Original Article

Effect of Levetiracetam Usage on Serum Creatine Phosphokinase Concentration in Patients with Epilepsy

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Background: Levetiracetam (LEV) is a widely used antiepileptic drug (AED) in the treatment of various type of seizures, including generalized epileptic seizure as well as focal seizures, and it is generally well tolerated. Common side effects of LEV are somnolence, asthenia, dizziness, mood changes, kidney dysfunction, minor infections, and thrombocytopenia. Recently, increased creatine phosphokinase (CPK) concentration or rhabdomyolysis after LEV administration has been reported. The goal of the study was to evaluate clinical risk factors associated with increased CPK concentration or rhabdomyolysis in LEV administration.

Materials and Methods: One hundred and sixty children were enrolled. The risk factors were retrospectively analyzed. Results: Among the 160 patients, 84 (52.5%) were boys and 76 (47.5%) were girls, and the mean age was 85.95 ± 49.03 months (9–188 months). Of the 160 patients, 66 (41.3%) were treated with monotherapy, and 94 (58.8%) with polytherapy. We detected increased CPK concentration or rhabdomyolysis in three patients (1.9%). The CPK values of these three patients were 943, 1504, and 5046, respectively. No significant differences were observed in the serum CPK concentration between the patients treated with LEV.

Conclusion: We detected that LEV may cause increased CPK concentration or rhabdomyolysis. When treating patients with LEV, clinicians should closely monitor serum CPK level. To the best of our knowledge, this is the first study of elevated CPK concentration or rhabdomyolysis associated with LEV therapy in children.

Keywords: Children, creatine phosphokinase level, levetiracetam

INTRODUCTION

Epilepsy is one of the common chronic illnesses of childhood. Antiepileptic drugs (AEDs) are used for its long-term treatment. This therapy may be associated with several side effects. Levetiracetam (LEV) is a highly effective new generation drug with a broad spectrum of actions. It is used for the treatment of partial-onset seizures or idiopathic or symptomatic generalized seizures. LEV does not bind to plasma proteins, and is eliminated by the kidneys. It has been argued that LEV can act on the N-type Ca\(^+\) channel and can reverse the gamma-aminobutyric acid and glycine-gated currents.[1] Side effects include fatigue, somnolence, infection, headache, behavioral changes, skin rashes, thrombocytopenia, and interstitial nephritis.[2-4]

LEV can rarely cause an elevated level of creatine phosphokinase (CPK) (also known as hyperCKemia) or rhabdomyolysis immediately after starting therapy. To the best of our knowledge, there are a few case reports of LEV-associated hyperCKemia or rhabdomyolysis in the literature.[5-8] However, there are no studies of LEV-associated hyperCKemia or rhabdomyolysis. Therefore, we planned a study designed to identify the frequency

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and risk factors associated with hyperCKemia or rhabdomyolysis during LEV therapy in children with epilepsy.

**Materials and Methods**

This retrospective study was performed in the pediatric neurology department of our hospital between January 2015 and January 2017. Patients with symptoms and signs of illnesses other than epilepsy (e.g., kidney, liver, myopathy, endocrine, and metabolic), and previous use of any drugs were not included in the study.

The patients were divided into two groups according to their therapy. Group 1 consisted of 66 patients treated with only LEV, group 2 consisted of 94 patients treated with add-on LEV. Group 1 patients had a history of new-onset epilepsy and were started on monotherapy with LEV. Group 2 was treated with add-on LEV and included patients with more treatment refractory epilepsy, who were taking 1–3 AEDs, and had been diagnosed with intractable epilepsy.

Possible risk factors that may have a role in the hyperCKemia or rhabdomyolysis prognosis such as age, sex, consanguinity, seizure frequency (less than once a week, more than once a week), seizure type (partial, generalized, and mixed), number of the AEDs (monotherapy or polytherapy), dosage of LEV, mental retardation, neurological abnormality, epileptic activities on electroencephalogram (EEG), neuroimaging findings, and etiology were investigated.

