ABSTRACT

Objective: The purpose of this investigation was to evaluate the effect of valproic acid therapy on dental and periodontal health of children with epilepsy and to compare salivary lysozyme concentrations of epileptic patients with an otherwise healthy group of children.

Material and Method: The study group included 27 patients with epilepsy and the control group consisted of 12 healthy children. Study group was divided into two sub-groups as; (VPA): 12 patients who were using only valproic acid and, (VPA+AED): 15 patients who were using valproic acid in combination with different antiepileptic drugs (AED). For the assessment of salivary lysozyme concentration, unstimulated mixed saliva was collected from each patient with expectoration method. Buffering capacity and flow rate of saliva were established using standard methods and the salivary concentration of lysozyme was evaluated using turbidimetric method. Intraoral examinations of all subjects were done according to WHO criteria.

Results: Salivary lysozyme levels were significantly higher in the study group as well as the plaque and gingival indices. There was no statistically significant difference between the groups in terms of dental experience scores, salivary buffering capacity and salivary flow rates. A positive correlation was observed between the clinical periodontal health and salivary lysozyme concentrations in epileptic patients.

Conclusion: Elevation of salivary lysozyme concentrations may directly affect periodontal and oral health of epileptic patients. We need more studies to develop new AEDs which are compatible with oral tissues.

Keywords: Valproic acid, epilepsy, antiepileptic drugs, plaque index, gingival index, lysozyme, saliva. Nobel Med 2017; 13(1): 26-30
EPİLEPSİLİ ÇOCUKLARDA VALPROİK ASİT TЕДАVİSİNİN PERIODONTAL VE DENTAL SAĞLIĞA ETKİSİ

ÖZET

Amaç: Bu araştırmanın amacı epilepsili çocuklarda valproik asit kullanımının periodontal ve diş sağlığı üzerindeki etkilerini değerlendirmek ve sağlıklı ve epilepsili çocuklar için kontrasıyonunun konsantrasyonlarını karşılaştırmaktır.

Materyal ve Metot: Araştırımımızda çalışma grubunu 27 epilepsili çocuk ve kontrol grubunu ise 12 sağlıklı çocuk oluşturdu. Çalışma grubu içerisinde, yalnız valproik asit kullanan epilepsili çocuklar (VPA) ve valproik asit ile kombine diğer antiepileptik ilaçları (AED) da kullanan epilepsili çocuklar (VPA+AED) olmak üzere iki alt grup oluşturuldu. Tüm tercih edilen antiepileptik ilacların (VPA, PHT, CBZ) ve ikinci faze antiepileptik ilacların (VPA, CBZ, TPM, AED) tükürük lizozim konsantrasyonlarını belirlemek için standart yöntemler kullanıldı. 

Sonuç: Tüm tercih edilen antiepileptik ilacların tükürük lizozim seviyelerini etkileyebilmesi için bu verilerin işgalında daha fazla çalışma ihtiyaç duyulduğunu düşünülmektedir.

Anahtar kelimeler: Valproik asit, antiepileptik ilaçlar, epilepsi, plak indeksi, gingival indeks, lizozim, tükürük.

INTRODUCTION

Epilepsy is a common chronic neurological disorder, characterized with recurrent seizures and affects 1-3% of the population, and almost 10% of the population have one or more seizures at some time in their lives.1-4 The current epilepsy treatment aims to improve the quality of life by suppressing seizures as well minimizing the possible side effects of drugs.5-9

Seizure control can be achieved by antiepileptic drugs (AEDs) in nearly 50% of patients; 2 trials of medications (either 2 monotherapies or a combination of 2 drugs) can increase the rate to 60%. Seizure control is provided in only an additional 5% of patients with third or fourth trial.6,7,10 Phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA), topiramate (TPM) are some of AEDs.11 One of the possible side effects of the medication may include bone loss, which can lead to osteoporosis over the long-term of use.1,2,4,11-14 Poor self-care of epileptic patients and the side effects of anticonvulsant drugs, cause the risk for oral and dental health. Especially, the use of phenobarbital (PHB) and PHT can be associated with gingival enlargement.15-17 The gingival hyperplasia resolves spontaneously within 1-6 months of PHT withdrawal.18,19 The patient may experience the following signs and symptoms: dry mouth; irritation or soreness of tongue and mouth; red, irritated, or bleeding gums; and swelling of the face, lips, tongue. Gingival overgrowth is observed more often in individuals with high plaque levels. PHT has been replaced by CBZ and VPA, which are equally effective but with fewer side effects.18,19 But also CBZ may cause oral complications such as xerostomia, ulceration, stomatitis and glossitis.18

