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Original Article

Efficiency of Choroidal Thickness Monitoring to Prevent Topiramate Induced Acute Angle Closure Glaucoma

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ABSTRACT

The aim of this study is to investigate early findings of the choroidal effusion induced by topiramate use which is thought to be responsible for bilateral acute angle closure glaucoma. Enhanced depth imaging (EDİ) spectral domain optical coherence tomography (SD-OCT) recordings of 34 patients who has been used topiramate for the prophylaxis of migraines, before and after 2 weeks of drug use were retrospectively investigated. Alterations in subfoveal choroidal layer thicknesses and peripapillary retinal nerve fiber layer (RNFL) thickness were measured manually by two masked observers. The mean measurements of subfoveal choroidal layer thickness were 315.67±80.98 µm before use of the drug and 314.89±76.40 µm in 2nd week of drug use. However, this slight decrease was not statistically significant. The mean peripapillary RNFL thickness was 104.47±10.48 µm before use of the drug, and significant thinning was found only in the temporal quadrant during follow-up after use of the drug (p=0.008). No subclinical subfoveal choroidal effusions were encountered using EDİ SD-OCT in patients after 2 weeks of topiramate use. Further studies are needed to find out the cause of bilateral ciliochoroidal effusion related with topiramate use.

Key words: *Choroidal effusion, topiramate, acute angle closure glaucoma, optical coherence tomography*

Topiramata Bağlı Akut Açı Kapanması Glokomunu Önlemede Koroidal Kalınlık İzleminin Etkinliği

ÖZET

Bu çalışmamızın amacı bilateral akut açı kapanması glokomu gelişiminden sorumlu olduğu düşünülen topiramatın neden olduğu koroidal effüzyona ait erken bulguları araştırmaktır. Migren profilaksisi için topiramat kullanan 34 hastanın, ilaç alımından önce ve 2 hafta sonra alınan enhanced depth imaging (EDİ) spektral optic koherens tomografi (S-OKT) kayıtları retrospektif olarak incelendi. Subfoveal koroidal tabaka ve peripapiller retinal sinir lifi tabakasındaki kalınlık değişimleri birbirine kör iki gözlemci tarafından manuel olarak ölçüldü. Subfoveal koroidal tabaka kalınlıklarının ortalaması ilaç kullanımından önce 315.67 ± 80.98 µm ve ilaç kullanımının 2. haftasında 314.89 ± 76.40 µm idi. Ancak bu hafif azalma istatistiksel olarak anlamlı değildi. Retina sinir lifi tabakası kalınlıklarının ortalaması ilaç kullanımından önce 104.47 ± 10.48 µm idi ve ilaç kullanımı sonrasındaki izlemde sadece temporal kadranda anlamlı bir incelme bulundu (P = 0.008). Topiramatın 2 haftalık kullanımı sonrasında EDİ S-OKT ile subklinik subfoveal koroidal effüzyona rastlanmamıştır. Topiramat kullanımı ile ilişkili olan bilateral siliokoroidal effüzyonun sebebini ortaya çıkarmak için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *Koroidal effüzyon, topiramat, akut açı kapanması glokomu, optik koherens tomografi*

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INTRODUCTION

Topiramate is a sulfamate-substituted monosaccharide that was approved as an effective and safe drug by the Food and Drug Administration in 1996 for the treatment of epilepsy and in 2004 for the prophylaxis of migraines (1). In recent years, the number of reported adverse effects of this drug has increased, and the use of the drug has broadened (2). In the literature, some patients developed bilateral acute angle-closure glaucoma (AACG) and acute myopia with the use of topiramate, the majority of these symptoms, were reported to develop especially during first two weeks of the treatment, and were independent of the dose (3). Upon examination performed with B-scan ultrasonography (USG), ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (OCT), these effects were associated with the forward displacement of the iris-lens diaphragm, which occurred secondary to the development of ciliochoroidal effusion (3-7). Blurred vision is the most frequent complaint, and acute myopia can also develop (4,6). Some patients, particularly those presenting with AACG, have been mistakenly diagnosed with migraine attacks and administered inappropriate treatment, the failure to decrease intraocular pressure (IOP) has led to permanent visual loss (3). In some cases of topiramate-associated angle-closure with acute myopia ciliochoroidal effusions can be observed by UBM, even when the IOP is low (4,7). While the pathophysiology remains unclear, ciliochoroidal effusions are thought to originate from an immune reaction related to the sulfonamide content of topiramate or from an idiosyncratic reaction (2,8). Two recent prospective studies reported no angle closure and no change in scleral thickness with topiramate use (8); however, an increase in retinal nerve fiber layer (RNFL) thickness was observed via OCT (9). Although serious ocular adverse effects are not observed in the majority of patients taking topiramate, the use of this drug may cause subclinical choroidal effusion. This phenomenon has not yet been reported in the literature.

