Archives of Clinical & Experimental Surgery

Original Article
Arch Clin Exp Surg 2019;8:28-32
doi:10.5455/aces.20180720071622

eJM eJManager OPEN ACCESS

Melatonin decreases eye pressure in depressive patients with normal intraocular pressure

Gokhan Ozdemir[1], Ebru Findikli[2]

ABSTRACT

Background/Aim: In this study, we aimed to show the effect of melatonin, a pineal hormone, on intraocular pressure in patients with depression and normal ocular tension.

Methods: Twenty depressive patients for whose agomelatine, a melatonin drug, was deemed necessary for treatment of the primary disease were enrolled in the study. Ocular pressures at baseline, second and fourth-week visits were recorded using a Tono-Pen and a Goldmann applanation tonometer.

Results: Our study revealed that oral agomelatine therapy reduced intraocular pressure in the normotensive patients. The baseline intraocular pressure was 12.6±2.8 mm Hg with the Tono-Pen and 14.8 mm Hg with applanation tonometry. At the fourth week visit, the pressure measured with Tono-Pen was 11.5±2.9 mm-Hg and the pressure measured with applanation tonometer was 13.5±2.8 mm-Hg ($p<0.05$ for both measurements). There was a pressure decline of 9% compared to the baseline.

Conclusion: Agomelatine is able to lower intraocular pressure in normotensive patients.

Key words: *Agomelatine, melatonin, intraocular pressure, depression*

Introduction

Melatonin (5-methoxy-N-acetyl tryptamine), a pineal hormone with versatile physiological functions, is secreted in all mammals including humans invariably. Discovered almost half a century ago, its unique actions, including calming effects, have subsequently been thoroughly researched by investigators [1].

Recent research has shown that melatonin, among many functions, may also serve in psychiatric disturbances. Ongoing studies suggest that depression may respond to treatment with some type of melatonin formulation. Currently, agomelatine, a melatonin drug, has been approved for the amelioration of depressive symptoms.

Intraocular pressure (IOP) is a functional condition maintained by the secretion of aqueous humor from the non-pigmented epithelium of the ciliary body. Although secretion of aqueous humor is necessary for the metabolism of intraocular tissues, over-secretion may elevate intraocular pressure and lead to a problematic illness, glaucoma, that may cause total vision loss.

Melatonin's ocular effects have been the focus of

Author affiliations : *[1]Department of Ophthalmology, [2]Department of Psychiatry, Faculty of Medicine, Kahramanmaraş Sütçüimam University, Kahramanmaraş, Turkey*
Correspondence : *Gokhan Ozdemir, MD, Department of Ophthalmology, Faculty of Medicine, Kahramanmaraş Sütçüimam University, Kahramanmaraş, Turkey*
e-mail: gozdemir@hotmail.com
Received / Accepted : *July 20, 2018 / October 05, 2018*

much research for some time. Melatonin may play a role in the maintenance of intraocular pressure. The existence of melatonin receptors in ocular tissues suggests that this hormone is involved in ocular pressure dynamics [2]. Although animal studies have revealed that melatonin may change intraocular pressure, human studies are still required to confirm this finding [3]. In this study, we aimed to show that melatonin, when given orally for the treatment of depression, changes intraocular pressures in nonglaucomatous eyes.

Materials and Methods

The research was approved by the Clinical Research Ethics Committee of the University and the Clinical Research Office of the Turkish Medicines and Medical Devices Agency (2016-144/142478). Patients who applied to the psychiatry polyclinic and were prescribed oral agomelatine (Valdoxan, Wicklow, Ireland) at 25 mg/day for the treatment of depression, were included in the study. The psychiatric problems encountered by the patients were considered appropriate to be treated by agomelatine independent from the study enrollment. Patients under any other systemic medications or with a history of ocular disease, past ocular surgery, any other ocular pathology confounding ocular pressure measurement, and those unable to conform study protocol were excluded from the study. Only the right eyes were used for statistical comparisons.

All patients were given the adequate explanation about the research and informed written consent was obtained. The drug was given to the patients based on the diagnosis of depression, which is a common indication of the drug. The patients underwent a complete ophthalmological examination including best corrected visual acuity, slit lamp biomicroscopy, posterior segment examination and intraocular pressure measurement. Intraocular pressure was measured by the same person masked to the treatment. IOP was measured with a Tono-Pen (Medtronic XL, Jacksonville, Florida, USA) after application of 5% topical proparacaine (Alcaine, Puurs, Belgium). After waiting 5 minutes to cancel the effect of Tono-Pen measurement on ocular pressure, intraocular pressure was measured with a Goldmann applanation tonometer after staining the ocular surface with fluorescein. For all measurements, the intraocular pressure was measured three times and the median was accepted as the valid pressure of the eye.

The ophthalmological examination and intraocular pressure measurement were performed at baseline, the second week and the end of one month, after which the study was terminated. The data was given as mean±standard deviation and analyses were performed by a statistics program (SPSS 17, IBM, Chicago ILL). The comparisons were made with paired t-test for parametric variables within the groups, and Student's t-test between the groups after the homogeneity of variances was found equal using Levene's test.

