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Levetiracetam and Valproic Acid: Effects on the Liver Functions and Ammonia Level in Children

Levetirasetam ve Valproik Asid: Çocuklarda Karaciğer Fonksiyonları ve Amonyak Düzeyleri Üzerine Etkileri

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ABSTRACT

Purpose: There is evidence that levetiracetam and valproic acid causes a changes of serum ammonia level and liver function tests. The aim of this study was to evaluate the liver function parameters and ammonia level in children with seizures on treatment with levetiracetam in comparison treated with valproic acid.

Materıals and Methods: Between March 2010 and October 2010, we treated 42 patients with epilepsy. We determined the serum concentration of antiepileptic drug, transaminases, g-glutamyl transferase, and ammonia level in 22 children treated with valproic acid, and in 20 children treated with levetiracetam.

Results: There were no significant differences in the serum transaminases, g-glutamyl transferase between the patients treated with valproic acid, and the patients treated with levetiracetam. Hyperammonemia was detected in patients treated with valproic acid.

Conclusıon: These results suggest that the treatment with levetiracetam does not alter the serum ammonia level, and liver functions.

Key Words: Levetiracetam, valproic acid, liver functions, ammonia.

ÖZET

Amaç: Levetirasetam ve valproik asidin, serum amonyak düzeyi ve karaciğer fonksiyon testlerinde bir değişikliğe neden olduğuna dair kanıtlar vardır. Bu çalışmanın amacı, valproik asid tedavisi ile karşılaştırıldığında, levetirasetam ile tedavi edilen epilepsili çocuklarda karaciğer fonksiyon parametreleri ve amonyak düzeyinin belirlenmesidir.

Materyal ve Metod: Mart 2010 ve Ekim 2010 tarihleri arasında, epilepsili 42 hasta tedavi ettik. Valproik asit ile tedavi edilen 22 çocuk ve levetirasetam ile tedavi edilen 20 çocuk çalışmaya alındı ve serum antiepileptik ilaç düzeyi, transaminazlar, G-glutamil transferaz ve amonyak düzeyleri değerlendirildi.

Bulgular: Valproik asit ile tedavi edilen hastalar ile levetirasetam ile tedavi edilen hastalar arasında serum g-glutamil transferaz ve transaminaz düzeyleri arasında herhangi bir farklılık yoktu. Valproik asit ile tedavi edilen hastalarda hiperamonyemi tespit edildi.

Sonuç: Bu sonuçlar, levetirasetam tedavisinin serum amonyak düzeyi ve karaciğer fonksiyonlarını değiştirmediğini düşündürmektedir.

Anahtar Kelimeler: Levetirasetam, valproik asit, karaciğer fonksiyonları, amonyak.

INTRODUCTION

Epilepsy is one of the most common neurological problem in worldwide. Many drugs areused to prevent epilepsy. Levetiracetam (LEV) is one of the newer antiepileptic drugs (AEDs), which is now widely used in the treatment of childhood epilepsy. The most frequently observed adverse effects were somnolence and behavioral

problems[1]. However, LEV induced thrombocytopenia, interstitial nephritis, fulminant liver failure, and rise of gama glutamyl transferase have been reported in rare patients in literature[2-5].

Valproic acid (VPA) is one of the most commonly used AED for childhood epilepsy. Common side effects include nausea, vomiting, tremors, mood and personality changes. Valproic acid can also cause hematologic side effects, gastrointestinal disturbances, metabolic changes, hepatotoxicity, and hyperammonemia[6].

The aim of this study was to evaluate the liver function parameters and ammonia level in children with seizures on treatment with LEV in comparison treated with VPA.

MATERIALS and METHODS

This study was conducted in the pediatric neurology out-patient department of our hospital between March 2010 and October 2010. Patients with history of new-onset seizure and diagnosed as epileptic were included in this study. Patients with symptoms and signs of illnesses other than epilepsy (eg, kidney, liver, endocrine, and metabolic), a history of status epilepticus, previous use of any antiepileptic drugs were not included in the study.

The patients were subdivided into two groups according to their therapy. Group 1 consisted of 20 patients who treated with only LEV, group 2 consisted of 22 patients treated with only VPA.

Levetiracetam was initially administered in a twice daily administration with a starting dose of 15 mg/kg per day. Further doses were titrated until patients were seizure-free. Valproic acid was started at a dose of approximately 10 mg/kg/day. The dose was increased until seizures were controlled. The patients were monitored for at least 6 months after starting of LEV or VPA. Serum concentrations of AEDs, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphotase (ALP), g-glutamyl transferase (GGT), and ammonia levels were measured in all patients.

For data analysis, the SPSS was used. Groups were compared by means of Kruskal-Wallis tests, and correlation were investigated using Spearman test; P values < .05 were considered statistically significant.