Until recently, choroidal thickness could only be evaluated by ultrasound. However, the detection of changes in choroidal thickness was difficult because of low image resolution (10). Recently, OCT, which is a repetitive and cross-sectional imaging technique with high resolution, has been more commonly utilized in the investigation of the retina and RNFL (11,12). Choroidal imaging with enhanced depth imaging (EDI) -OCT, is defined by Spadie et al. (13), has led to the opportunity to investigate the effects of many ocular diseases and associated physiological changes of the choroid layer (14-16). In our department, EDI - OCT is used for routine eye examination, as well as for all of the control patients referred from neurology department after initiating topiramate.

Because the early recognition of choroidal changes can prevent poor outcomes of AACG in topiramate use, we aimed to determine whether subclinical changes in the choroidal layer occur by using EDI - OCT recordings before and after the drug use.

MATERIALS AND METHODS

This is a retrospective observational study, which was conducted at the ophthalmology and neurology departments of the Konya Training and Research Hospital between June 2011 and July 2012. Neurology patients; who were referred to ophthalmology department to investigate the adverse effects of topiramate treatment for migraine prophylaxis were included in this study. Of 89 patients whose records were investigated, 34 patients were enrolled in the study due to their regular use of the study drug and their compliance with follow-ups. The study was conducted under a protocol approved by the Canakkale Onsekiz Mart University Medical Faculty Ethics Committee and was in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. All patients referred for an ophthalmology consult underwent an ophthalmic examination in our department, which include corrected visual acuity, IOP, and anterior and posterior segment evaluations. Patients with suspected glaucoma also underwent a visual field test. During the same examination, EDI - OCT and RNFL measurements were performed on the right eyes of each patient with OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Those with normal eye findings before the use of topiramate were enrolled. İndividuals who had a history of intraocular trauma, glaucoma, unstable and uncontrolled cardiovascular, renal or pulmonary diseases, diabetes, pregnancy, spherical and cylindrical refractive errors over ± 3 diopters were excluded.

For EDI - OCT, foveal-centered vertical and horizontal two line scans were performed in an assay of 100 frames, 30° and high resolution (HR). The subfoveal thickness was calculated by obtaining a mean measurement of vertical and horizontal thicknesses. The choroidal thickness was manually measured via the software in the OCT de-

vice with magnified images (×200). The distance from the hyperreflective line at the base of retina pigment epithelium layer to the hyporeflective line in the outer sclerochoroidal interface was accepted as the choroidal thickness. To obtain better images of the choroidal layer, contrast assays were altered; if necessary. However, automatic measurements performed by the device at the peripapillary, nasal, superior, temporal and inferior quadrants were recorded for thickness of the RNFL, and recordings with a quality (Q) below 20 were excluded. In addition to a general eye examination, EDI-OCT and RNFL measurements were performed on the right eyes of each patient at 2 weeks after referral to our clinic subsequent to the initiation of topiramate (25 mg/day during the 1st week and 50 mg/day starting the 2nd week). Using the eye tracking feature of the Spectralis OCT, which relies on retinal recognition technology, an accurate comparison could be performed between sequential scans. Subfoveal choroidal thickness measurements were thus obtained from the same region for all visits. To decrease the effect of diurnal changes, only the patients whose measurements were conducted during the same time frames (morning and afternoon) were enrolled in the study. Two masked observers (S.K and M.O) independently measured all recorded OCT images of patients.

A statistical analysis was performed using IBM SPSS; version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented the average, standard deviation and median [interquartile range]. After the assessment of normality assumption, a paired samples t-test and the Wilcoxon Rank Sum test were used to compare the distribution of choroidal and RNFL thickness between the initial examination and the 2nd week. Paired samples t-test was used to compare measurements of observers. A P-value of less than 0.05 ($p< 0.05$) was regarded as statistically significant.

