Evaluation of the Effects of Duloxetine Treatment on Anterior Segment Parameters by Optical Coherence Tomography

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Abstract

Purpose: To evaluate the effects of Duloxetine on anterior segment parameters and intraocular pressure(IOP) in open angle eyes.

Methods: 38 eyes of 38 patients with fibromyalgia who had open or wide open angles according to the Shaffer classification. Anterior segment optic coherence tomography was performed before and after (month 3) Duloxetine treatment. IOP, central corneal thickness(CCT), corneal endothelial cell density(CECD) and anterior chamber depth(ACD) were also recorded and evaluated.

Results: No statistically significant difference was determined in IOP, CCT and CECD($p > 0.05$). However, a statistically significant increase was determined in both the temporal and nasal anterior chamber angle, angle opening distance, nasal trabecular-iris space area and ACD values between the baseline and month 3 ($p < 0.001$).

Conclusion: We think that the short term use of Duloxetine does not lead to clinically significant changes despite their statistically significant effects on the anterior chamber parameters.

Introduction

Duloxetine is a strong serotonin (5-HT) and norepinephrine reuptake inhibitor (SNRI) and is commonly used in the treatment of major depressive disorder, diabetic neuropathic pain, stress urinary incontinence, generalized anxiety disorder, and fibromyalgia. [1]. Some studies in the literature have reported that duloxetine [2, 3] and Selective Serotonin Reuptake Inhibitors (SSRI) [4–6] may lead to angle-closure glaucoma. However, these have been in the form of case reports or case series. Before starting the use of these and similar drugs in our clinical practice for patients referred to us from various clinics, cases with a risk of angle closure or with a narrow angle are first determined. Patients whose treatment plan continues unaltered despite such findings are informed about angle-closure glaucoma and followed-up closely. However, the effects of these drugs on parameters related to the anterior chamber and angle have not been fully clarified, especially in open-angle eyes. We aimed to reveal how the use of duloxetine in open-angle eyes affects the intraocular pressure(IOP), irido-corneal angle parameters such as anterior chamber angle(ACA), angle opening distance(AOD), nasal trabecular-iris space area (TISA) and other anterior segment parameters such as central corneal thickness(CCT), anterior chamber depth(ACD) and corneal endothelial cell density(CECD) in this study.

Methods

Study population

The study was started after permission was obtained from the local ethics committee. The 38 eyes of 38 patients over the age of 18 years who had not undergone intraocular surgery previously, had an intraocular pressure below 20 mmHg, did not use anti-glaucoma treatment, had grade 3 (20-34 degrees)

or 4 (35-45 degrees) angles according to the Shaffer classification; did not suffer from hypertension, diabetes, or other diseases or use any systemic medication; volunteered to participate in the study, and could read and understand the informed consent form were included in the study. The right eye was used when both eyes were suitable for inclusion as the measurements generally showed a positive correlation between the two eyes [7].

Duloxetine Treatment

The IOP was measured with Goldmann applanation tonometry and the anterior chamber and angle parameters of CECD, ACD and CCT were determined with anterior segment optical coherence tomography (AS-OCT) at the beginning and at the end of the 3rd month of treatment in patients who were started Duloxetine capsule 30 mg once a day for the diagnosis of fibromyalgia at the physical treatment and rehabilitation clinic.

AS-OCT

The baseline and 3rd month AS-OCT (NIDEK RS-3000, NIDEK Co. Ltd, Japan) measurements were performed by the same AS-OCT operator, nasal and temporal quadrant (180° and 0° meridians) images were obtained with the patient in a darkened room. Adequate centration and quality for the analysis were ensured by using the ACA while the CCT was measured using the corneal radial scan pattern.

The angle between the posterior corneal angle and the tangential iris line was measured to calculate the ACA width. The apex of the iris recess and the scleral spur were first identified manually, followed by the use of standard parameters for ACA width analysis. The perpendicular distances to the iris anterior surface from the trabecular meshwork at positions 750 μ m and 500 μ m anterior to the scleral spur were accepted as the angle opening distances (AOD 750 and AOD 500, respectively). The trapezoid-shaped area with boundaries constituted by the AOD 750 or AOD 500, the anterior iris surface, the inner corneoscleral wall, and the perpendicular distance from the scleral spur to the opposing iris was accepted as the trabecular iris space area (TISA 750 and TISA 500, respectively) (Fig. 1).