RESULTS

Fourty two children, mean age 10.21 ± 1.95 (7-14 years) years, were included in this study. All epileptic children had been treated for at least six months with either LEV alone, in a dose ranging from 25 to 34 mg/kg/d (mean dose 29.5 ± 2.0 mg/kg/d), or VPA alone, in a dose ranging from 20 to 32 mg/kg/d (mean dose 23.7 ± 4.1 mg/kg/d). The LEV group included 20 patients (12 males and 8 females, mean age 10.15 ± 2.00 years), and the VPA group included 22 patients (12 males and 10 females, mean age 10.27 ± 1.95 years). The age and sex distributions between the two groups were not significantly different.

The changes in the liver function tests and ammonia results during the treatment period in the LEV group are presented in Table 1. There were no statistically significant differences in AST, ALT, ALP, GGT, and ammonia levels in the sixth month of treatment compared with pre-treatment levels. The values of the variables measured in VPA group are summarized in Table 2. There were also no statistically significant differences in AST, ALT, ALP and GGT in the sixth month of treatment compared with pre-treatment levels. But, the ammonia level increased significantly in the sixth month of treatment compared with pre-treatment values. In the patients treated with VPA, correlations were not obtained between ammonia and total dosage, and serum concentration of the drug.

Table 1. Changes in liver function test and ammonia results during levetiracetam treatment.

	Pretreatment	During treatment Sixth month
Aspartate aminotransferase (U/L)	22.85 ± 5.02	22.20 ± 2.41
Alanine aminotransferase (U/L)	15.90 ± 5.14	15.83 ± 2.44
g-glutamyl transferase (U/L)	15.55 ± 3.01	15.75 ± 2.77
Ammonia (mmol/L)	30.20 ± 8.29	30.1 ± 8.11
Alkaline phosphotase (U/L)	347.85 ± 64.51	360.00 ± 70.60
Dosage (mg/kg per day) Drug concentration (mg/mL)		29.50± 2.01

Table 2. Changes in liver function test and ammonia results during valproic acid treatment

	Pretreatment	**During treatment Sixth month**
Aspartate aminotransferase (U/L)	23.05 ± 6.56	23.23 ± 4.21
Alanine aminotransferase (U/L)	15.27 ± 2.88	15.68 ± 4.24
g-glutamyl transferase (U/L)	15.59 ± 3.62	14.23 ± 3.72
Ammonia (mmol/L)	30.91 ± 7.42	39.27 ± 12.99
Alkaline phosphotase (U/L	351.09 ± 44.71	378.45 ± 77.03
Dosage (mg/kg per day)		23.70 ± 4.12
Drug concentration (mg/mL)		75.61 ± 9.80

There were no statistically significant differences in AST, ALT, ALP, and GGT between the patients treated with LEV and VPA group. However, ammonia levels were significantly high in the VPA group than in the LEV group in the sixth month of treatment compared with pre-treatment levels (Figure 1) ($P < .001$). The GGT levels were lower in the VPA group than in the LEV group in the sixth month of treatment compared with pre-treatment levels. But, there was no statistically significant differences in GGT in two groups.

DISCUSSION

Levetiracetam has a favorable pharmacological profile, with almost complete absorption after oral administration, linear pharmacokinetics, and a low extent of metabolism. Levetiracetam is unlikely to interact with other AEDs, because it has a low protein binding[7]. The most common adverse effects are somnolence, asthenia, and dizziness, which usually appear early after initiation of LEV therapy and generally resolve without medication withdrawal. A literature review identified that have been rarely seen LEV induced hepatic failure[4]. Another antiepileptic drug, VPA may involve various systems. It has been reported in several studies that VPA use can alter the liver function tests and ammonia levels[6,8].

In literature, Altunbasak et al.[8] found subclinical hyperammonemia in 5.6% of patients as monotheraphy, and 16.67% of patients as polytheraphy in 68 children treated with VPA. In another report, Yilmaz et al.[9] reported that the ammonia level was significantly high in the third month of treatment than the initial, and the sixth month values returned to the pretreatment values in VPA. In another study, Gago et al.[10] observed no hepatic dysfunction in patients treated with VPA. However, hyperammonemia, which was detected in 8 patients habitually associated with carnitine deficiency. The significant correlation noted between the VPA concentration in serum and the concentration of ammonia suggest a direct effect of this drug. We have not found hepatic

dysfunction during treated with VPA in our patients.

There have been two reported fulminant hepatic failure with LEV[4]. Skopp et al.[11] reported a case of fatal fulminant hepatic failure in a patient with refractory epilepsy treated with as combination with carbamazepine and LEV. However, Tan et al.[4] also reported fulminant hepatic failure in a patient with LEV. Also, Broli et al.[5] described an epileptic patient who developed a significant increase in GGT while on LEV monotherapy.