RESULTS

The measurements of 34 eyes (3 men and 31 women) were assessed. The mean age of the patients was 37±9.99 years (range: 17-64 years). The best corrected visual acuity was 20/20 in all patients at their initial and second week examination. Also the anterior and posterior segments were within normal limits at second visits. In terms of IOP, no significant differences were observed among the patients before the use of the drug (mean IOP was

***Table 1**. Change of subfoveal choroidal and retinal nerve fiber layer (RNFL) thickness with optical coherence tomography (OCT) at 2nd week*

Mean±Standard Deviation Median (Interquartile Range)	İnitial (n=34)	2nd week (n=34)	p-value *
Choroidal thickness			
Subfoveal	315.67±80.98	314.89±76.40	
	301.75 (134)	319.75 (119)	ap=0.887
RNFL thickness			
Temporal	73.68±11.41	72.44±11.11	
	70.50(14)	69(16)	bp=0.008
Temporal inferior	151.47±20.16	150.53±21.11	
	155(30)	152.50(30)	ap=0.480
Temporal superior	142.29±16.55	141.24±16.88	
	142.50(24)	141.50(23)	ap=0.437
Nasal	80.74±14.28	80.74±14.63	
	83(20)	81(21)	ap=1.000
Nasal inferior	132.12±29.16	133.09±31.83	
	132.50(36)	136.50(46)	ap=0.549
Nasal superior	100.38±18.13	99.53±19.27	
	97.50(25)	102.50(28)	ap=0.521
Mean	104.47±10.48	104±10.86	
	104.50(19)	105(18)	ap=0.339

* Comparisons between initial and 2nd week
ap- Paired samples t test
bp- Wilcoxon Rank Sum test

14.71±2.69 mmHg). All IOP measurements were lower than 21 mmHg during the follow-up visits.

The mean subfoveal choroidal thickness was 315.67±80.98 µm at the initial visit and 314.89±76.40 µm at the 2nd week visit. No statistically significant difference was seen between the initial and 2nd week subfoveal choroidal thickness measurements (n = 34) (p> 0.05) (Table). Mean thickness of peripapillary RNFL were 104.47±10.48 at the initial visit and 104 ± 10.86 at the 2nd week visit. A significant decrease in RNFL thickness in the temporal quadrant was observed between the initial and 2nd weeks (p= 0.008). No correlation was seen between age and temporal RNFL thickness (p= 0.881).

Between the findings of the two observers performing the manual measurements with OCT software, there was no statistically significant difference (paired samples t-test) (p> 0.05).

DISCUSSION

Topiramate, a sulfamate-containing monosaccharide, is increasingly utilized in a growing number of diseases, such as obesity (17), bipolar disorder (18) and alcohol addiction (19). The increased use of topiramate has led to an increase in the occurrence of ocular adverse effects, the most significant of which is bilateral AACG, a condition that requires urgent treatment (3). In patients with bilateral AACG resulting from topiramate use, ciliochoroidal effusion and anterior displacement of the iris-lens diaphragm are observed upon examination with a B-scan USG, UBM, Scheimpflug camera and anterior segment OCT (4-7). These findings may account for the mechanism of developmental of AACG and acute myopia. Anterior displacement of the iris-lens diaphragm may be due to ciliary thickness, zonular relaxation and distention of the lens. In a study performed by Craig et al. (6), lens thickness was shown to be decreased, suggesting that a change in choroidal thickness might be the primary factor in the etiology of topiramate-induced glaucoma. Measurements performed in the posterior segment where the choroid is thicker may increase the accuracy of the evaluation. In particular, evaluation of subfoveal choroidal thickness may be valuable to detect early changes.

Until recently, the choroidal layer of the posterior pole could only be evaluated by B-scan USG, which was unable to show minimal changes in choroidal thickness. Previously reported cases of topiramate-induced AACG have been diagnosed and documented by demonstrating significant choroidal and/or ciliochoroidal effusion by B-scan USG or UBM (3-7). Although IOP was not significantly increased in some patients, retinal changes with OCT (4,7,9) and ciliary effusion upon examination via UBM (4) could be demonstrated within the first two weeks. Gualtieri and Janula (20) also reported isolated (unassociated with glaucoma and/or induced myopia) acute maculopathy after taking 100 mg of topiramate for 6 days, stratus OCT in this study showed, retinal folds and choroidal layer plicae. When we consider these reported cases, it appears that the posterior segment, particularly the choroidal layer, can be evaluated to detect early signs of topiramate associated ocular adverse effects. In a prospective study by Leung et al. that included 20 patients, no ciliochoroidal effusion was detected with UBM during a 4 - week follow-up period (8). In our study, changes in subfoveal choroidal thickness were monitored with EDI - OCT after 2 weeks of topiramate use; however, our results demonstrated that there was not a statistically significant difference between the thickness at the two time periods (initial and 2nd week) (P > 0.05). In both studies, topiramate was not shown to result in subclinical choroidal changes in the study group. Ocular adverse effects are likely to occur only in patients who are sensitive to topiramate and who may have idiosyncratic or immune reactions to the drug. This explanation is supported by our findings.

