

Three Pediatric Cases of Accidental Levetiracetam Overdose Administration for Long Term

Uzun Dönem, Yüksek Dozda Levetirasetam Alımı Olan Üç Pediatrik Olgu

Özlem YAYICI KÖKEN^a,
 Ülkühan ÖZTOPRAK^a,
 Ayşegül DANIŞ^a,
 Ayşe AKSOY^a,
 Deniz YÜKSEL^a

^aClinic of Child Neurology,
 University of Health Sciences
 Ankara Sami Ulus Maternity,
 Child Health and Diseases
 Training and Research Hospital,
 Ankara, TURKEY

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Correspondence:
 Özlem YAYICI KÖKEN
 University of Health Sciences
 Ankara Sami Ulus Maternity,
 Child Health and Diseases
 Training and Research Hospital,
 Clinic of Child Neurology, Ankara,
 TURKEY/TÜRKİYE
 drozlemkoken@gmail.com

ABSTRACT Levetiracetam therapy in infancy and childhood epilepsies has become more preferred due to being an effective and well tolerated. There are many articles about levetiracetam side effects. But, up to this time, few datas were reported about the side effects due to accidentally long term use of levetiracetam with the doses higher than recommended in childhood. We evaluated three pediatric cases diagnosed with epilepsy given accidentally high-dose levetiracetam in this article. Patients were administered accidentally 87 mg/kg/d, 100 mg/kg/d and 166 mg/kg/d doses of levetiracetam oral form for one to three months. Surprisingly, no side effects were observed with these high doses of use.

Keywords: Levetiracetam; overdose; epilepsy

ÖZET Süt çocukluğu ve çocukluk dönemi epilepsilerinde etkili ve iyi tolere edilebilir olması nedeni ile levetirasetam daha fazla tercih edilir olmuştur. Levetirasetam yan etkileri ile ilgili pek çok makale bulunmaktadır. Ancak, bu zamana kadar yanlılıkla, ebeveynler tarafından, önerilen dozlardan daha yüksek dozlarda uzun süreli kullanım ile ilgili az sayıda bilgi mevcuttur. Biz, bu yazıda, yanlılıkla yüksek dozda levetirasetam verilen üç pediatrik olguyu değerlendirdik. Hastalar 87mg/kg/g, 100 mg/kg/g ve 166 mg/kg/g dozlarda oral levetirasetamı 1 ile 3 ay arasında kullanmışlardı. Şaşırtıcı şekilde, bu yüksek dozlarda kullanıma bağlı yan etki görülmedi.

Anahtar Kelimeler: Levetirasetam; yüksek doz; epilepsi

Levetiracetam, one of the new generation antiepileptic drugs, has been approved as an adjunctive therapy in the treatment of partial-onset epilepsy seizures in patients aged ≥ 1 months, as an adjunctive therapy in the treatment of myoclonic seizures in patients aged ≥ 12 years with juvenile myoclonic epilepsy, and as an adjunctive therapy for primary generalized tonic-clonic seizures in patients aged ≥ 6 years with idiopathic generalized epilepsy.¹ The dose is usually started at 10 mg/kg/d and up titrated to 40 to 60 mg/kg/d. There is a limited number of clinical data on high-dose oral levetiracetam intake and overdose administration. In this article, we present three pediatric cases at varying ages in whom levetiracetam was used above the range of recommended dose in the long-term without any serious side effects.

Written informed consent was obtained from the parents of the patients who participated in this study.

CASE REPORTS

CASE 1

A five-month-old male was diagnosed with hypoxic-ischemic encephalopathy and was treated with phenobarbital at 6 mg/kg/d and levetiracetam at 35 mg/kg/d. On his outpatient clinic visit, we realized that he was given levetiracetam accidentally by her mother at a dose of 87 mg/kg/day (435 mg/day) for one month. Vital parameters were within normal limits. Neurological examination revealed hypertonia with increased deep tendon reflexes which were not different from the previous examination. Biochemical parameters including serum electrolytes and creatinine phosphokinase (CK) levels, and liver and kidney function test were within normal limits. The serum concentration of levetiracetam was 19.25 µg/mL (normal range: 12-46 µg/mL). Electrocardiographic and echocardiographic findings were also normal. The patient's treatment was interrupted for 72 hours (six doses) and was, then, resumed to 35 mg/kg/d.

