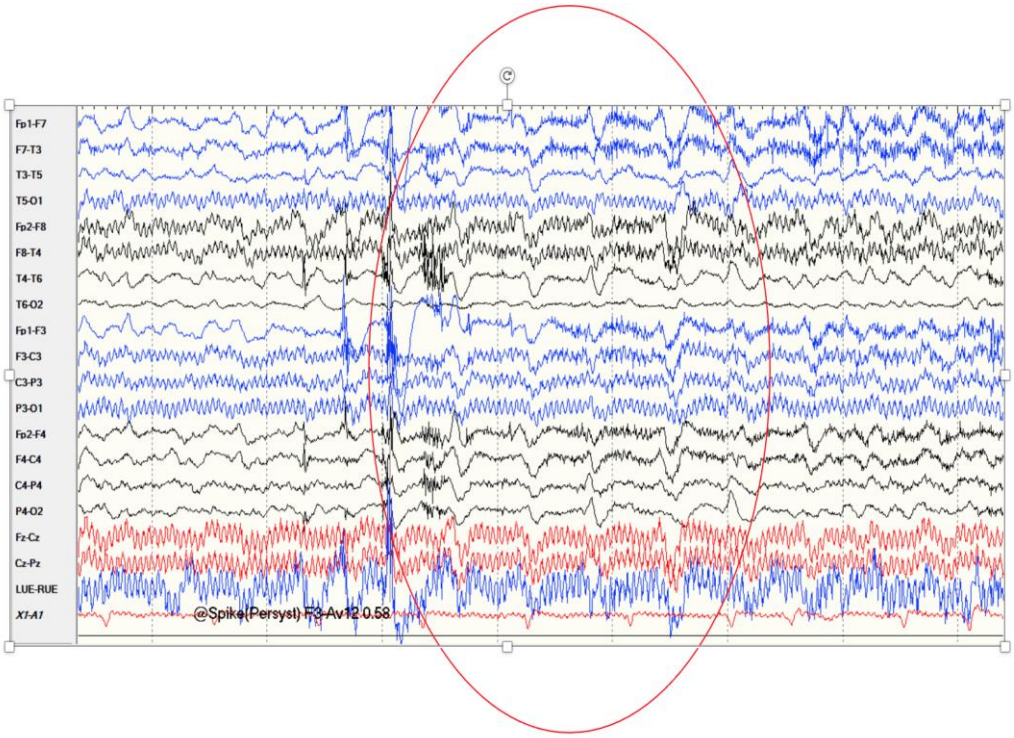

Figure 2 showing resolution of triphasic waves post HD.