Topiramate is generally administered at a dose of 50 - 100 mg/day and this dose is achieved by increasing the dose by 25 mg/day per week. Although adverse effect due to topiramate may be seen with a therapeutic dose (21), overdoses of topiramate have not been associated with abnormal ocular findings; this finding supports the theory that the adverse effects are secondary to an idiosyncratic reaction (22). In another study conducted by Fraunfelder et al., 3 patients who developed AACG showed an improvement after discontinuation of topiramate but also showed recurrence of the adverse effect after readministration of topiramate (3). The recurrence of the ocular adverse effects in only a portion of the patients treated with topiramate is considered to be effective an idiosyncratic reaction. According to previously presented case series, AACG develops primarily in 2 weeks (83%) following the treatment of migraines with topiramate at doses of 25 or 50 mg/day (2,3,6). Therefore, measurements taken prior to drug initiation and during the 2nd weeks of drug administration is appropriate to determine whether

the topiramate exerts adverse effects on the eyes.

Of the adverse effects, the most significant one that requires urgent treatment is bilateral AACG. In patients treated with topiramate who present with AACG, the first action is to discontinue topiramate and start antiglaucomatous treatment. Findings such as acute myopia and macular stria also improved with the discontinuation of topiramate (3,4). Iridotomy remains ineffective because the development of glaucoma is not a result of pupillary block. In a study by Fraunfelder et al. with 115 patients, surgical and laser iridectomy was performed on 21 patients, but permanent visual loss was reported in 7 cases despite these interventions (3). The diagnosis of AACG should considered because if this diagnosis is not considered, the treatment protocol instituted may be inappropriate for the treatment of primary angle-closure glaucoma. Complaints of eye pain are often diagnosed as novel migraine attacks. Neurologists may subsequently increase the dose of topiramate and ophthalmologists may perform peripheral laser iridectomy and give topical pilocarpine for suspected primary angle-closure; this increases the duration of patients' exposure to high IOP. In patients with previously diagnosed glaucoma and with advanced-stage glaucoma, a higher IOP may lead to dramatic outcomes and even to complete visual loss because the number of intact neurons decreases. The investigation of subfoveal choroidal thickness performed with EDI - OCT in the present study may be beneficial for early detection. The mean subfoveal choroidal thickness in the controls prior to drug intake was 315.67 ± 80.98, however, in other studies, mean subfoveal choroidal thicknesses in normal individuals were reported to be lower at thicknesses of 272±81 (23), 287±76 (24) and 270±51 (25). These differences may arise from ethnic differences. The values of normal choroidal thicknesses as determined by a larger series may be used as a reference for the early diagnosis of AACG in topiramate uptake.

A prospective study performed by Ozturk et al.(9) suggested that the thickness of the RNFL may be affected by the carbonic anhydrase isoenzymes in the Muller cells, an increase was detected in the mean peripapillary RNFL thickness in patients treated with topiramate after the measurements. However, when each quadrant was analyzed individually, no differences were observed. The increase seen in the mean RNFL thickness was attributed to an increase in the thickness of the internal limiting membrane into which the Muller cells extend. In our study, we assessed alterations in peripapillary RNFL thicknesses via OCT; while significant thinning was detected in the temporal quadrant (P = 0.008), no significant difference was found when the quadrants were averaged (P > 0.05). On the basis of this finding, it was suggested that topiramate at lower doses (25 - 50 mg/day) may affect RNFL thickness via carbonic anhydrase enzymes in patients who do not have idiosyncratic reactions to topiramate. However, the observed differences most likely originated from the small number of participants in both studies.

Because our study was retrospective, it had various limitations. No gonioscopy or measurements of axial length were performed in each patient because the patients using topiramate were only scanned to detect adverse effects and because there was no predetermined decision to investigate several parameters. Those with glaucomatous alterations on ophthalmic examination were excluded from the study. However, patients with narrow-angle glaucoma who had not yet developed symptoms may have still been included. In the study by Leung et al.(8), two patients were reported to have narrow-angle prior to drug intake, but no angular change was observed after the initiation of topiramate. Having narrow-angle is not yet clear contraindication for use of topiramate, because choroidal effusions and anterior displacement of the ciliary body have not been observed in every patient who use topiramate.

