THE EFFECT OF VALPROIC ACID THERAPY ON DENTAL AND PERIODONTAL HEALTH OF CHILDREN WITH EPILEPSY

Sevgi Zorlu[1], Didem Öner Özdaş[1], Gökşen İkikarakayalı[2], Arzu Pınar Erdem[2], Elif Sepet[2], Şule Can Trosola[3], Yegane Güven[3], Pınar Kıymet Karataban[1], Burak Tatlı[4], Meliha Mine Çalışkan[4]

[1]Istanbul Aydın University, Faculty of Dentistry, Department of Pediatric Dentistry, Istanbul
[2]University of Istanbul, Faculty of Dentistry, Department of Pediatric Dentistry, Istanbul
[3]University of Istanbul, Faculty of Dentistry, Department of Biochemistry, Istanbul
[4]University of Istanbul, Faculty of Medicine, Department of Pediatric Neurology, Istanbul

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 TEDAVİSİNİN PERİODONTAL VE DENTAL SAĞLIĞA ETKİSİ

ÖZET

Amaç: Bu araştırmanın amacı epilepsili çocuklarda valproik asit kullanımının periodontal ve diş sağlığı üzerine etkilerini değerlendirmek ve sağlıklı ve epilepsili çocuklarda tükürük lizozim konsantrasyonlarını karşılaştırmaktır.

Materyal ve Metot: Araştırmamızda 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. Tükürük lizozim konsantrasyonunu belirleyebilmek için her bir hastadan stimüle edilmemiş mikst tükürük toplandı. Tükürük akış hızı ve tamponlama kapasitesini belirlemek için standart yöntemler; tükürük lizozim konsantrasyonunu belirlemek üzere turbidimetrik yöntem kullanıldı. Çalışma ve kontrol grubu hastaların ağız-içi muayeneleri WHO (Dünya Sağlık Örgütü) kriterlerine uygun olarak yapıldı.

Bulgular: Epilepsisi olan çocuklarda tükürük lizozim seviyesi kontrol grubuna göre anlamlı derecede yüksek bulundu. Çalışma grubunun dişeti ve plak indeksi skorları da aynı şekilde yüksek olarak belirlendi. Gruplar arasında diş çürüğü, tükürük akış hızı ve tamponlama kapasitesi arasında anlamlı farklılık bulunmadı. Epilepsili çocuklarda periodontal sağlık ve tükürük lizozim seviyesi arasında pozitif korelasyon tespit edildi.

Sonuç: Tükürük lizozim seviyesindeki artışın epilepsili çocuklarda periodontal sağlığı doğrudan etkileyebileceği göz önüne alınarak ağız-içi dokulara daha uyumlu ve daha az yan etkili antiepileptik ilaçlar geliştirilebilmesi için bu verilerin ışığında daha fazla çalışmaya ihtiyaç duyulduğunu düşünmekteyiz.

Anahtar kelimeler: Valproik asit, antiepileptik ilaçlar, epilepsi, plak indeksi, gingival indeks, lizozim, tükürük. **Nobel Med 2017; 13(1): 26-30**

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.[2,5-9]

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.[4,6,7,10] Phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA), topiramate (TPM) are some of AEDs.[4,11] One of the possible side effects of the medication may include bone loss, which can lead to osteoporosis over the long-term of use.[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.[2,15-17] 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, or 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.[18] 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 platelet count resulting in 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.

	VPA	VPA+other AEDs	Control group	Total
Age(mean±SD)	9.78±2.86	9.4±1.84	10.83±2.04	9.82±2.16
Girls	n=6	n=8	n=6	n=39
Boys	n=6	n=7	n=6	

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

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

	VPA	VPA+other AEDs	Control group	*p**
df-t (mean±SD)	3.91±3.37	3.60±4.15	2.08±2.74	0.414
DMF-T (mean±SD)	1.58±2.11	2.00±2.10	1.50±1.51	0.745

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

cationic protein secreted primarily by intercalated duct cells. It is a muramidase that can lyse bacterial cells by cleaving peptidoglycans in the cell wall. Lysozyme may promote lysis when its enzymatic activity is blocked, possibly through activation of bacterial autolysins. It may inhibit the growth of candida. In addition to these antimicrobial effects, lysozyme can also aggregate bacteria or promote their adherence to saliva-coated hydroxyapatite.[22]

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 (dft) 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 split 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, clobazam).