ACD at baseline and the 3rd month of treatment was determined using biometry with the Monitor A&B Scan. A topical corneal anesthetic was administered and the biometry probe placed vertically at the central cornea. The mean value of five consecutive measurements was calculated to determine the ACD.

The IOP was measured with Goldmann applanation tonometry at baseline and the 3rd month of Duloxetine treatment.

Statistical analysis

The Kolmogorov-Smirnov test was used for confirmation of the normal distribution of study data. The t-test was used for statistical calculations between two dependent groups and p values < 0.05 and < 0.001 were accepted as statistically significant. The analysis software was SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the patients included in the study was 48.5 ± 13.9 years (range: 33 - 65 years). The 38 eyes (34 right eyes and 4 left eyes) of 38 patients (18 females, 20 males) were included in the study.

No statistically significant difference was found on comparing the IOP, CECD and CCT measurements before and after the treatment (p ; 0.214, 0.311, and 0.117, respectively). The demographic data and the IOP, CECD, and CCT values are summarized in Table-1.

Table-2 shows that the mean ACD value was 3.71 ± 0.57 mm (3.2 - 4.2 mm) before treatment and 3.13 ± 0.46 mm (3 - 3.8mm) after treatment ($p < 0.001$). The ACA, AOD 500 and 750, and TISA 500 and 750 measurements were statistically significantly higher at baseline than after treatment ($p < 0.001$).

Conclusion

SNRIs are commonly used in the treatment of major depressive disorder, diabetic neuropathic pain, stress urinary incontinence, generalized anxiety disorder, and fibromyalgia, due to their strong effect, favorable safety profile, and good tolerability. Venlafaxine and Duloxetine are the best-known drugs in this group. They act by blocking the reuptake of presynaptic serotonin and noradrenaline, and also dopamine to a smaller extent, in the central and peripheral nervous system. In this way, they increase the amount and effect of serotonin, noradrenaline, and dopamine in the synaptic gap. Considering that receptors for these neurotransmitters can be found in the ciliary body, iris, and various other parts of the eye [1], we believe think that frequent and long-term use of SRNIs could lead to various ocular effects.

Review of the baseline and 3rd month results of the patients with open and wide open iridocorneal angles referred to us in our study revealed no significant difference between the IOP, CECD, and CCT measurements. However, the anterior chamber depth was lower at the end of the study with a narrowing/decrease of angle parameters. There was no significant finding requiring discontinuation of Duloxetine treatment in any patient when the intraocular pressure and angle status were taken into account.

There are few clinical studies on the ocular side effects of the commonly used medication groups of SNRIs (Duloxetine, Venlafaxine, etc.) and SSRIs (Fluoxetine, Sertraline). Seitz et al. have evaluated the use of antidepressants in the last year in angle-closure glaucoma patients and found a positive correlation between such use and angle-closure in a population-based study [8]. SSRI agents have been reported to increase the intraocular pressure in another review, but this did not require discontinuation of the drugs and only required follow-up by the Ophthalmology team [9]. However, some case reports have indicated that SNRIs such as Duloxetine [2, 10] and Venlafaxine [11, 12], and SSRIs such as sertraline [13], paroxetine [14], and citalopram [15] can cause angle-closure glaucoma. The reason is reported in these studies as the serotonin receptors in the iris, cornea, and ciliary body. In other words, the increased adrenergic effects, weak anticholinergic activity, or ciliary congestion due to increased serotonin levels and mydriasis are thought to be the cause. We did not measure the pupillary diameter to evaluate the

mydriatic effects of these agents as there is already a consensus in the literature. The above studies emphasized that these drugs could increase the IOP and cause angle-closure glaucoma, but we do not believe the mechanism was fully elucidated as regards the effect on the iris, anterior chamber angle, and with detailed angle parameters. We believe there are many unexplained issues about the effects of these drugs on the anterior chamber and angle parameters, especially in eyes with an open angle. This group of drugs is generally used for a long time and in the population over a certain age. Concordantly, we believe that taking precautions in patients who are scheduled for anterior segment surgery due to retinal nerve fiber damage associated with chronic IOP elevation or possible anterior chamber narrowing, in addition to considering the effects of visual disturbances and light sensitivity due to the potential mydriasis on the quality of life are important in clinical practice. Gündüz et al. evaluated the ACA, ACD, ACV, CCT, IOP, and pupil diameter in patients using Duloxetine/Venlafaxine in their comprehensive study on patients using SSRIs. A significant increase in PD was found when compared to the control group in patients diagnosed with depression who had used Duloxetine/Venlafaxine for shorter and longer than 6 months, indicating the presence of mydriasis. Besides, a significant decrease in ACD was detected in the case of using the medication for more than 6 months. Another finding was a significant decrease in the IOP after long-term use [16]. Chen et al similarly revealed that long-term use of SSRIs does not increase the risk for IOP, and open or closed angle glaucoma [17]. However, another study published in 2017 reported in contrast that long-term and high-dose SSRI use increased the IOP and glaucoma risk. The same study also indicated that excluding severe systemic diseases and the relevant systemic medications was a weakness of the study design. [18]. Botha et al. have reported increased IOP with Venlafaxine that was started later in a patient diagnosed with open angle glaucoma in a case report [19]. Some other studies on the effects of SSRI agents on the IOP have also reported that the IOP may increase with the use of these drugs [9, 19]. We found no statistically significant difference in the IOP compared to the baseline after a usage period of 3 months in our study. We believe that the exclusion of patients with other systemic diseases and/or systemic medications in the current study makes our results more reliable.

