

Levetiracetam (Keppra): Evidence-Based Polypharmacy in Two Patients With Epilepsy

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Abstract

Introduction: Epilepsy is a prolonged disorder characterized by repeated violent epileptic seizures. Its managements depend on proper classification of the seizure category and the epileptic pattern. Levetiracetam (Keppra®) has been approved as monotherapy or for adjunctive management of partial onset seizures, juvenile myoclonic epilepsy, and idiopathic generalized epilepsy. Case reporting of levetiracetam polypharmacy shows adverse effects linked to evidence-based clinical and laboratory data in two patients with epilepsy. Case reporting of levetiracetam polypharmacy, based on evidence-based clinical and laboratory data was of interest that investigated.

Case Presentation: Two cases were studied, one patient was a 32-year-old male and the other was a 14-year-old female. The key words relevant to search topics were surveyed using PubMed (United States national library of medicine). Articles related to the levetiracetam prescription in epileptic patients were selected and considered separately. Pharmacotherapy based on levetiracetam, primidone, phenytoin, and topiramate in a 32-year-old epileptic male showed a decrease in white blood cell count (3400 cells/mL), red blood cell count (4.4 mil/mm³) hemoglobin (11.8 g/dL) and hematocrit (36.7%). The drug regimen for the 14-year-old epileptic female was a levetiracetam polypharmacy in combination with primidone and sodium-valproate simultaneously. In this patient, there was a decrease in hemoglobin (10.4 g/dL) and hematocrit (34%). An increase in lymphocyte (84%) was also observed.

Conclusions: Administration of AEDs in general and levetiracetam in particular should be based on attention to pharmacokinetic behavior in terms of monotherapy or polypharmacy.

Keywords: Levetiracetam, Side-effects, Hematology, Biochemistry, Epilepsy

1. Introduction

Epilepsy is a common long-lasting complaint that necessitates long-term pharmacotherapy with anti-epileptic drugs (AEDs). Around 50% of epileptic patients fail the preliminary AED and about 35% are intractable to pharmacotherapy, emphasizing the continuous need for more effective and better-tolerated drugs. To craft an appropriate pharmacotherapy policy in epileptic patients, an evidence-based pharmacotherapy study could be valuable. The magnitudes of decision for prescription of AEDs are challenging due to the narrow therapeutic window related to the old generation of this category, and also require plenty of awareness related to the seizure as a symptom and epilepsy as a condition. AEDs must include a prescription based on polypharmacy or monotherapy, and the ability to monitor effectiveness or adverse effects (1-7). Monotherapy remains the "gold standard," because the concurrent prescription of AEDs in patients with epilepsy could cause side effects. Related to the mechanism of action for the first generation of AEDs, such as carbamazepine, phenytoin, sodium

valproate, Lamotrigine, clonazepam, and clobazam, two main models could be described by increasing γ -amino butyric acid (GABA) or decreasing excitation due to glutamate. These drugs also act through ionic channels (2-11).

Since 2000, levetiracetam has been marketed as an AED (1). While the exact mechanism of its action in epilepsy is unknown, it seems that modulation of synaptic neurotransmitter release, through binding to the synaptic vesicle protein (SV2A) in the brain, could exhibit a novel mechanism of action. Therefore, levetiracetam acts as a neuro-modulator by reducing the release of neurotransmitters. The routes of drug administration could be oral or intravenous. The drug has a urinary route of excretion. Less than 10% of the drug binds to plasma protein. With a mean concentration of 12.9 and 9.5 $\mu\text{g/mL}$, levetiracetam has a half-life of 6 to 8 hours. The mean plasma concentrations in responders and non - responders were 12.9 and 9.5 $\mu\text{g/mL}$, respectively (1-16). Due to enzymatic hydrolysis of the acetamide group, the pattern of metabolism is completely different than first-generation AEDs that are cytochrome P450 inducers or inhibitors (3). This paper reports on cases

of two epileptic patients with hematological and biochemical changes under treatment of levetiracetam, based on AED polypharmacy.

2. Case Presentation

The United States National Library of Medicine was searched, using three relevant keywords: 1) "levetiracetam in epilepsy," 2) "keppra in epilepsy," and 3) "levetiracetam hematological and biochemical side-effects." A total of 1724 articles (from 1993 - 8 August 2015), 1025 (from 1992 - June 2015), and 30 (from November 2014 - September 2014) were found. Consequently, manuscripts applicable to the pharmacotherapy management of levetiracetam in epilepsy were identified and studied individually.

According to previous publications on pharmacotherapy, using levetiracetam for partial epilepsy, myoclonic seizure in patients with juvenile myoclonic epilepsy, or generalized tonic-clonic seizures in the setting of idiopathic generalized epilepsy might be considered as preliminary or early add-on therapy (1). There are only a few published papers reporting the therapeutic drug monitoring methods of levetiracetam (17). In this study, a 32-year-old male patient had been admitted to the Isfahan/Kashani hospital epilepsy ward in 2011. His first seizure attack was around the age of 6. Since then he had been taking antiepileptic drugs. He stayed for two days in the hospital.