We classified seizures according to the International League Against Epilepsy (ILAE) criteria. According to the guidelines of ILAE, seizures were divided into partial, generalized, and mixed seizures. Etiologies of the epilepsies were divided into three groups as symptomatic, idiopathic, and cryptogenic. Cerebral computed tomography and/or magnetic resonance imaging (MRI) studies were performed in all patients. Considering the related neuroradiological studies, the patients were divided into two groups: normal and abnormal. The tests used to determine the degree of mental retardation of the patients were the Wechsler Intelligence Scale for Children (standardized for Turkish children) in patients aged 6–16 years and the Stanford–Binet (American format) for patients aged 2–6 years.

LEV was initially administered twice daily with a starting dose of 10 mg/kg per day. Further doses were titrated until patients were seizure free. Patients who were started at the beginning of the study and followed for at least 6 months were included in the study. We could not determine the serum concentration level of LEV due to lack of study in our hospital. Serum CPK concentration was measured in all patients. The CPK values were defined as normal in the limits 28–204 U/L in our hospital laboratory. The CPK values were recorded before the initiation of LEV treatment and at the first month of treatment. As hyperCKemia or rhabdomyolysis has the potential to develop during the early phase of LEV treatment, we measured CPK concentration at 1 month of treatment with LEV.

**Statistical analysis:** Data were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 21.0 (SPSS Inc, Chicago, USA). Categorical data were analyzed using the chi-square test. Mann–Whitney U test was used for pairwise comparisons of numerical data. Numerical data were presented as the mean values and standard deviation, and categorical data as the numbers and percentages. A P value < 0.05 was considered statistically significant.

**Results**

One hundred and sixty children, mean age 85.95 ± 49.03 months (9–188 months), were included in this study. Among the 160 patients, 84 (52.5%) were boys and 76 (47.5%) were girls, and the mean age at the seizure onset was 52.38 ± 50.75 months (1–182 months). Of the 160 patients, 66 (41.3%) were treated with monotherapy, and 94 (58.8%) with polytherapy. Most of the patients were found to have CPK within the normal range, and increased CPK concentration or rhabdomyolysis was recorded in three patients (1.9%). Among the three patients with increased CPK concentration or rhabdomyolysis, one patient was treated with monotherapy and two patients with polytherapy. The CPK values of these three patients were 943, 1504, and 5046, respectively. Of the three patients, two patients were asymptomatic, and other was symptomatic (symptoms such as mild myalgia and discomfort). HyperCKemia or rhabdomyolysis was diagnosed with clinical and biochemical findings. We thought LEV may be the cause of those complaints and ceased LEV therapy. Hydration therapy was started to avoid potential complications. After stopping LEV, serum CPK levels gradually decreased and returned to normal values. Muscle biopsy was not performed in all the patients. Also, we detected that three patients had normal levels of plasma carnitine and free carnitine. The described characteristics of all the patients are shown in Table 1.

No correlation was observed between increased CPK concentration or rhabdomyolysis and age, sex, consanguinity, seizure frequency, seizure type, number of the AEDs, LEV dose, mental retardation,
neurological abnormality, epileptic activities on EEG, abnormal cerebral MRI findings, and etiology. Table 2 shows the association between concentration of CPK or rhabdomyolysis and risk factors.

**DISCUSSION**

LEV is an AED, used for the treatment of generalized or partial seizures, either monotherapy or add-on therapy. LEV has unique pharmacokinetic profile, and it works by binding to synaptic vesicle protein 2A (SV2A). It also acts by inhibiting N-type calcium channels. It is rapidly absorbed orally and excreted exclusively through kidneys. Once absorbed, approximately 34% of the drug is metabolized to inactive metabolites and rest is excreted unchanged through kidneys. It does not possess any cytochrome P-450 isozyme activity and is not involved in any drug interactions including with AEDs.[1,2]

Comparing with the other AEDs, it was found that LEV use is gradually increasing due to its favorable pharmacokinetics and safety. Common adverse effects of LEV include somnolence, asthenia, dizziness, mood changes, kidney dysfunction, and minor infections. Although the most common adverse effects of this drug are minor, serious adverse effects such as thrombocytopenia, interstitial nephritis, and suicide attempt have been reported.[2-4]