Gündüz et al. have also investigated the anterior chamber and angle parameters in their study published in 2017 on open angle eyes in patients using SSRIs [19]. A decrease in the IOP was observed in depressed patients using SSRIs. A statistically significant increase was found in the pupil diameter but there was no significant change in the CCT, ACD, ACV, and ACA measurements. We also found no increase in IOP with SSRI use in the current study but there was a significant decrease in the angle parameter values and ACD. The reason could be some differences in the study design. For example, the Gündüz et al. [19] study included the 325 eyes of 166 patients using 6 different SSRI agents, while only one agent (Duloxetine, SNRI) was included in our study. Besides, we included only one eye of each patient in our study as we thought that it would show a statistically similar trend. However, our results may have been affected by our patient population not having other comorbid systemic diseases and not using any systemic drugs. The difference could also be explained by Duloxetine also blocking noradrenaline reuptake, unlike SSRI agents.

The eye contains nerves originating from the central and peripheral nervous system. All neurotransmitters/neuromediators of the brain and the relevant receptors are found in the neurons of the

iris, ciliary body, cornea, choroid, and also the retina, which is a part of the central nervous system. Serotonin (5-hydroxytryptamine or 5-HT) is found in the aqueous humor, and receptor sub-types such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₇, 5-HT₅, and 5-HT₄ have been detected in the iris-ciliary body complex. This suggests that serotonin may have effects on aqueous production, IOP regulation, iris configuration, and pupil diameter [20, 21]. We believe that the somewhat contradictory results from studies on SSRIs and SNRIs in the literature are due to the different effects of different receptors. For example, it has been revealed that 5-HT_{1A} and 2A decrease the IOP [22], while 5-HT_{2C} and 7 increase the IOP and cause mydriasis with their effect on the pupil sphincter [9]. Among the noradrenaline receptors, α -1 and α -2 have also been shown to decrease the IOP and cause mydriasis with their effect on the pupil dilator muscle [23]. Besides, Dopamine DA₁ and DA₂ receptors have been proven to act in regulating the IOP in various ways [24]. Considering all the above-mentioned mechanisms, these drugs could act on the IOP, ACD, and other anterior chamber parameters through various receptors and in various ways.

In conclusion, we found the use of Duloxetine in patients with no additional systemic disease or medication and with an open and wide anterior chamber angle decreased the anterior chamber depth and angle parameters although it did not lead to intolerable side-effects or major changes in the IOP and anterior chamber parameters. We think that the use of this drug for 3 months does not lead to clinically significant changes despite their statistically significant effects on the anterior chamber parameters. We also think that further studies with a longer duration and on a larger patient population are required to validate and develop these data.

Declarations

Acknowledgment

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Compliance with ethical standards

Conflicts of interest The author declare that they have no conflict of interest.

References

1. Knadler MP, Lobo E, Chappell J, Bergstrom R (2011) Duloxetine: clinical pharmacokinetics and drug interactions. Clin Pharmacokinet 50(5):281–294. doi: 10.2165/11539240-000000000-00000
2. Mahmut A, Tunc V, Demiryurek E, Gursoy A (2017) Bilateral acute angle-closure glaucoma induced by duloxetine. Ideggyogy Sz 30(9–10):358–360. doi: 10.18071/isz.70.0358
3. Shifera AS, Leoncavallo A, Sherwood M (2014) Probable Association of an Attack of Bilateral Acute Angle-Closure Glaucoma with Duloxetine. Ann Pharmacother 48(7):936–939. doi: 10.1177/1060028014529645