A review of his medication history confirmed that his prescribed pharmacotherapy was based on levetiracetam, 250 mg/B.I.D. in combination with: 1) primidone; 50 mg/T.D.S, 2) phenytoin, 100 mg/T.D.S., and 3) topiramate; 50 mg/T.D.S. Hematological results confirmed a decrease in white blood cell count (WBC; 3400 cells/mcL, versus a normal range of 3500 - 10500 cells/mcL), red blood cell count (RBC; 4.4 mil/mm³ versus a normal value of M: 4.5 - 5.9 mil/mm³), hemoglobin (Hb; 11.8 g/dL versus a normal value of 14 - 17.5 g/dL) and hematocrit (Ht; 36.7% versus a normal value of 41.5% - 50.5%). Another admitted case to the Isfahan/Kashani hospital epilepsy ward (also in 2011) was a 14-year-old female who had her first seizure attack around the age of 7-year-old. Levetiracetam, 250 mg/B.I.D., had been taken with primidone, 50 mg/T.D.S., and sodium-valproate, 200 mg/T.D.S. Hematological results confirmed a decrease in hemoglobin (Hb; 10.4 g/dL versus a normal value of 12.3 - 15.3 g/dL) and hematocrit (Ht; 34% versus a normal value of 35.9% - 44.9%) and an increase in lymphocyte (Lymph; 84 versus a normal value of 20% - 40%). Neither patient was on any additional medications other than the AEDs. Prior to starting the AEDs no effort was made to achieve the level of biochemistry and hematology parameters, therefore the abnormal results reflect the dysfunction prevailing around the time of study.

3. Discussion

While previous pharmacokinetic studies show that levetiracetam is usually well tolerated (18), side effects can include sleepiness, faintness, shaking step, exhaustion, management difficulties, headache, discomfort, amnesia, nervousness, bad temper or distress, giddiness, uneasiness, damage of taste, nausea, diarrhea and constipation, gullet aching, and deviations in skin pigmentation. Hopelessness, deliriums, desperate opinions, worse or dissimilar seizures, high fever, marks of contagion, dual image, puffiness of the face, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other serious side effects related to levetiracetam therapy (19).

A previous study confirmed that cytochrome enzyme inducer AEDs like phenytoin and oxcarbazepine are strongly associated with increased levels of total cholesterol, low-density lipoprotein cholesterol, high - density lipoprotein cholesterol, and triglyceride, whereas valproate and levetiracetam showed no significant changes (20). It seems that encephalopathy subsequent to the prescription of levetiracetam should be mentioned as an infrequent incidence. But a recent case report described a patient receiving levetiracetam who was treated with valproic acid for partial seizures and secondary generalization. There was a developing hyperammonemic encephalopathy that improved after withdrawal of the drug (21). Another study related to the Iranian epileptic population confirmed that the efficiency of AEDs pharmacotherapy should be qualified by the close monitoring of AEDs in relation to clinical conditions and laboratory records. Any major alteration in patients' laboratory archives may necessitate close confirmation of the rapid detection AEDs side-effects (5). In conclusion, this report highlights that levetiracetam with other AEDs might cause significant decreases in hemoglobin, hematocrit, and white blood cell count, as well as an increase in lymphocytes (22-27).