In our study, we observed no hepatic dysfunction during in the six month of treatment with LEV. There were no significant differences in AST, ALT, GGT, ALP, and ammonia in the sixth month of treatment compared with pre-treatment levels. Also, we found no hepatic dysfunction in our patients treated with VPA in the sixth month of treatment compared with pre-treatment levels. However, increased ammonia levels, which was detected in the sixth month of VPA treatment was not correlated with clinic findings. Also, the correlations were not obtained between ammonia and total dosage, and serum concentration in with treated VPA.

In conclusion, however there have been several reports, further large sample and controlled studies for evaluating the effect of LEV on liver especially in pediatric patients are required.

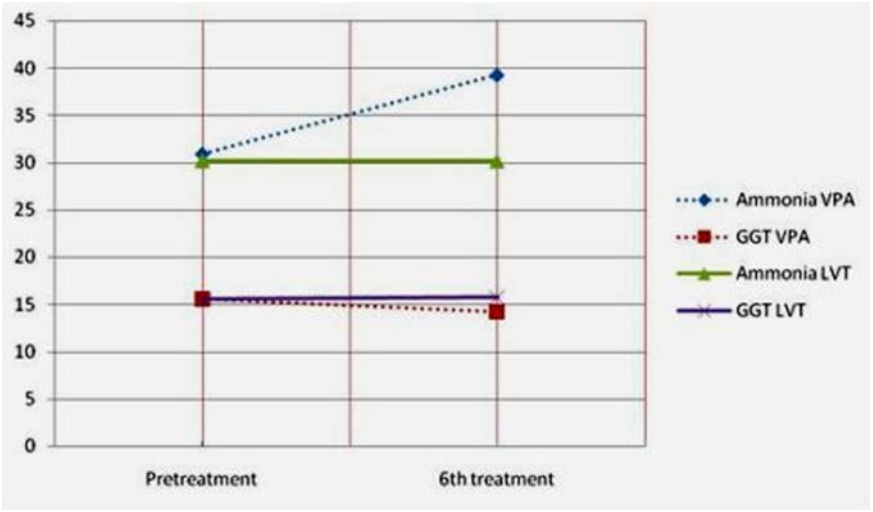

Figure 1. The mean serum levels of ammonia and GGT of the LEV using group and VPA using group before (baseline) and between sixth treatment.

REFERENCES

1. Callenbach PM, Arts WF, ten Houten R, Augustijn P, Gunning WB, Peeters EA, et al. Add-on levetiracetam in children and adolescents with refractory epilepsy: results of an open-label multi-centre study. Eur J Paediatr Neurol. 2008;12: 321-7.
2. Kimland E, Höjeberg B, von Euler M. Levetiracetaminduced thrombocytopenia. Epilepsia. 2004;45:877-8.
3. Hurwitz KA, Ingulli EG, Krous HF. Levetiracetam induced interstitial nephritis and renal failure. Pediatr Neurol 2009;41:57-8.
4. Tan TC, de Boer BW, Mitchell A, Delriviere L, Adams LA, Jeffrey GP, et al. Levetiracetam as a possible cause of fulminant liver failure. Neurology. 2008;71:685-6.
5. Broli M, Provini F, Naldi I, Bisulli F, Sama C, Baruzzi A, et al. Unexpected gamma glutamyltransferase rise increase during levetiracetam monotherapy. Epileptic Disord 2010;12:81-2.

6. Dreifuss FE. Valproic acid toxicity. In: Levy RH, Mattson RH, editors. Antiepileptic Drugs. 4th ed. New Jersey: Lippinvott-Raven Healthcare. 1996:641-8.

7. Grosso S, Cordelli DM, Franzoni E, Coppola G, Capovilla G, Zamponi N, et al. Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. Seizure. 2007;16:345-50.

8. Altunbaşak S, Baytok V, Tasouji M, Hergüner O, Burgut R, Kayrin L. Asymptomatic hyperammonemia in children treated with valproic acid. J Child Neurol. 1997;12:461-3.

9. Yilmaz Y, Tasdemir HA, Paksu MS. The influence of valproic acid treatment on hair and serum zinc levels and serum biotinidase activity. Eur J Paediatr Neurol. 2009;13:439-43.

10. Castro-Gago M, Gómez-Lado C, Eirís-Puñal J, Díaz-Mayo I, Castiñeiras-Ramos DE. Serum biotinidase activity in children treated with valproic acid and carbamazepine. J Child Neurol. 2010;25:32-5.

11. Skopp G, Schmitt HP, Pedal I. Fulminant liver failure in a patient on carbamazepine and levetiracetam treatment associated with status epilepticus. Arch Kriminol. 2006;17:161-75.

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