VPA and TPM are widely used and highly effective antiepileptic drugs.19 Liver function may be affected with VPA and sodium valproate leading an increase on the liver transaminase levels and a decrease of liver synthesis including coagulation factors. Another side effect of VPA is the thrombocytopenia, and decrease on the liver transaminase and the clotting problems. Also a case of Stevens-Johnson syndrome due to valproic acid with combination of lamotrigine was reported.20 VPA has been associated with delayed healing.21

Some well-known severe side effects of VPA have not been described for the TPM. The common side effects of TPM may include mental slowing, impaired concentration, dizziness, ataxia, confusion and kidney stones. Beside these systemic side effects oral adverse effects of TPM are, glossitis, stomatitis, gingival hyperplasia and very rarely tongue edema.18,21

It was reported that, the amount of lysozyme in saliva was increased by using PHT.22 Modeer et al. reported the amount of lysozyme was increased depending on infiltrates of mononuclear cells in the connective tissue in PHT-induced gingival overgrowth.23 Lysozyme is a...
Table 1. Age and gender distribution of the study and control groups.

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>VPA+other AEDs</th>
<th>Control group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(mean±SD)</td>
<td>9.78±2.98</td>
<td>9.4±1.84</td>
<td>10.83±2.04</td>
<td>9.82±2.16</td>
</tr>
<tr>
<td>Girls</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Boys</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

VPA: 12 patients who were using only valproic acid, VPA+other AEDs: 15 patients who were using valproic acid in combination with different antiepileptic drugs.

Table 2. The (mean±SD) df-t and DMF-T Index scores of the study and control groups

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>VPA+other AEDs</th>
<th>Control group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>df-t (mean±SD)</td>
<td>3.81±3.37</td>
<td>3.60±4.15</td>
<td>2.08±2.74</td>
<td>0.91±3.37</td>
</tr>
<tr>
<td>DMF-T (mean±SD)</td>
<td>1.58±2.11</td>
<td>2.00±2.10</td>
<td>1.50±1.51</td>
<td>0.74±0.74</td>
</tr>
</tbody>
</table>

SD: Standard deviation, df-t: decayed, filled teeth, DMF-T: decayed, missing, and filled teeth, VPA: 12 patients who were using only valproic acid, VPA+other AEDs: 15 patients who were using valproic acid in combination with different antiepileptic drugs, *: Kruskal–Wallis test

According to this point of view, the aim of the present study was to evaluate salivary lysozyme levels of children with epilepsy being treated with VPA or/and VPA and other AEDs combination; and also determine the dental and periodontal health of children with epilepsy.

MATERIAL AND METHOD

A total of 39 children aged between 7-16 years were evaluated in this study (AED users n=27 and healthy controls n=12). Subjects in the study were classified according to the usage of AEDs as only VPA (VPA group) or VPA in combination of another antiepileptic (VPA+AED). The 27 epileptic children undergoing regular AED treatment in the Department of Pediatric Neurology were included into the study. Randomly selected 12 children attending Pediatric Dentistry Clinics were included in the study as the healthy controls. The Ethical approval for this investigation was obtained from the Local Research Ethics Committee, Istanbul, Turkey (2006/2063). All patients and their parents were informed of the objectives of the study and informed consent was obtained from the parents/legal guardians.

The study group included 27 patients with epilepsy and the control group consisted of 12 healthy children. Study group was divided into two sub-groups as; Group1 (VPA): 12 patients who were using only valproic acid and Group2 (VPA+AED): 15 patients who were using valproic acid in combination with different antiepileptic drugs.