Among the limited number of AEDs, a few cases of rhabdomyolysis with valproic acid and phenytoin have been reported.[10,11] Recently, a few cases have reported hyperCKemia or rhabdomyolysis secondary to LEV in literature.[5-8] In the recent reports, Akiyama et al.[5] reported a 29-year-old woman with epilepsy, in whom rhabdomyolysis was induced by LEV. Di Lorenzo and Li[12] described LEV-induced increase in CPK levels in a 27-year-old patient. Another case, a 19-year-old man, was described by Isaacson et al.[6] Incecik et al.[8] reported a 13-year-old girl with rhabdomyolysis induced from LEV therapy. In the literature, to the best of our knowledge, this is the first report of rhabdomyolysis due to LEV therapy in the children. According to marketing information on LEV, the number of the patients taking

| Parameters                        | n | %  |
|----------------------------------|---|----|
| **Age**                          |   |    |
| <5 years                         | 55| 34.4|
| ≥5 years                         | 65| 65.6|
| **Sex**                          |   |    |
| Girl                             | 76| 47.5|
| Boy                              | 84| 52.5|
| **Age of seizure onset**         |   |    |
| <5 years                         | 107| 66.9|
| ≥5 years                         | 53| 33.1|
| **Consanguinity**                |   |    |
| Yes                              | 44| 27.5|
| No                               | 116| 72.5|
| **Type of seizure**              |   |    |
| Partial                          | 90| 56.2|
| Generalized                      | 38| 23.8|
| Mixed                            | 32| 20  |
| **Seizure frequency**            |   |    |
| Less than 1/week                 | 89| 55.6|
| ≥1/week                          | 71| 44.4|
| **Number of the AEDs**           |   |    |
| Monotherapy                      | 66| 41.3|
| Polytherapy                      | 94| 58.7|
| **Dose of LEV**                  |   |    |
| <30 mg/kg                        | 65| 40.6|
| ≥30 mg/kg                        | 95| 59.4|
| **Neurologic deficits**          |   |    |
| Yes                              | 80| 50  |
| No                               | 80| 50  |
| **Mental retardation**           |   |    |
| Yes                              | 106| 66.3|
| No                               | 54| 33.7|
| **Neuroimaging findings**        |   |    |
| Normal                           | 62| 38.7|
| Abnormal                         | 98| 61.3|
| **EEG findings**                 |   |    |
| Normal                           | 0 | 0   |
| Abnormal                         | 100| 100|
| **Etiology**                     |   |    |
| Symptomatic                      | 88| 55  |
| Cryptogenic                      | 23| 14.4|
| Idiopathic                       | 49| 30.6|
| **HyperCKemia or rhabdomyolysis**|   |    |
| Yes                              | 3 | 1.9 |
| No                               | 157| 98.1|
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the drug in Japan is around 80,000–100,000, and the incidence of rhabdomyolysis among them is reported to be 0.001–0.00125%, which is extremely low.

Previously conducted large multicenter clinical trials on LEV reported somnolence, asthenia, irritability, dizziness, headache, and fatigue as major side effects,[2-4] but no hyperCKemia or rhabdomyolysis was reported. It can also cause, although rarely, an increase in CPK levels after the initiation of the therapy. No clinical studies of hyperCKemia or rhabdomyolysis have been reported with its use in the literature. Therefore, we conducted a study designed to identify the frequency and risk factors associated with hyperCKemia or rhabdomyolysis during LEV therapy in children with epilepsy. We detected that 3 of 160 patients (1.9%) had hyperCKemia or rhabdomyolysis during LEV therapy. So far, to the best of our knowledge, this is the first study of hyperCKemia or rhabdomyolysis secondary to LEV treatment in the literature. We found no significant difference between the risk factors and hyperCKemia or rhabdomyolysis during LEV therapy.

Rhabdomyolysis is the destruction of skeletal muscle and the release of various cellular components, including CPK and myoglobin into the bloodstream. The main causes of rhabdomyolysis may be direct muscle damage, intense physical exercise, certain drugs (some of them commonly used, such as statins), toxins, infections, and genetic defects. Its mechanism is known to involve fusion and necrosis of skeletal muscle cells.[13] However, the exact hyperCKemia or rhabdomyolysis mechanism of LEV is not fully explained. One speculation was proposed by Carnovale et al.[7] The authors focused on potentiation of cholinergic neurotransmission via synaptic vesicle protein SV2A binding of LEV, thereby exerting high stress in muscles, leading to rhabdomyolysis. Another hypothesis is the direct toxicity of LEV on muscle membrane.[6] Although, this is not entirely clear.

