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Case Report

Apparent dose-dependent levetiracetam-induced *de novo* major depression with suicidal behavior☆,☆☆

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ABSTRACT

Levetiracetam (LEV) is a novel antiepileptic drug (AED) approved for the adjunctive treatment of generalized and partial seizures. LEV has no clinically significant drug interactions and has limited adverse effects. The psychiatric adverse effects of LEV include *de novo* psychosis, affective disorder, and aggression. LEV-induced suicidal behavior has been reported infrequently with a past history of affective disorders. The authors report an apparent dose/concentration-dependent LEV-induced *de novo* major depression with near fatal suicide attempt in a patient without prior history of affective disorder. Psychiatric evaluation with emphasis on historic/current affective disorders, impulsive–aggressive behaviors, and assessment of risk factors for suicidal behaviors is indicated in treating patients with epilepsy with LEV. Clinicians should consider therapeutic drug monitoring to optimize therapeutic LEV treatment.

1. Introduction

Levetiracetam [(S)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide] (LEV) is a second generation anticonvulsant approved by the European Medicines Agency (EMA) and/or the U.S. Food and Drug Administration (FDA) for the following: 1) monotherapy treatment of partial seizures, with or without secondary generalization (EMA); 2) adjunctive treatment of partial seizures, with or without secondary generalization (FDA/EMA); 3) adjunctive treatment of myoclonic seizures associated with juvenile myoclonic epilepsy (FDA/EMA); and 4) adjunctive treatment of primary generalized tonic–clonic seizures associated with idiopathic generalized epilepsy (FDA/EMA) [1,2]. LEV uniquely binds to synaptic vesicle protein 2A (SV2A) with resultant broad spectrum anticonvulsant activity [3,4].

LEV has no clinically significant pharmacokinetic drug interactions [5]. A review of clinical trials demonstrated that LEV was well tolerated with limited psychiatric adverse effects [6]. LEV-induced psychiatric adverse effects are not dose-dependent [7,8]. Improved depression and anxiety have been reported in patients with epilepsy treated with LEV [9]. A recent study suggested that LEV is cognitively benign [10]. The pharmacokinetic, tolerability, psychiatric, and neuropsychological profiles of LEV have led to it being studied for the off-label treatment of neurologic disorders (Parkinson's disease, Huntington's disease, tardive dyskinesia, dystonia, multiple sclerosis), psychiatric disorders (bipolar disorder, panic disorder, posttraumatic stress disorder, social anxiety, impulsive aggression, alcohol dependence, alcohol withdrawal, behavioral and psychological symptoms of dementia), and pain disorders (migraine and neuropathic) with mixed results [11,12].

LEV-emergent suicidal behaviors (ideation and attempt) have been infrequently reported [6,13]. In two studies, all suicidal behaviors were associated with a previous history of psychiatric disorders [13,14]. This case report presents what the authors believe to be the first instance of dose/concentration-dependent LEV-induced *de novo* major depression with a near fatal suicide attempt following dose

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adjustment in a patient without prior psychiatric history and with long-term stability on LEV.

2. Method

Case analysis with PUBMED literature review was employed.

3. Case

A 66-year-old male with diabetes, diabetic neuropathy, hypertension, and past alcohol dependence with withdrawal features had two seizures following a traumatic brain injury with an intracranial hemorrhage in 2007. He remained seizure-free on LEV 500 mg total daily dose until being admitted to an academic medical center (AMC) on 4/22/2012 with elevated CPK (1731 U/l), hyperglycemia (428 mg/dl), hypocalcemia (6.9 mg/dl), anemia (hemoglobin: 11.6 g/dl, hematocrit: 34.2%), and an undetectable blood alcohol level. His admission LEV blood level was 10.9 μg/ml. Routine EEG was normal, and head MRI/CT revealed central and cortical atrophy, moderate small vessel ischemic disease, and old bilateral basal ganglia and right thalamic lacunar infarcts. He was medically stabilized and discharged on LEV 500 mg bid only to be readmitted on 8/3/2012 for recurrent seizures following LEV noncompliance for one week.