Oral and dental clinical examinations were carried out for all the children using a disposable dental mirror and available light source as declared in the WHO (World Health Organization, 1997) criteria. Dental health status was evaluated using decayed, missing, and filled teeth (DMF-T) and decayed, filled teeth (df-t) indices for children over 7 years. Gingival index and plaque index scores of all children were recorded.

Unstimulated mixed saliva samples were collected from each subject by the same researcher with a standard method. All subjects were instructed to stop eating and drinking for at least 1 h before the sampling procedure. After the waiting period, they were asked not to swallow saliva exactly 5 min and then to spit the saliva accumulated in their mouths into the graduated tubes. Flow rates were calculated as milliliters of saliva secreted per minute. Saliva buffering capacity was quantified by using Ericsson method. The concentration of lysozyme was evaluated by turbidimetric method.

The data were processed statistically with the NCSS 2007 and PASS 2008 Statistical program. One-way Anova, Kruskal–Wallis and Mann-Whitney-U tests were applied for intergroup comparison and Spearman’s Rho Correlation analysis was performed to determine the relationships between parameters. p value of less than 0.05 was considered to be statistically significant.

RESULTS

The age and gender distributions of the individuals are presented in Table 1.

A total of 39 children (boy n=19, girls n= 20) were examined. The mean age of the groups for VPA, VPA+AEDs and healthy subjects were (9.78±2.86), (9.4±1.84) and (10.83±2.04) years, respectively.

Concerning AEDs at the time of the study, 44% of patients were using only VPA and 56% were using VPA in combination with other AEDs (TPM, PHB, CBZ, oxcarbazepine, diazepam, clonazepam).

The mean treatment period with VPA and VPA+ other AEDs were; 3.12±2.33 and 4.00±2.95 years, respectively.

The df-t and DMF-T Index scores of study and control groups are presented in Table 2.

The df-t and DMF-T scores for VPA, VPA+AEDs and healthy controls were: 3.91±3.37, 1.58±2.11, 3.60±4.15; 2.00±2.10 and 2.08±2.74; 1.5±1.51 respectively.
There was no statistically significant difference in dental experience scores between the study and control groups.

The salivary flow rates, buffering capacity and salivary lysozyme concentrations of study and control groups were presented in Table 3. There was no significant difference in salivary flow rate and buffering capacity scores between the study and control groups. Salivary lysozyme concentrations were significantly higher in children with epilepsy than the control group (p=0.001).

There was a significant correlation between salivary lysozyme concentration and buffering capacity in epilepsy groups (r=0.387, p=0.04).

No correlation was found between the time of AED treatment and salivary lysozyme concentrations (r=0.043, r=0.064, p>0.05).

The plaque and gingival index scores and salivary lysozyme concentrations of study groups were presented in Table 4. The plaque index, gingival index and salivary lysozyme concentrations were significantly higher in children with epilepsy than the control group. A positive correlation was found between the clinical evaluation of periodontal health and salivary lysozyme concentrations in patients with epilepsy (r=0.609; p=0.047).

**DISCUSSION**

Oral health is an important aspect of quality of life, and therefore every effort should be made to improve oral health, especially in a group of people already disadvantagedly affected by their disease. Prevention of oral disease and a careful dental treatment plan is essential for the oral and over-all health of individuals with epilepsy.

There are limited studies on oral health and dental status of patients with epilepsy. Most of the studies have been concentrated on the periodontal status in relation to antiepileptic medications. Salivary effects of VPA are reported in a few studies.

The periodontal index scores are significantly higher in patients with epilepsy. The dental and periodontal health of children with epilepsy are probably the result of a combination of such factors as, neglected oral hygiene, oral cavity injuries and possible side effects of AEDs. Gingival overgrowth due to PHT usage has been well studied. Gingival hyperplasia was notified about 50% of patients taking this medication. Despite the development of new alternative medications which are equally effective but with fewer side effects, PHT remains to be one of the most commonly used drugs.

None of the patients in our study was using PHT. Gingival enlargement was observed in 3 patients who were using only VPA, and in 2 patients who were receiving a combined AED’s, VPA with CBZ.