4. Chen HY, Lin CL, Lai SW, Kao CH (2016) Association of Selective Serotonin Reuptake Inhibitor Use and Acute Angle-Closure Glaucoma. *J Clin Psychiatry* 77(6):e692–e696. doi: 10.4088/JCP.15m10038
5. Ho HY, Kam KW, Young AL, Chan LK, Yu EC (2013) Acute angle closure glaucoma after sertraline. *Gen Hosp Psychiatry* 35(5):575.e1-2. doi: 10.1016/j.genhosppsy.2012.09.001
6. Achiron A, Aviv U, Mendel L, Burgansky-Eliash Z (2015) Acute angle closure glaucoma precipitated by olanzapine. *Int J Geriatr Psychiatry* 30(10):1101–1102. doi: 10.1002/gps.4327
7. Zhang HG, Ying GS (2018) Statistical approaches in published ophthalmic clinical science papers: a comparison to statistical practise two decades ago. *Br J Ophthalmol* 102(9):1188–1191. doi: 10.1136/bjophthalmol-2017-311529
8. Seitz DP, Campbell RJ, Bell CM et al (2012) Short-term exposure to antidepressant drugs and risk of acute angle-closure glaucoma in older adults. *J Clin Psychopharmacol* 32:403–407. doi: 10.1097/JCP.0b013e31825420a1
9. Costagliola C, Parmeggiani F, Sebastiani A (2004) SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 18(8):475–484. doi: 10.2165/00023210-200418080-00001
10. Shifera AS, Leoncavallo A, Sherwood M (2014) Probable Association of an Attack of Bilateral Acute Angle-Closure Glaucoma With Duloxetine. *Ann Pharmacother* 48(7):936–939. doi: 10.1177/1060028014529645
11. Zhou N, Zhao JX, Zhu YN, Zhang P, Zuo Y (2018) Acute Angle-Closure Glaucoma Caused by Venlafaxine. *Chin Med J (Engl)* 20(12):1502–1503. doi: 10.4103/0366-6999.233952
12. Ezra DG, Storoni M, Whitefield LA (2006) Simultaneous bilateral acute angle closure glaucoma following venlafaxine treatment. *Eye (Lond)*. 2006 20(1):128-9. doi: 10.1038/sj.eye.6701815
13. Ho HY, Kam KW, Young AL, Chan LK, Yu EC (2013) Acute angle closure glaucoma after sertraline. *Gen Hosp Psychiatry* 35(5):575.e1-2. doi: 10.1016/j.genhosppsy.2012.09.001
14. Sierra-Rodriguez MA, Saenz-Frances F, Santos-Bueso E, Garcia-Feijoo J, Gonzelez-Romero JC (2013) Chronic angle-closure glaucoma related to paroxetine treatment. *Semin Ophthalmol* 28(4):244–246. doi: 10.3109/08820538.2013.771193
15. Croos R, Thirumalai S, Hassan S, Davis Jda R (2005) Citalopram associated with acute angle-closure glaucoma: case report. *BMC Ophthalmol* 4:5:23. doi: 10.1186/1471-2415-5-23
16. Uçan Gündüz G, Parmak Yener N, Kılınçel O, Gündüz C (2018) How Does Usage of Serotonin Noradrenaline Reuptake Inhibitors Affect Intraocular Pressure in Depression Patients? *J Ocul Pharmacol Ther* 34(4):354–359. doi: 10.1089/jop.2017.0133
17. Chen HY, Lin CL, Kao CH (2015) Long-Term Use of Selective Serotonin Reuptake Inhibitors and Risk of Glaucoma in Depression Patients. *Med (Baltim)* 94(45):e2041. doi:10.1097/MD.0000000000002041
18. Chen VC, Ng MH, Chiu WC et al (2017) Effects of selective serotonin reuptake inhibitors on glaucoma: A nationwide population-based study. *PLoS ONE* 12(3):e0173005.

