Acute Levetiracetam Overdose Presented with Mild Adverse Events

Sirichai Chayasirisobhon[1], Wuttichai V Chayasirisobhon[1], Cassidy C Tsay[2]

Abstract-

Purpose: Overdose of levetiracetam may produce neurotoxicity.

Case report: We reported a patient with epilepsy who took an overdose of 63 grams of levetiracetam with mild adverse events. The patient presented mild blurred vision and mild ataxia that rapidly subsided within one day with supportive care. The laboratory tests showed mild leucopenia and mild thrombocytopenia that gradually returned to normal within 2 months.

Conclusion: The pharmacokinetics, tolerability and adaptation of levetiracetam might play a role in the mild adverse events of levetiracetam overdose in our patient.

Key Words: overdose, levetiracetam

Acta Neurol Taiwan 2010;19:292-295

INTRODUCTION

Levetiracetam is currently used as adjunctive therapy in adult patients with partial-onset seizures. Its efficacy and tolerability were demonstrated in three pivotal clinical trials[1,2,3]. The recommended starting dose of levetiracetam for adult patients ≥16 years of age is 1000 mg/day (500 mg twice a day). It can be increased by an additional 1000 mg/day at 2-week interval to a maximum dose of 3000 mg/day in 2 divided doses [4,5]. The most common adverse effects reported with levetiracetam at the recommended dose have been somnolence, irritability, asthenia and dizziness. The higher adverse effects are more prevalent at higher dose [6]. However, the highest known dose of oral levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Cases of somnolence, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdose in postmarketing use [7]. We reported a patient with epilepsy who took levetiracitam overdose with mild adverse events.

CASE REPORT

This was a 41 years old Caucasian male who had complex partial seizures from the age of 29 years. His

From the Departments of [1]Neurology; [2]Medicine, Kaiser Permanente Medical Center, Anaheim, California, U.S.A.
Received March 26, 2010. Revised March 31, 2010.
Accepted August 2, 2010.
Correspondence to: Sirichai Chayasirisobhon, MD. FAAN, Kaiser Permanente Medical Center, Department of Neurology, 3460 E. La Palma Avenue, Anaheim, California, U.S.A. 92806, U.S.A.
E-mail: siri.chayasirisobhon@kp.org

seizures were resistant to antiepileptic medications. Then two years prior to drug overdose, the patient underwent right anterior temporal lobectomy. After the surgery, he was treated with carbamazepine extended-release 700 mg twice a day and lamotrigine 300 mg twice a day. The patient continued to have seizures averaging one every two months. A few months prior to drug overdose, levetiracetam was added to his drug regimen before tapering him off lamotrigine. Levetiracetam was gradually increased up to 1500 mg twice a day. The patient had been also diagnosed with bipolar disorder for 2 years. He was treated with citalopram 40 mg once a day, amitriptyline 25 mg once a day and clorazepate 15 mg at night. His moods were stable until a few days prior to admission. He became depressed due to family and financial problems. At 9:10 AM on the day of admission, he took 126 tablets of levetiracetam 500 mg tablet or total 63 grams within 20 minutes. At 10:00 AM, his vision became mildly blurry and his gait became unsteady, and he decided to call the crisis center. He was then taken to an emergency room of a nearby hospital at 10:34 AM, where he was evaluated. He was still alert and oriented. Laboratory tests showed no significant abnormalities in his electrolytes, blood urea nitrogen, creatinine, and calcium. Complete blood cell counts showed hemoglobin 14.7 gm/dl, leucocyte count 3,800 /μl and platelet count 115,000 /μl. Electrocardiogram showed a normal sinus rhythm. Urine toxicology showed that the patient was positive for benzodiazepine and tricyclic antidepressant that he had been on. A Certified Poison Control Center was contacted and recommended charcoal therapy. The patient was given 100 grams of activated charcoal at 10:50 AM. The patient was admitted to the hospital for observation for central nervous system and respiratory depression. At 1:30 PM, he stated that his blurred vision disappeared. He denied any headaches, dizziness, shortness of breath, chest pain, nausea, vomiting, or diarrhea. Then the patient was transferred to Kaiser Permanente Medical Center in Anaheim, California, for further observation. On admission at 5:00 PM, his vital signs were temperature 97.8 degree Fahrenheit, pulse 72/min, respiration 16/minute, and blood pressure 124/58 mm Hg. His weight was 141 Kg.

Physical examination was unremarkable. On neurological examination, he was awake and alert. His mental status, speech, cranial nerves, motor system, sensory system and reflexes were all normal. The coordination was normal, except tandem gait was mildly impaired. The gait was completely normal on the next day.

Laboratory tests including electrolytes, glucose, blood urea nitrogen, creatinine, liver function test, magnesium, calcium, and phosphorus were repeated and normal. Complete blood cell counts showed hemoglobin 13.7 gm/dl, leucocyte count 3,300 /μl and platelet count 125,000 /μl. Carbamazepine level was 6.7 μg/ml. Levetiracetam level obtained at 7:10 PM or 10 hours after the overdose, was 220 μg/ml; complete blood cell counts gradually returned to normal within 2 months.