Children with epilepsy who are prescribed AEDs in syrup form may have caries problems due to the higher sugar content in the medication, particularly if the dose is taken at night. In present study, 27 children with epilepsy were examined. Although there is no statistically significance in df-t scores between two study groups, the scores were estimated to be higher in epilepsy groups than the control subjects.

The more recent antiepileptic drugs produce oral problems rarely. Xerostomia and stomatitis have been reported rarely as side effects of CBZ, and rash that may involve the oral cavity has been associated with lamotrigine and can be exacerbated by the concomitant use of VPA. Medication-related changes in the saliva of epileptic patients include elevations in antimicrobial proteins. Although salivary protein concentrations may be higher, the actual amount of saliva present in the mouth is very little. Lysozyme is produced by neutrophils. Lysozyme is a major constitutive product continuously secreted by the inflammatory cells of the monocyte-macrophage series. The presence of lysozyme in biological fluids such as saliva is an important factor in the non-specific defense mechanism of the body against microbial invasion. There has been a significant amount of effort on the part of various investigators to relate differences in the concentration of lysozyme in human saliva to various oral or systemic disease states. Epileptic patients on long-term therapy with a single anticonvulsant showed enhanced

### Table 3. The (mean±SD) salivary flow rates, buffering capacity and salivary lysozyme concentrations of study and control groups.

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>VPA+other AEDs</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary Flow Rate*</td>
<td>0.33±0.12</td>
<td>0.41±0.12</td>
<td>0.50±0.38</td>
<td>0.389</td>
</tr>
<tr>
<td>Buffering Capacity**</td>
<td>4.91±1.05</td>
<td>4.40±0.68</td>
<td>4.96±0.51</td>
<td>0.174</td>
</tr>
<tr>
<td>Lysozyme* Concentrations</td>
<td>97.39±92.48</td>
<td>118.92±91.51</td>
<td>7.80±4.42</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SD: Standard deviation, VPA: 12 patients who were using only valproic acid, VPA+other AEDs: 15 patients who were using valproic acid in combination with different antiepileptic drugs.

* Kruskal Wallis, ** One-way ANOVA Test

### Table 4. The (mean±SD) plaque index, gingival index scores and salivary lysozyme concentrations of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>VPA+other AEDs</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque index</td>
<td>1.64±0.60</td>
<td>2.06±1.08</td>
<td>0.43±0.17</td>
<td></td>
</tr>
<tr>
<td>Gingival index</td>
<td>1.66±0.50</td>
<td>2.40±1.07</td>
<td>0.58±0.51</td>
<td></td>
</tr>
<tr>
<td>Lysozyme concentrations</td>
<td>97.39±92.48</td>
<td>118.92±91.51</td>
<td>7.80±4.42</td>
<td></td>
</tr>
</tbody>
</table>

One-way ANOVA Test, between groups, Spearman Correlation test r=0.609, p=0.047. SD: Standard deviation, VPA: 12 patients who were using only valproic acid, VPA+other AEDs: 15 patients who were using valproic acid in combination with different antiepileptic drugs.
expression of peripheral benzodiazepine receptors (pBDZrs) on neutrophils, monocytes and lymphocytes. Neutrophils from patients on VPA and CBZ had impaired phagocytosis frequency. In this study, salivary flow rates were found in normal limits in all groups. Salivary buffering capacity in VPA+AEDs group was under critical limits and salivary lysozyme concentrations were significantly higher in VPA and VPA+AEDs groups. Low buffering capacity in VPA+AEDs group can be explained by concomitant use of drugs and inability to buffer the oral administration of exogenous acids. The higher lysozyme activity found in unstimulated saliva is in agreement with Smith and Hamilton and Modeer et al.

**CONCLUSION**

Although salivary flow rate and buffering capacity were not effected in epileptic patients using VPA, lysozyme concentration was effected dramatically. Combined usage of VPA and other AEDs also increased the oral side effects. Elevation of salivary lysozyme concentrations may directly affect periodontal and oral health of epileptic patients. We need more studies to develop new AEDs which are compatible with oral tissues.

*The authors declare that there are no conflicts of interest.*

**REFERENCES**