Specifically, the patient ran out of his AED pending a mail-order prescription. His wife (a health-care professional) witnessed a tonic-clonic seizure of >3 min in duration with postictal altered mental status. In the ER, the medical staff witnessed a further tonic-clonic seizure of 90 s in duration for which the patient received lorazepam 4 mg IV and phenytoin 1000 mg IV. Admission laboratories and diagnostics included the following abnormal results — LEV blood level: <2.0 μg/ml, WBC: 13.6, hemoglobin: 11.7 g/dl, hematocrit: 35.5%, glucose: 426 mg/dl, sodium: 130 mEq/l, potassium: 2.5 mEq/l, chloride: 97 mEq/l, total CO_2: 20.3 mEq/l, magnesium: 1.3 mg/dl, HgbA1c: 11.9%, unchanged CT scan findings, and EKG with fist degree AV block and prolonged QTc of 505 ms. Blood alcohol level and urine drug screen were negative. LEV was increased to 1000 mg bid with a subsequent LEV blood level of 32.9 μg/ml. A routine EEG with photic stimulation performed 3 days after the presenting seizures revealed left temporal focal slowing (theta and delta activity) without epileptiform discharges. The patient remained without further seizures on the increased LEV, his postictal state cleared, and after medical stabilization, he was discharged to the home setting on LEV 1000 mg bid.

Prior to LEV being increased to 1000 mg bid, this patient had no history of psychopathology excluding alcohol dependence with withdrawal seizures. After LEV was increased to 1000 mg bid, the wife described the patient discussing suicide and stating "life is not worth living." Within one month, he developed a complete vegetative–affective cluster consistent with a *de novo* major depressive episode according to DSM-IV criteria [15], attempted a nearly fatal insulin overdose (80 units) with field glucose of only 1mg/dl, and was seen in psychiatric consultation after admission to the same AMC. Admission laboratories included the following abnormal results — hemoglobin: 12.0 g/dl, hematocrit: 35.4%, potassium: 2.8 mEq/l, calcium: 8.3 mg/dl, magnesium: 1.3 mg/dl, and HgbA1c: 10.6%. His alcohol blood level was 24.6 mg/dl with urine drug screen, salicylate level, and acetaminophen level all negative. His admission LEV blood level was 38.9 μg/ml. A routine EEG with photic stimulation performed on the day of admission revealed mild, infrequent, independent, bilateral frontotemporal polymorphic delta activity without epileptiform discharges. Upon medical stabilization, discontinuation of LEV, and initiation of oxcarbazepine 300 mg bid, the patient was transferred to an inpatient psychiatric unit and lost to follow-up.

4. Discussion

This unique case raises a series of important points specifically related to this patient that should be considered in the general treatment of patients with LEV and other AEDs.

First, though LEV-induced psychiatric adverse effects are not considered to be dose-related [7,8], this case suggests that dose-dependence may be a significant factor in developing affective disorders with suicidal behaviors. The patient did not have any psychiatric features during a five-year period on LEV 500 mg total daily dose with a mildly subtherapeutic blood level. Even with LEV increased to 1000 mg total daily dose, there were no psychiatric features. With LEV increased to 2000 mg total daily dose and a high therapeutic blood level, the patient developed a *de novo* major depression and attempted a nearly fatal insulin overdose within one month of dose titration.

Second, AED therapeutic drug monitoring with reference range and individual therapeutic range is important in the optimal clinical treatment of patients with epilepsy [16]. As there is a minimal and optimal threshold concentration for AED efficacy, this case suggests that the development of adverse events for specific AEDs may also require a threshold concentration which can be within the reference range (LEV: 12–46 μg/ml).

Third, literature addressing suicidal behavior associated with AEDs in patients with epilepsy has focused on the significant increased risk of this behavior when there is a prior history of affective disorder [13,14,17]. This case clearly points out that an apparent LEV-induced major depression with suicidal behavior may occur in the absence of prior affective disorder. This is consistent with a recent study that did not find psychiatric history to be a significant predictor of either positive or negative LEV-induced psychotropic effects [8].