DISCUSSION

In a review of safety profile of levetiracetam, the highest known dose received during clinical development was 6000 mg/day which was taken accidentally [7]. About 45 % of patients receiving 4000 mg/day reported somnolence [8]. A data on file from UCB Pharma, Inc reported a total of 5 patients with overdoses of levetiracetam as high as 50 grams [9]. A patient with overdose of 50 grams was comatose for 2 days; a patient with overdose of 27 grams became aggressive, angry, and irritable; a patient with overdose of 15 grams developed transient leucopenia and thrombocytopenia, and two patients with overdose of 15 grams had drowsiness. No patients died as a result of overdose. Two children accidentally took levetiracetam overdose. The first child was a 2-year old Caucasian girl who was accidentally administered 10 times the recommended dosage of levetiracetam by her mother for 10 days with no side effects. The second child was a 5-year old African-American girl who was administered four times the recommended dosage of levetiracetam by her mother with no side effects [10]. Another pediatric patient received a dosage of 71.4 mg/kg/day instead of the target dosage of 40 mg/kg/day during the last 4 weeks of an open-label study. The patient completed the study with no notable adverse effects from the

higher dosage [11]. An adult female took overdose of 60 levetiracetam tablets (500 mg) resulted in vomiting, obtundation, diminished deep tendon reflexes, and decreased muscle tone; these resolved with rapid elimination of the drug and recovered without sequelae over the next 24 hours [12].

Our patient took a single dose of 63 grams of levetiracetam, and when his serum level was checked 10 hours after the overdose and charcoal therapy, it was much higher than the trough serum level (3-37 μg/ml) and the peak serum level (10-60 μg/ml), In spite of very high dose of levetiracetam, he did not have somnolence, asthenia or respiratory depression except for mild adverse events including some blurred vision and mild ataxia. His complete blood cell counts showed only transient leucopenia and thrombocytopenia.

The above reports suggested that adverse events associated with levetiracetam overdose differed among the patients. The severity of dose-related adverse events depends on different mechanisms. They include genetic susceptibility to adverse effects of antiepileptic drugs, variation in the regulation and expression of the drug-metabolizing enzymes and genetic or environmental impairment of cytochrome P450 activity that may lead to drug toxicity [13]. Antiepileptic drugs that are susceptible to adverse effects due to the above mechanisms include carbamazepine, ethosuximide, felbamate, oxcarbazepine, phenobarbital, phenytoin, tiagabine, topiramate and zonisamide [14].

The pharmacokinetics of levetiracetam differ from the above mechanisms, it has the short plasma half-life (6 to 8 hours), with peak plasma concentrations occurring about one hour following oral administration. Levetiracetam is not significant protein-bound and is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renal excreted [15].

This difference makes levetiracetam a higher safety profile than other antiepileptic drugs

In addition, tolerability and adaptation to dose-related adverse events also vary for many reasons which include medical factors and also the patient's culture, marital status, need for specific high levels of function, expectations and financial concern [13]. We concluded that the pharmacokinetics, tolerability and adaptation might play a role in the mild adverse events of levetiracetam overdose in our patient.

Another possible factor that influenced the ability of our patient to tolerate somnolence was the preexisting insomnia related to the bipolar disorder.

Finally, there is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; and usual precautions should be observed to maintain airway. General supportive care of the patient is also indicated, including monitoring of vital signs and observation of the patient's clinical status. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with levetiracetam. Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50 % in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment [1].

REFERENCES

1. Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. Epilepsia 2000;41:1179-1186.
2. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000; 55:236-242.
3. Ben-Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group. Epilepsia 2000;41:1276-1283.
4. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacol Ther 2000;85:77-

85.
5. Patsalos PN. The pharmacokinetic characteristics of levetiracetam. Methods Find Exp Clin Pharmacol 2003;25:123-129.
6. Hovinga CA. Levetiracetam: a novel antiepileptic drug. Pharmacotherapy 2001;21:1375-1388.
7. Harden C. Safety profile of levetiracetam. Epilepsia 2001; 42:36-39.
8. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 2000;9:80-87.
9. Data on file, UCB Pharma, Inc., Smyrna, GA, 1999.
10. Awaad Y. Accidental overdose of levetiracetam in 2 children caused no side effect. Epilepsy Behav 2007;11:247.
11. Glauser TA, Pellock JM, Bebin EM, Fountain NB, Ritter FJ, Jensen CM, Shields WD. Efficacy and safety of levetiracetam in children with partial seizures: an open-label trial. Epilepsia 2002;43:518-524.
12. Barrueto Jr F, Williams K, Howland MA, Hoffman RS, Nelson LS. A case of levetiracetam (Keppra) poisoning with clinical and toxicokinetic data. J Toxicol Clin Toxicol 2002;40:881-884.
13. Greenwood RS. Adverse effects of antiepileptic drugs. Epilepsia 2000;41:S42-S52.
14. Patsalos PN, Fröscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia 2002;43:365-385.
15. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet 2004;43:707-724.