In conclusion, we conclude that LEV may cause hyperCKemia or rhabdomyolysis. As hyperCKemia or rhabdomyolysis has the potential to develop during the early phase of LEV treatment, clinicians should pay attention to the possible development of this side effect despite its rare incidence. It might be reasonable

Table 2: Risk factors associated with hyperCKemia or rhabdomyolysis

| Parameters                  | HyperCKemia or rhabdomyolysis | No hyperCKemia or rhabdomyolysis | P value |
|-----------------------------|-------------------------------|----------------------------------|---------|
|                             | n                | %                  | n      | %                  |
| Age                        |                  |                    |        |                    |
| <5 years                   | 1                | 1.8                | 54     | 98.2               | 0.728   |
| ≥5 years                   | 2                | 1.9                | 103    | 98.1               |         |
| Sex                        |                  |                    |        |                    |
| Girl                       | 1                | 1.3                | 75     | 98.7               | 0.538   |
| Boy                        | 2                | 2.4                | 82     | 97.6               |         |
| Age of seizure onset       |                  |                    |        |                    |
| <5 years                   | 2                | 1.9                | 105    | 98.1               | 0.704   |
| ≥5 years                   | 1                | 1.9                | 52     | 98.1               |         |
| Consanguinity              |                  |                    |        |                    |
| Yes                        | 2                | 4.5                | 42     | 95.5               | 0.184   |
| No                         | 1                | 0.9                | 115    | 99.1               |         |
| Type of seizure            |                  |                    |        |                    |
| Partial                    | 2                | 2.2                | 88     | 97.8               | 0.607   |
| Generalized                | 1                | 2.6                | 37     | 97.4               |         |
| Mixed                      | 0                | 0                  | 32     | 100                |         |
| Seizure frequency          |                  |                    |        |                    |
| Less than 1/week           | 1                | 1.1                | 88     | 98.9               | 0.415   |
| ≥1/week                    | 2                | 2.8                | 69     | 97.8               |         |
| Number of the AEDs         |                  |                    |        |                    |
| Monotherapy                | 1                | 1.5                | 65     | 98.5               | 0.631   |
| Polytherapy                | 2                | 2.1                | 92     | 97.9               |         |
| Dose of LEV                |                  |                    |        |                    |
| <30 mg/kg                  | 1                | 1.5                | 64     | 98.5               | 0.640   |
| ≥30 mg/kg                  | 2                | 2.1                | 93     | 97.8               |         |
| Neurologic deficits        |                  |                    |        |                    |
| Yes                        | 2                | 2.5                | 78     | 97.5               | 0.500   |
| No                         | 1                | 1.3                | 79     | 98.7               |         |
| Mental retardation         |                  |                    |        |                    |
| Yes                        | 2                | 1.9                | 104    | 98.1               | 0.737   |
| No                         | 1                | 1.9                | 53     | 98.1               |         |
| Neuroimaging findings      |                  |                    |        |                    |
| Normal                     | 1                | 1.6                | 61     | 98.4               | 0.667   |
| Abnormal                   | 2                | 2.0                | 96     | 98.0               |         |
| Etiology                   |                  |                    |        |                    |
| Symptomatic                | 2                | 2.3                | 86     | 97.7               | 0.770   |
| Cryptogenic                | 0                | 0                  | 23     | 100                |         |
| Idiopathic                 | 1                | 2.0                | 48     | 98.0               |         |
to check level of CPK in such patients at 2–3 weeks from the initiation of LEV. Also, further large sample and controlled studies for evaluating the effect of LEV on hyperCKemia or rhabdomyolysis, especially in pediatric patients, are required.

**Ethical approval**
All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent**
Informed consent has been obtained by all study objects, and the study was approved by the Institutional Review Board.

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**Conflicts of interest**
There are no conflicts of interest.

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