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 groups 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).

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

	VPA	VPA+other AEDs	Control group	*p*
Salivary Flow Rate*	0.33±0.12	0.41±0.12	0.50±0.38	0.389
Buffering Capacity**	4.91±1.06	4.40±0.68	4.96±0.81	0.174
Lysozyme* Concentrations	97.39±92.48	118.92±91.51	7.80±4.42	0.001

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.

	VPA	VPA+other AEDs	Control group
Plaque index	1.64±0.60	2.06±1.08	0.43±0.17
Gingival index	1.66±0.50	2.40±1.07	0.58±0.51
Lysozyme concentrations	97.39±92.48	118.92±91.51	7.80±4.42

Oneway 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

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 disadvantageously affected by their disease.[19] Prevention of oral disease and a careful dental treatment plan is essential for the oral and over-all health of individuals with epilepsy.[2]

There are limited studies on oral health and dental status of patients with epilepsy.[2,4,15,19] Most of the studies have been concentrated on the periodontal status in relation to antiepileptic medications.[2,4] Salivary effects of VPA are reported in a few studies.[24,25]

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.[2,4,15,16,18] Gingival overgrowth due to PHT usage has been well studied.[4,16] 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.[4,26]

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.[27,28] 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 Iamotrigine 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.[22] Lysozyme is produced by neutrophils.[29] Lysozyme is a major constitutive product continuously secreted by the inflammatory cells of the monocyte-machrophage series.[23,30,31] 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.[29] Epileptic patients on long-term therapy with a single anticonvulsant showed enhanced

expression of peripheral benzodiazepine receptors (pBZrs) on neutrophils, monocytes and lymphocytes. Neutrophils from patients on VPA and CBZ had impaired phagocytosis frequency.[32] 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*.[23,33]

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.

CORRESPONDING AUTHOR: Sevgi Zorlu University of Istanbul Aydin, Faculty of Dentistry Department of Pediatric Dentistry, Kucukcekmece-Istanbul, 34295, Turkey. sevgizorlu@aydin.edu.tr