CASE 2

A two-year-old male was followed with the diagnosis of epilepsy and mental motor delay. During the outpatient clinic visit, we realized that he was prescribed levetiracetam 40 mg/kg/d; however, his parents accidentally gave 100 mg/kg/day (1500 mg/day) for the past 44 days. His family did not notice any change in the general status of the patient. Vital parameters were within normal limits. Neurological examination revealed microcephaly, severe hypotonia, and increased deep tendon reflexes. The liver and kidney function tests, serum electrolytes, and CK levels were normal. The serum concentration of levetiracetam was 65.54 µg/mL (normal range: 12-46 µg/mL). Electrocardiography showed normal sinus rhythm and echocardiographic findings were also normal. The patient's treatment was discontinued and he was switched to topiramate.

CASE 3

A four-year-old female with the diagnosis of epilepsy was prescribed a double dose of oral levetiracetam at 20 mg/kg/d. During the outpatient

clinic visit, we realized that she was given levetiracetam at 166 mg/kg/d (3000 mg/d) for three months. Vital parameters and neurological examination were within normal limits. Kidney and liver function tests and biochemical parameters were all normal and serum levetiracetam levels were measured as 45.5 µg/mL (normal range: 12-46 µg/mL). Electrocardiography showed normal sinus rhythm and echocardiographic findings were also normal. The patient's treatment was interrupted for 72 hours (six doses) and, then, the target dose was up titrated to 20 mg/kg/d and resumed.

DISCUSSION

Although levetiracetam is known to be a well-tolerated anticonvulsant, it has been associated with certain adverse effects. The most common neurological problems are asthenia, ataxia, diplopia, dizziness, dysarthria, fatigue, headache, light-headedness, nystagmus, paresthesia, somnolence, and tremor, although these side effects are either dose-related or transient. Behavioral effects include agitation, anxiety, depression, emotional lability, hostility, nervousness, and psychosis which are less related to the drug, dose or tolerance. In a review of four pivotal double-blind, placebo-controlled studies, the most common side effects associated with levetiracetam in combination with other antiepileptic medications were somnolence, asthenia, infection, and dizziness.²⁻⁴

In accordance with the full prescribing information of levetiracetam, maximum daily dose is 60 mg/kg/day for patients under 4 years of age. Based on these data, all of our cases received a high-dose of medication.

The toxic plasma level of levetiracetam is still unknown, and almost none of the reported cases of levetiracetam overdose had plasma measurements was performed. There is no specific antidote for levetiracetam overdose. Fortunately, no mortality directly related to high-dose levetiracetam was observed in the reported cases.

Table 1 summarizes high-dose and long-term use of levetiracetam in infants and children reported in the literature.⁵⁻⁸ In only one case report,

TABLE 1: High-dose and long-term use of levetiracetam in infants and children reported in the literature.

Age (mo.)	Sex	Amount and duration of levetiracetam	Other medications received	Underlying disease	Clinical sequelae	Levetiracetam plasma level	References
36	F	115 g/kg/d for one month	Carbamazepine	Epilepsy	Irritability	None	Öztürk et al.
3	F	300 mg/kg/d for about one month	None	Epilepsy	None	None	Öztürk et al.
84	F	300 mg/kg/d for 55 days	None	CP / Epilepsy	None	None	Kartal et al.
24	F	10x recommended dose for one week	None	CP / Epilepsy	None	None	Awaad et al.
60	F	10x recommended dose for four week	Unknown	Epilepsy	Mild itching	None	Awaad et al.
10	F	300 mg/kg/d for 35 days	Vigabatrin + Topiramate + Calcium folinate + Vitamin B6	Ohtahara Syndrome	Apathy, drowsiness	None	Özkale et al.

CP: Cerebral palsy.

cardiovascular toxicity associated with levetiracetam overdose was described.⁹In this case report, a 43-year-old woman was admitted to the hospital multi-drug intoxication due to a suicide attempt. She received 60 to 80 g levetiracetam which appears to cause bradycardia and hypotension by acting at M2 and M3 muscarinic receptors at very high concentrations.⁹ Our cases were also evaluated for cardiovascular toxicity, although they are not exposed to such high doses. Electrocardiography showed normal sinus rhythm in all cases.

In addition, two cases of rhabdomyolysis and one case of increased CK concentration level were previously reported related to the treatment of recommended dose of levetiracetam.¹⁰ However, we found no increase in CK levels in our cases. Furthermore, none of our cases experienced side effects. However, the treatment was discontinued for 72 hours in all cases and was, then, resumed.

In conclusion, clinicians should be careful in daily practice for levetiracetam overdose due to increased prescription rates of levetiracetam in recent years. There is no specific antidote for levetiracetam, and mortality and severe reactions

may develop, although not reported until now. We believe that this article would attract attention of pediatricians and pediatric neurologists to levetiracetam overdose to avoid malpractice and increase patient’s benefits. In addition, we highlight the importance of informing the family about the dose, and the administration of the drug should be controlled at every visit in the outpatient clinic.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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