doi:10.1371/journal.pone.0173005

19. Gündüz GU, Parmak Yener N, Kılınçel O, Gündüz C (2018) Effects of selective serotonin reuptake inhibitors on intraocular pressure and anterior segment parameters in open angle eyes. *Cutan Ocul Toxicol* 37(1):36–40. doi: 10.1080/15569527.2017.1330270
20. Chidlow G, Hiscott PS, Osborne NN (2014) Expression of serotonin receptor mRNAs in human ciliary body: a polymerase chain reaction study. *Graefes Arch Clin Exp Ophthalmol* 242(3):259–264. doi:10.1007/s00417-003-0785-7
21. Sharif NA, Senchyna M (2006) Serotonin receptor subtype mRNA expression in human ocular tissues, determined by RT-PCR. *Mol Vis* 12:1040–1047
22. Sharif NA, McLaughlin MA, Kelly CR et al (2009) Cabergoline: Pharmacology, ocular hypotensive studies in multiple species, and aqueous humor dynamic modulation in the Cynomolgus monkey eyes. *Exp Eye Res* 88(3):386–397. doi:10.1016/j.exer.2008.10.003
23. Sharif NA (2010) Serotonin-2 receptor agonists as novel ocular hypotensive agents and their cellular and molecular mechanisms of action. *Curr Drug Targets* 11:978–993. doi: 10.2174/138945010791591278
24. Langham ME (1971) Role of adrenergic mechanisms in development and therapy of open-angled glaucoma. *Proc Roy Soc Med* 64:622–628

Tables

Table-1: Demographics and change in intraocular pressure, central corneal thickness and corneal endothelial cell density before and after duloxetine treatment.

	n=38	Before	After(month 3)	<i>p</i>
Age	Mean ± SD	48.5 ± 13.9		
	Range	33-65		
Gender F/M		18/20		
Eye R/L		34/4		
IOP,mmHg	Mean ± SD	14.1 ± 4.8	13.6 ± 6.3	0.19
	Range	10–19	9–21	NS
CCT, μm	Mean ± SD	532.9 ± 42.5	528.7 ± 40.9	0.33
	Range	471–588	471–588	NS
CECD, mm	Mean ± SD	2891.5 ± 212.3	2804.8 ± 204.7	0.4
	Range	2679–3122	2651–3107	NS
IOP intraocular pressure, CCT central corneal thickness, CECD corneal endothelial cell density, NS non-significant.				

Table-2: Change in anterior chamber depth and angle parameters after and before duloxetine therapy

	N=38	Before	After(month 3)	p
ACD,mm	Mean ± SD	3.71 ± 0.41	3.13 ± 0.46	0,021
	Range	3,2–4,1	3–3,8	S
Temporal angle				
ACA T, degree	Mean ± SD	33.17 ± 4.9	29.07 ± 5.81	0,001
	Range	27.8–41.1	25.2–36.3	HS
AOD500 T, µm	Mean ± SD	548.2 ± 73.6	501.6 ± 75.8	0,001
	Range	479–591	452–550	HS
AOD750 T, µm	Mean ± SD	732.5 ± 137.8	675.5 ± 112.9	0,001
	Range	674–787	624–732	HS
TISA500 T, mm ²	Mean ± SD	0.2002 ± 0.0718	0.172 ± 0.0703	0,001
	Range	0.167–0.209	0.151–0.202	HS
TISA750 T, mm ²	Mean ± SD	0.3097 ± 0.0547	0.266 ± 0.0501	0,001
	Range	0.288–0.315	0.236–0.302	HS
Nasal angle				
ACA N, degree	Mean ± SD	35.11 ± 6.9	28.99 ± 4.01	0,001
	Range	28.5–43.4	25.1–35.1	HS
AOD500 N, µm	Mean ± SD	569.4 ± 93.1	510.5 ± 76.9	0,001
	Range	499–604	459–563	HS
AOD750 N, µm	Mean ± SD	761.4 ± 187.1	735.4 ± 102.5	0,012
	Range	693–801	679–784	S
TISA500 N, mm ²	Mean ± SD	0.2311 ± 0.0815	0.1835 ± 0.0847	0,001
	Range	0.196–0.269	0.151–0.223	HS
TISA750 N, mm ²	Mean ± SD	0.3307 ± 0.0616	0.286 ± 0.0415	0,001
	Range	0.294–0.426	0.251–0.317	HS
ACD anterior chamber depth, ACA anterior chamber angle, AOD temporal angle opening distance AOD N, TISA nasal trabecular-iris space area, T temporal, N nasal, S significant, HS highly significant				

Figures

Figure 1

ACA, anterior chamber angle measuring the angle between the posterior angle of the cornea and the tangential iris line; AOD (angle opening distance) perpendicular distances from the trabecular meshwork and 500 mm; TISA (trabecular iris space area) the trapezoidal area bounded by the AOD 500, the anterior iris surface, the inner corneo-scleral wall and the perpendicular distance between the scleral spur and the opposing iris.