

Is high dose levetiracetam safe in the management of neonatal convulsion?

Yenidoğan konvülziyon tedavisinde yüksek doz levatirasetam güvenli mi?

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SUMMARY

Levetiracetam is a novel anticonvulsant drug that was approved by the FDA in adult and pediatric convulsions. There is not sufficient information regarding the use of newborn such as the appropriate dose and interval, its safety, efficacy and adverse effects. We present a case of a 10 day-old male, who was accidentally administered 75 mg/kg/d levetiracetam for 3 days by his mother at home. The patient was discharged 4 days after admission to hospital without any signs and symptoms. The case demonstrated that high dose levetiracetam might be safe in newborn convulsions.

Keywords: Levetiracetam, newborn, convulsion, dose, safe

ÖZET

Levatirasetam erişkin ve pediatrik konvülziyonlarda FDA tarafından onaylanan yeni bir antikonvülziyon ilaçtır. Yenidoğan kullanımı ile ilgili doz ve aralığı, güvenliği, etkinliği ve yan etkileri konusunda yeterli bilgi bulunmamaktadır. Annesi tarafından evde 3 gün boyunca kaza ile 75 mg/kg/gün levatirasetam verilen 10 günlük bir erkek bebek olguyu sunuyoruz. Hasta, hastaneye başvurduktan 4 gün sonra hiçbir bulgu ve semptom olmadan taburcu edildi. Bu olgu yüksek doz levatirasetam yenidoğan konvülziyonlarında kullanılabileceğini gösterdi.

Anahtar sözcükler: Levatirasetam, yenidoğan, konvülziyon, doz, güvenlik

INTRODUCTION

Seizures are more common during the neonatal period than any other time in life. The incidence varies depending on the underlying disease. The overall incidence is 1 to 4 per 1000 live births in term infants¹. Although there is potential harm of seizures in the immature brain, there also is concern about possible adverse effects of anticonvulsant medications on the developing brain².

Phenobarbital is the most frequently used medication to treat neonatal seizures³. However, animal and long-term human

studies demonstrated that this drug could have deleterious effects such as cognitive dysfunction and learning impairment on the developing brain after treatment^{4,5}.

Pharmacokinetic studies in adults indicate that levetiracetam has good bioavailability, rapid achievement of steady-state concentrations, less requirement for therapeutic drug monitoring, minimal protein binding compared to first generation antiepileptics (<10%)⁶.

Case series suggest that levetiracetam may be a safe and effective for seizure treatment in all pediatric age groups^{7,8}. In this

case, our aim is to discuss whether high doses levetiracetam is safe in neonatal seizures.

CASE REPORT

A full term, 4050 g, male infant was admitted to neonatal intensive care unit (NICU) with neonatal convulsion at postnatal 2 days. The infant was the first child of a 23 years old woman who did not have any perinatal problems. The parents were not consanguineous. In family history, his uncle was diagnosed as epilepsy at the age 2.5 years. The patient was born via cesarean section due to cephalopelvic disproportion. Apgar score was 8 and 9 at 1st and 5th minutes, respectively. Cord blood gases were normal. On the second day of life, myoclonic jerks were noted on physical examination. The vital signs were noted as: axillary temperature 37.1 °C, heart rate 148/min., respiratory rate 60/min., saturation on pulse oximetry 94% in room air and blood pressure 60/35 mmHg. His birth weight was 4150 g (>97th centile), birth length was 51 cm (50th-75th centile) and head circumference was 36 cm (50th centile). Physical examination did not show any other abnormal findings.

Arterial blood gas analysis in room air revealed a pH: 7.45, pCO₂:35 mmHg, pO₂:78 mmHg, HCO₃: 22 mEq/L and base deficit: -4.5. The laboratory studies showed the following results: hemoglobin 17.7 g/dL, hematocrit 54%, leukocyte count 16800/mm³ (68% neutrophils, 32% lymphocytes), platelet count 524000/mm³, C-reactive protein 2.31 mg/L and blood glucose 96 mg/dL. Other biochemical stud-

ies were within normal limits. Computed tomography of the brain, echocardiography, metabolic studies, and neurosonography were also normal.

On the day of admission, he had 6 seizures characterized by focal myoclonic jerks lasting from 1 minute to five minutes. Levetiracetam was initiated orally at 20 mg/kg/day. The patient's clinical status improved and no additional seizures were noted. Electroencephalogram (EEG) demonstrated focal epileptic activity with isolated sharp slow-wave discharges at the centrotemporal areas of right hemisphere that were clinically accompanied by focal myoclonic jerks (Figure 1a). He was discharged from the hospital in a good clinical condition at one week old. After the discharge from the NICU, he was administered 75 mg/kg/day levetiracetam for 3 days by his mother at home. Patient was hospitalized again due to pre-diagnosis of LV intoxication. The National Poison Center was contacted by telephone. Close monitoring of the patient for up to 24 hours recommended because of the risk of respiratory and central nervous system depression. Meanwhile, EEG was normal for conceptional age (Figure 1b). Serum concentration of levetiracetam was measured by using a validated gas chromatography technique and levetiracetam level was 30.1 mg/dL (Normal level: 5-45 mg/dL). He was discharged 4 days after admission to hospital without any signs and symptoms. The baby has being followed up regularly in pediatric neurology department and he has normal neurologic development according to his age.

levetiracetam has low affinity for plasma protein binding as the volume distribution is close to the volume of total body water¹². In our case, despite the use of high doses of levetiracetam, serum level was within normal limits. Normal serum levels after high doses of levetiracetam may be due to high metabolic rate, tolerability during dosing and to the distribution of increased total body water in neonates.

Levetiracetam shows a favorable pharmacokinetic profile in the pediatric population and has also been recommended for treatment of neonatal convulsion¹³. The case reported by Tanriverdi et al.¹⁴. Demonstrated that levetiracetam was effective in other antiepileptic-resistant neonatal status epilepticus. Although off-label use of intravenous and oral levetiracetam formulation for neonatal seizures is very common, the efficacy and safety have not been evaluated extensively in neonates. The drug is well absorbed after oral administration and peak concentration within 2 hours. Bioavailability is not affected by foods. The drug is excreted mainly in the urine. Dose should be adjusted in patients with renal impairment. There are few drug interactions. In a study by Merhar et al.¹⁵ in 18 neonatal seizures, levetiracetam were found to have lower clearance, higher volume of distribution, and a longer half-life compared with older children and adults. The plasma half-life of levetiracetam in newborns is longer (8.9 h) than in older children (5-7 h). Signs and symptoms of levetiracetam toxicity include somnolence, behavioral problems anxiety, depression, emotional instability and headache. These effects are commonly observed in adult patients, in whom anticonvulsant therapy other than levetiracetam are used. In the use of levetiracetam, such side effects have rarely been reported in childhood^{16, 17}. Cutaneous reactions caused by antiepileptic drugs have a wide range of clinical features, from mild cutaneous erythematous rash to life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis¹⁸. Although the lesions are observed in 15% of patients treated with first generation antiepileptic drugs, with a second generation antiepileptic drug like levetiracetam have been rarely reported¹⁹. Recently,

Koklu et al.²⁰ reported intravenous levetiracetam-induced anaphylaxis in a newborn. Our patient was closely monitored for 48 hours for signs and symptoms of levetiracetam intoxication. No clinical side effects were observed.

Although the use of high dose levetiracetam has rarely documented in neonatal seizures, we did not reveal any clinical side effect compared with prior studies. Moreover, the serum level was also normal. It seems that high dose levetiracetam may be safely used in newborn convulsion; however further pharmacokinetic and clinical studies are needed to prove this assumption.

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