Fourth, the 2008 FDA advisory that AEDs are associated with significantly increased suicidal behaviors resulted in a series of studies attempting to address AED-specific suicidal behavior risk [18–20]. Conflicting findings from these studies are considered to be secondary to flaws in methodology, specifically controlling for prior suicidal behavior [20]. This suggests the need for appropriate psychiatric assessments in all patients treated with AEDs such that meaningful data can be obtained. This also supports the need for detailed case reports when suicidal behavior occurs following initiation of AED treatment [19]. In this case, there was no pre-LEV history of psychiatric illness, impulsive–aggressive behaviors, or suicidal behaviors excluding past alcohol dependence.

Fifth, though the clinical trials revealed limited behavioral adverse effects [6], more recent studies emphasized aggressive behavior as an important negative psychotropic effect that may require LEV discontinuation [8,21,22]. This patient did not have any aggressive behaviors on long-term LEV 500 mg total daily dose or when increased to 1000 mg total daily dose, but rather the suicide attempt occurred at 2000 mg total daily dose.

Sixth, a clinical model of suicidal behavior suggests that suicide is an impulsive–aggressive act and that a critical risk factor for suicide is increased impulsive–aggressive trait with familial/genetic transmission of impulsive–aggressive trait correlating to an increased suicide risk independent of psychopathology [23]. Literature supports genetic neurotransmitter variants as etiological factors for impulsivity, suicidal behavior, alcoholism, and aggression [23,24]. A recent study reported an association between dopamine genetic variants and LEV aggression [25]. Though no genetic data are available for this patient, suicidal behaviors with AEDs may be associated with a genetic predisposition independent of known psychiatric illness.

Seventh, recent literature supports a bidirectional relationship among epilepsy, psychiatric disorders, and suicidality [26,27]. Though this case describes a clear temporal relationship between LEV dose titration and *de novo* major depressive episode with suicide attempt, the potential for epilepsy being the causative or predisposing factor must be considered. Further potential risk factors for the development of major depression and/or suicidal behaviors present in this case included basal ganglia and thalamic lacunar infarcts, traumatic brain injury with intracranial hemorrhage, and past alcohol dependence [23,28,29].

Eighth, in the context of multiple potential risk factors for the development of *de novo* major depression with suicide attempt (epilepsy, treatment with AED, LEV titration, past alcohol dependence, traumatic

brain injury with intracranial hemorrhage, basal ganglia and thalamic lacunar infarcts, and potential genetic predisposition), the probability of LEV titration inducing the *de novo* major depression with associated near fatal suicide attempt was determined by the Naranjo's Adverse Reaction Probability Scale as probable (scored as 5) [30].

There are specific limitations to this paper. As a case report (N = 1), the findings cannot be generalized. The patient did not have any psychiatric assessment done prior to and following the traumatic brain injury and initiation of LEV to assess general psychopathology, affective disorders, and, specifically, impulsive aggression. Neuroimaging studies and initial EEGs following the 2007 seizures were not available for comparison. LEV blood level was not obtained when the patient was on 1000 mg total daily dose. Standardized psychometric scales for depression and impulsive aggression were not obtained. For ethical reasons, the patient could not be rechallenged with LEV 2000 mg total daily dose. Finally, the patient was lost to clinical follow-up precluding determination of recurrent impulsive-aggressive behaviors or affective features after discontinuation of LEV.

5. Conclusions

LEV-induced suicidal behavior is an infrequent adverse effect noted in patients with a prior history of affective disorder. The authors report an apparent dose/concentration-dependent LEV-induced *de novo* major depressive episode with near fatal suicidal attempt in the absence of prior affective history following chronic stable treatment with LEV. Clinicians should monitor affective features when treating patients with epilepsy with LEV and other AEDs, be cognizant of other potential additive risk factors for suicidal behaviors, and consider therapeutic drug monitoring to optimize therapeutic treatment. Further studies are required to address dose/concentration-dependent LEV-induced psychiatric adverse effects.

Conflict of interest statement

There are no conflicts of interest to declare.