In the present study, alterations in choroidal thicknesses due to the use of topiramate were meticulously investigated by EDI - OCT. The drug did not to lead to subclinical choroidal effusion in patients who did not develop AACG after 2 weeks of topiramate use. EDI - OCT may be beneficial for differentiating primary AACG due to the use of topiramate, but these findings would need to be supported with more long-term studies with a larger sample size.

REFERENCES

1. *United States Food and Drug Administration; Ortho-McNeil Pharma- ceutical Inc. FDA approved labeling text. 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020505s040s045,020844s035s037lbl.pdf. Accessed August 27, 2012.*
2. *Abtahi MA, Abtahi SH, Fazel F et al. Topiramate and the vision: a systematic review. Clin Ophthalmol 2012;6:117-31.*
3. *Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. Ophthalmology 2004;111:109-11.*

4. Natesh S, Rajashekhara SK, Rao AS, Shetty B. Topiramate-induced angle closure with acute myopia, macular striae. Oman J Ophthalmol 2010;3(1):26-8.

5. Aminlari A, East M, Wei W, Quillen D. Topiramate induced acute angle closure glaucoma. Open Ophthalmol J 2008;2:46-7.

6. Craig JE, Ong TJ, Louis DL, Wells JM. Mechanism of topiramate-induced acute-onset myopia and angle closure glaucoma. Am J Ophthalmol 2004;137(1):193-5.

7. Van Issum C, Mavrakanas N, Schutz JS, Shaarawy T. Topiramate-induced acute bilateral angle closure and myopia: pathophysiology and treatment controversies. Eur J Ophthalmol 2011;21(4):404-9.

8. Leung DY, Leung H, Baig N et al. Topiramate and asymptomatic ocular angle narrowing: a prospective pilot study. Eye (Lond) 2009;23(11):2079-81.

9. Ozturk BT, Genc E, Tokgoz M, Kerimoglu H, Genc BO. Ocular changes associated with topiramate. Curr Eye Res 2011;36(1):47-52.

10. Malhotra A, Minja FJ, Crum A, Burrowes D. Ocular anatomy and cross-sectional imaging of the eye. Semin Ultrasound CT MR 2011;32:2-13.

11. Regatieri CV, Branchini L, Fujimoto JG, Duker JS. Choroidal imaging using spectral-domain optical coherence tomography. Retina 2012;32(5):865-76.

12. Kotowski J, Wollstein G, Folio LS, Ishikawa H, Schuman JS. Clinical use of OCT in assessing glaucoma progression. Ophthalmic Surg Lasers Imaging 2011;42:6-14.

13. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008;146(4):496-500.

14. Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. Eye (Lond) 2010;24:1743-56.

15. Koizumi H, Yamagishi T, Yamazaki T, Kawasaki R, Kinoshita S. Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol 2011;249(8):1123-8.

16. Torres VL, Brugnoni N, Kaiser PK, Singh AD. Optical coherence tomography enhanced depth imaging of choroidal tumors. Am J Ophthalmol 2011;151:586-93.

17. Supuran CT, Di Fiore A, De Simone G. Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. Expert Opin Emerg Drugs 2008;13(2):383-92.

18. Mula M, Cavanna AE, Monaco F. Psychopharmacology of topiramate: from epilepsy to bipolar disorder. Neuropsychiatr Dis Treat 2006;2(4):475-88.

19. Johnson BA, Ait-Daoud N. Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. Curr Pharm Des 2010;16(19):2103-12.

20. Gualtieri W, Janula J. Topiramate maculopathy. Int Ophthalmol 2013;33(1):103-6.

21. Spaccapelo L, Leschiutta S, Aurea C, Ferrari A. Topiramate-associated acute glaucoma in a migraine patient receiving concomitant citalopram therapy: a case-report. Cases J 2009;2(1):87.

22. Wiśniewski M, Łukasik-Głebocka M, Anand JS. Acute topiramate overdose--clinical manifestations. Clin Toxicol (Phila) 2009;47(4):317-20.

23. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. Am J Ophthalmol 2010;150(3):325-9.

24. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol 2009;147(5):811-5.

25. Shin JW, Shin YU, Cho HY, Lee BR. Measurement of choroidal thickness in normal eyes using 3D OCT-1000 spectral domain optical coherence tomography. Korean J Ophthalmol 2012;26(4):255-9.