DELIVERING DATE: 24 / 11 / 2015 • **ACCEPTED DATE:** 14 / 06 / 2016

REFERENCES

1. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 1996; 71: 578-586.
2. Gurbuz T, Tan H. Oral health status in epileptic children. Pediatr Int 2010; 52: 279-283.
3. Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, Wiebe S. National and regional prevalence of self-reported epilepsy in Canada. Epilepsia 2004; 45: 1623-1629.
4. Aragon CE, Burneo JG. Understanding the patient with epilepsy and seizures in the dental practice. J Can Dent Assoc 2007; 73: 71-76.
5. Wallace SJ. Definitions. In Wallace SJ, editor. Epilepsy in children. pp. 1-4. London: Chapman and Hall; 1996.
6. Connock M, Frew E, Evans BW, et al. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. Health Technol Assess 2006; 10: 118.
7. Appleton R, Gibbs J. Epilepsy in childhood and adolescence. London: Martin Dunitz; 1995.
8. Hadjiloizou SM, Bourgeois BF. Antiepileptic drug treatment in children. Expert Rev Neurother 2007; 7: 179-193.
9. Mehmet GS, Ilknur G, Mehmet S. Patient's viewpoint: information and understanding about epilepsy. Nobel Med 2011; 7: 94-101.
10. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 314-319.
11. Jacobsen PL, Eden O. Epilepsy and the Dental Management of the epileptic patient. J Contemp Dent Pract 2008; 9: 54-62.
12. Greenwood M, Meechan JG. General medicine and surgery for dental practitioners. Part 4: Neurological disorders. Br Dent J 2003; 195: 19-25.
13. Sobaniec H, Sobaniec W, Sendrowski K, Sobaniec S, Pietruska M. Antioxidant activity of blood serum and saliva in patientswith periodontal disease treated due to epilepsy. Adv Med Sci 2007; 52: 204-206.
14. Turner MD, Glickman RS. Epilepsy in the oral and maxillofacial patient: current therapy. J Oral Maxillofac Surg 2005; 63: 996-1005.
15. Tan H, Gurbuz T, Dagsuyu IM. Gingival enlargement in children treated with antiepileptics. J Child Neurol 2004; 19: 958-963.
16. Sukuroglu E, Guncu GN, Kilinc K and Caglayan F. Using salivary nitrite and nitrate levels as a biomarker for drug-induced gingival overgrowth. Front Cell Infect Microbiol 2015; 5: 87.
17. Costa AL, Yasuda CL, Shibasaki W, et al. The association between periodontal disease and seizure severity in refractory epilepsy patients. Seizure 2014; 23: 227-230.
18. Jovanović S, Gajić I, Radivojević V. Risk factors for oral changes in children with epilepsy – Informative Article. Serbian Dental Journal 2009; 56: 33-39
19. Károlyházy K, Kovács E, Kivovics P, Fejérdy P, Arányi Z. Dental status and oral health of patients with epilepsy: an epidemiologic study. Epilepsia 2003; 44: 1103-1108.
20. Kavitha S, Anbuchelvan T, Mahalakshmi V, et al. Stevens-Johnson syndrome induced by a combination of lamotrigine and valproic acid. J Pharm Bioallied Sci 2015; 7: 756-758.
21. Fiske J, Boyle C, Epilepsy and Oral Care, Dental Update 2002; 29: 180-187.
22. Rudney JD, Smith QT. Relationships between levels of lysozyme, lactoferrin, salivary peroxidase, and secretory immunoglobulin a in stimulated parotid saliva. American Society for Microbiology 1985; 469-475.
23. Modeer T, Dahllof G, Theorell K: Oral health in non-institutionalized epileptic children with special reference to phenytoin medication. Community Dent Oral Epidemiol 1986; 14: 165–168.
24. Henskens YM, Strooker H, van den Keijbus PA, Veerman EC, Nieuw Amerongen AV. Salivary protein composition in epileptic patients on different medications. J Oral Pathol Med 1996; 25: 360-366.
25. Siqueira WL, Santos MT, Elangovan S, Simoes A, Nicolau J. The influence of valproic acid on salivary pH in children with cerebral palsy. Spec Care Dentist 2007; 27: 64-66.
26. Stoopler ET, Sollecito TP, Greenberg MS. Seizure disorders: update of medical and dental considerations. Gen Dent 2003; 51: 361-366.
27. Menezes VA, Cavalcanti G, Mora C, Garcia AFG, Leal RB. Pediatric medicines and their relationship to dental caries Braz. J Pharm Sci 2010; 46: 157-164.
28. Neves BG, Pierro VS, Maia LC. Perceptions and attitudes among parents and guardians on the use of pediatric medicines and their cariogenic and erosive potential. Cien Saude Colet 2007; 12: 1295-1300.
29. Jenzano JW, Hogan SL, Lundblad RL. Factors influencing measurement of human salivary lysozyme in lysoplate and turbidimetric assays. J Clin Microbiol 1986; 24: 963-967.
30. Gordon S, Todd J, Cohn ZA. In vitro synthesis and secretion of lysozyme by mononuclear phagocytes. Exp Med 1974; 139: 1228-1248.
31. Gordon LI, Doikm-As SD, Kay NE, et al. Modulation of inflammation by lysozyme, a product of inflammatory cells. Clin Res 1978; 26: 554.
32. Caldiroli E, Marino F, Cosentino M, et al. Peripheral benzodiazepine receptor expression on leukocytes and neutrophil function during anticonvulsant monotherapy. Pharmacology 1998; 57: 215-221.
33. Smith QT, Hamilton MJ. Salivary composition, phenytoin ingestion and gingival overgrowth. J Periodontol 1981; 52: 673-679.