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References

[1] Kaufman KR. Monotherapy treatment of bipolar disorders with levetiracetam. Epilepsy Behav 2004;5(6):1017–20.
[2] Lyseng-Williamson KA. Spotlight on levetiracetam in epilepsy. CNS Drugs 2011;25(10):901–5.
[3] Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. PNAS 2004;101(26):9861–6.
[4] Kamminski RM, Matagne A, Leclercq K, Gillard M, Michel P, Kenda B, et al. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology 2008;54(4):715–20.
[5] Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet 2004;43(11):707–24.
[6] Cramer JA, De Rue K, Devinsky O, Edrich P, Trimble MR. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or anxiety disorder during clinical trials. Epilepsy Behav 2003;4(2):124–32.
[7] Mula M, Trimble MR, Yuen A, Liu RS, Sander JW. Psychiatric adverse events during levetiracetam therapy. Neurology 2003;61(5):704–6.
[8] Helmstaedter C, Fritz NE, Kockelmann E, Kosanetzky N, Elger CE. Positive and negative psychotropic effects of levetiracetam. Epilepsy Behav 2008;13(3):525–41.
[9] Mazza M, Martini A, Scoppetta M, Mazza S. Effect of levetiracetam on depression and anxiety in adult epileptic patients. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(2):539–43.
[10] Cumbo E, Ligori LD. Levetiracetam, lamotrigine, and phenobarbital in patients with epilepsy and Alzheimer's disease. Epilepsy Behav 2010;17(4):461–6.
[11] Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. Epilepsy Behav 2011;21(1):1–11.
[12] Farooq MU, Bhatt A, Majid A, Gupta R, Khasnis A, Kassab MY. Levetiracetam for managing neurologic and psychiatric disorders. Am J Health Syst Pharm 2009;66(6):541–61.
[13] Mula M, Sander JW. Suicidal ideation in epilepsy and levetiracetam therapy. Epilepsy Behav 2007;11(1):130–2.
[14] Lee JJ, Song HS, Hwang YH, Lee HW, Suh CK, Park SP. Psychiatric symptoms and quality of life in patients with drug-refractory epilepsy receiving adjunctive levetiracetam therapy. J Clin Neurol 2011;7(3):128–36.
[15] Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994 .
[16] 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 by the subcommittee on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49(7):1239–76.
[17] VanCott AC, Cramer JA, Copeland LA, Zeber JE, Steinman MA, Dersh JJ, et al. Suicide-related behaviors in older patients with new anti-epileptic drug use: data from the VA hospital system. BMC Med 2010;8:4.
[18] U.S. Food and Drug Administration. Statistical review and evaluation: antiepileptic drugs and suicidality. [Available at:] www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf . [Accessed on May 17, 2013].
[19] Kaufman KR, Struck PJ. Activation of suicidal ideation with adjunctive rufinamide in bipolar disorder. Epilepsy Behav 2011;20(2):386–9.
[20] Mula M, Kanner AM, Schmitz B, Schachter S. Antiepileptic drugs and suicidality: an expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychiatry. Epilepsia 2013;54(1):199–203.
[21] Dinkelacker V, Dietl T, Widman G, Lengler U, Elger CE. Aggressive behavior of epilepsy patients in the course of levetiracetam add-on therapy: report of 33 mild to severe cases. Epilepsy Behav 2003;4(5):537–47.
[22] Stephen LJ, Kelly K, Parker P, Brodie MJ. Levetiracetam monotherapy — outcome from an epilepsy clinic. Seizure 2011;20(7):554–7.
[23] Mann JJ, Waternaux C, Haas GL, Malone KM. Towards a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 1999;156(2):181–9.
[24] Stoltenberg SF, Christ CC, Highland KB. Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. Prog Neuropsychopharmacol Biol Psychiatry 2012;39(1):182–91.
[25] Helmstaedter C, Mihov Y, Toliat MR, Thiele H, Nuernberg P, Schoch S, et al. Genetic variation in dopaminergic activity is associated with the risk for psychiatric side effects of levetiracetam. Epilepsia 2013;54(1):36–44.
[26] Adelow C, Andersson T, Ahlbom A, Tomson T. Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy. Neurology 2012;78(6):396–401.
[27] Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. Ann Neurol 2012;72(2):184–91.
[28] Wasserman L, Shaw T, Vu M, Ko C, Bollegala D, Bhalerao S. An overview of traumatic brain injury and suicide. Brain Inj 2008;22(11):811–9.
[29] Pompili M, Venturini P, Campi S, Seretti ME, Montebovi F, Lamis DA, et al. Do stroke patients have an increased risk of developing suicidal ideation or dying by suicide? An overview of the current literature. CNS Neurosci Ther 2012;18(9):711–21.
[30] 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.