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References

1. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. *Neuropsychiatr Dis Treat*. 2008;**4**(3):507-23. [PubMed: 18830435].
2. Tolou Ghamari Z, Mehavari Habibabadi J, Palizban A. Evidence-Based Pharmacotherapy of Epilepsy. *Arc Neur J*. 2014;**2**(2) doi: 10.5812/arch-neurosci.18468.
3. Tolou-Ghamari Z. Antiepileptic drugs (AEDs) polypharmacy could lead to buried pharmacokinetic interactions due to CYP450. *Drug Metab Lett*. 2012;**6**(3):207-12. [PubMed: 23140557].
4. Tolou-Ghamari Z, Zare M, Habibabadi JM, Najafi MR. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. *J Res Med Sci*. 2013;**18**(Suppl 1):S81-5. [PubMed: 23961295].
5. Tolou-Ghamari Z, Zare M, Habibabadi JM, Najafi MR. Antiepileptic drugs: a consideration of clinical and biochemical outcome in patients with epilepsy. *Int J Prev Med*. 2013;**4**(Suppl 2):S330-7. [PubMed: 23776747].
6. Tolou-Ghamari Z, Najafi MR, Habibabadi JM, Zare M. Preliminary Analysis of Carbamazepine (CBZ) Co in Patients Visited Isfahan Epileptic Clinics. *Int J Prev Med*. 2013;**4**(Suppl 2):S343-6. [PubMed: 23776749].
7. Kashipazha D, Mohammadiany Nejad SA, Sadr F, Tarahomi S, Sadr S. Comparison of Levetiracetam With Sodium Valproate in Controlling Seizure in Patients Suffering From Juvenile Myoclonic Epilepsy. *Jentashapir Health Res J*. ;5(4):ee21875. doi: 10.5812/jjhr.21875.
8. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuopharmacol*. 2010;**8**(3):254-67. doi: 10.2174/157015910792246254. [PubMed: 21358975].
9. Walia KS, Khan EA, Ko DH, Raza SS, Khan YN. Side effects of antiepileptics—a review. *Pain Pract*. 2004;**4**(3):194-203. doi: 10.1111/j.1533-2500.2004.04304.x. [PubMed: 17173601].
10. Guberman A. Monotherapy or polytherapy for epilepsy?. *Can J Neurol Sci*. 1998;**25**(4):S3-8. [PubMed: 9827238].
11. French JA, Faught E. Rational polytherapy. *Epilepsia*. 2009;**50** Suppl 8:63-8. doi: 10.1111/j.1528-1167.2009.02238.x. [PubMed: 19702736].
12. Lynch BA, Lambeng N, Nocka K, Kensch-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A*. 2004;**101**(26):9861-6. doi: 10.1073/pnas.0308208101. [PubMed: 15210974].
13. Vogl C, Mochida S, Wolff C, Whalley BJ, Stephens GJ. The synaptic vesicle glycoprotein 2A ligand levetiracetam inhibits presynaptic Ca²⁺ channels through an intracellular pathway. *Mol Pharmacol*. 2012;**82**(2):199-208. doi: 10.1124/mol.111.076687. [PubMed: 22554805].
14. Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res*. 2006;**69**(3):273-94. doi: 10.1016/j.eplepsyres.2006.02.004. [PubMed: 16621450].
15. Chaluvadi S, Chiang S, Tran L, Goldsmith CE, Friedman DE. Clinical experience with generic levetiracetam in people with epilepsy. *Epilepsia*. 2011;**52**(4):810-5. doi: 10.1111/j.1528-1167.2011.03025.x. [PubMed: 21426334].
16. Nowack A, Malarkey EB, Yao J, Bleckert A, Hill J, Bajjalieh SM. Levetiracetam reverses synaptic deficits produced by overexpression of SV2A. *PLoS One*. 2011;**6**(12):ee29560. doi: 10.1371/journal.pone.0029560. [PubMed: 22220214].
17. Ratnaraj N, Doheny HC, Patsalos PN. A micromethod for the determination of the new antiepileptic drug levetiracetam (ucb LO59) in serum or plasma by high performance liquid chromatography. *Ther Drug Monit*. 1996;**18**(2):154-7. [PubMed: 8721278].
18. Gambardella A, Labate A, Colosimo E, Ambrosio R, Quattrone A. Monotherapy for partial epilepsy: focus on levetiracetam. *Neuropsychiatr Dis Treat*. 2008;**4**(1):33-8. [PubMed: 18728811].
19. Clinical Epilepsy, Pediatrics. 46. USA: Epilepsia; 2005. p. 142-67.
20. Manimekalai K, Visakan B, Salwe KJ, Murugesan S. Evaluation of Effect of Antiepileptic Drugs on Serum Lipid Profile among Young Adults with Epilepsy in a Tertiary Care Hospital in Pondicherry. *J Clin Diagn Res*. 2014;**8**(8):HC05-9. doi: 10.7860/JCDR/2014/8744.4682. [PubMed: 25302212].
21. Roh SY, Jang HS, Jeong EH, Kim BS, Sunwoo MK. Valproic Acid-induced Hyperammonemic Encephalopathy Promoted by Levetiracetam. *J Epilepsy Res*. 2014;**4**(2):82-4. doi: 10.14581/jer.14017. [PubMed: 25625094].
22. Suchopar J, Prokes M. [Polypharmacy and drug interactions]. *Vnitř Lek*. 2011;**57**(9):755-9. [PubMed: 21957770].
23. Givon L, Porter S, Padmanabhan B, Goren J, Cohen PA. Levetiracetam, seizures, and suicidality. *Harv Rev Psychiatry*. 2011;**19**(1):47-55. doi: 10.3109/10673229.2011.549777. [PubMed: 21250896].
24. Lo BW, Kyu HH, Jichici D, Upton AM, Akl EA, Meade MO. Meta-analysis of randomized trials on first line and adjunctive levetiracetam. *Can J Neurol Sci*. 2011;**38**(3):475-86. [PubMed: 21515509].
25. Panda S, Joshi SS. Paradoxical seizures and status epilepticus with newer antiepileptic drugs. *Neurol India*. 2011;**59**(3):479-80. doi: 10.4103/0028-3886.82757. [PubMed: 21743195].
26. Kramer MA, Cash SS. Epilepsy as a disorder of cortical network organization. *Neuroscientist*. 2012;**18**(4):360-72. doi: 10.1177/1073858411422754. [PubMed: 22235060].
27. Benedetti MS. Enzyme induction and inhibition by new antiepileptic drugs: a review of human studies. *Fundam Clin Pharmacol*. 2000;**14**(4):301-19. [PubMed: 11030437].