Results

Twenty patients, 12 female and eight male, were recruited in the study. The median age was 45 ±11 years (31-62 years). The mean age of the males was 44 ± 9 years and of the females was 45 ± 11 years. There was no difference between males and females with regard to age, weight and systemic disorders. Intraocular pressure was also the same at baseline between males and females. The mean baseline eye pressure was 12.7 mm-Hg in males and 12.4 mm-Hg in females ($p > 0.05$; Table 1). As we did not intend to evaluate any discrepancies or agreements between measurements obtained by the two methods (Goldmann and Tono-Pen), we did not compare them.

The intraocular pressure changed between 0.9 mm-Hg and 1.1 mm-Hg with Tono-Pen and 1.3 mm-Hg with applanation tonometry. We observed a reduction of approximately 1 mm-Hg in intraocular pressure after oral agomelatine therapy.

Discussion

Melatonin, a highly lipid and aqueous soluble neurohormone, is secreted from the pineal gland in both nocturnal and diurnal animals during the night [4]. It is also referred as the hormone carrying the message of darkness to the cells throughout the body. Having recently been approved for the treatment of depression, its use in medicine has gained wide acceptance. Several authors pointed out a hypotensive ocular effect after melatonin use in various studies [5].

We designed this study to reveal the effect of oral agomelatine therapy on intraocular pressure in depressive patients without glaucoma. Agomelatine caused 9% reduction in ocular pressure in our cohort. The patients attained approximately 1 mm-Hg reduction in

Table 1. Intraocular pressures after agomelatine use. Data are expressed as a mean ± standard deviation.

	Measurement Method	
	Tonopen (mm Hg) (Mean ± Standard Deviation)	**Applanation Tonometry (mm Hg) (Mean ± Standard Deviation)**
Baseline	12,6 ± 2,8	14,8 ± 2,2
2nd Week Visit	11,7 ± 2,6*	13,5 ± 2,4*
4th Week Visit	11,5 ± 2,9*	13,5 ± 2,8*

* p < 0,05 compared to the baseline measurement within the group

Table 2. The mean change in intraocular pressures after agomelatine use. Data are expressed as a mean ± standard deviation.

	Measurement Method	
	Tonopen (mm Hg) (Mean ± Standard Deviation)	**Applanation Tonometry (mm Hg) (Mean ± Standard Deviation)**
2nd Week Visit	-0,9 ± 0,1*	-1,3 ± 0,2*
4th Week Visit	-1,1 ± 0,2*	-1,3 ± 0,3*

* p <0,05 compared to the baseline

the pressure, the clinical implications of which should be further studied.

In our study, the mean intraocular pressure was relatively low (around 12.5 mm-Hg) at baseline. In this low range, it is difficult to diminish pressure further due to episcleral venous pressure, (approximately 9-10 mm Hg), unless other routes such as unconventional pathways work. This hypotensive effect may increase in patients with higher pressures such as glaucomatous and hypertensive disorders. This pressure reduction may offer new modalities in the treatment of patients with glaucoma. Animal investigations have revealed that melatonin may further reduce intraocular pressure under ocular hypertensive conditions [3] and treating the two diseases concurrently is an advantage that should be taken into account for the management of these patients.

There are a few studies in the literature investigating the effect of agomelatine in various clinical situations. In depressive patients with primary open angle glaucoma, melatonin successfully lowered intraocular pressure by 30% in both eyes when given orally [6]. These patients in the study were receiving glaucoma treatment and required additional precautions to control intraocular pressure (including filtration surgery). When agomelatine therapy was added, these patients attained further pressure reductions and avoided surgery. Although the follow-up period was not very long, this study showed the potency of agomelatine for glaucoma management.

Melatonin may also diminish oxidative stress to help glaucoma. Oxidative stress might cause progression of optic disc cupping. Melatonin has strong antioxidative and neuroprotective effects in experimental animal models [7]. Melatonin promotes cell survival and antioxidant pathways that are associated with hyperglycemia-induced biochemical changes [8]. Thus, melatonin is a good candidate for glaucoma treatment [9].

Glaucoma and depression may be interrelated disorders. It has been reported that beta blockers used to treat glaucoma may induce depression [10]. In the systemic circulation, these drugs may cause or worsen depressive manifestations such as disturbed sleep, memory problems, weakness, and confusion. Some protective measures such as digital pressure on canaliculi to decrease nasolacrimal sac flow have been proposed in an attempt to lower systemic absorption. Avoiding beta-blockers is also recommended in these patients where depression is suspected.

Depression may be seen in glaucoma due not only to the side effects of the glaucoma medications but also the underlying etiology both diseases may possibly share. Since glaucoma may be regarded as a neurodegenerative disease where other neuropsychiatric problems can coexist, clinicians may encounter both simultaneously due to the compound nature of these

two diseases. Thus, melatonin may offer some help for the concurrent treatment of both diseases. Since melatonin has psychotropic effects, it can regulate sleep disturbances, mood deterioration, memory problems, fatigue and confusion encountered by depressive patients while reducing the side effects of glaucoma drugs and decreasing intraocular pressure.

When administered systemically, melatonin may reach ocular tissues at low levels. Thus, topical application to the eye could achieve higher intraocular concentrations and may have greater effects on intraocular pressure. This requires the development of new drug formulations.

How melatonin reduces eye pressure remains a valid question. There are some reports that melatonin may increase outflow facility [11]. Trabecular endothelial cells have melatonin receptors and can respond melatonin analogs dynamically, augmenting escape of aqueous fluid from the eye. There is evidence that melatonin receptors also exist in the ciliary body [2]. Immunohistochemical analyses in white rabbits confirmed the existence of melatonin receptors in the basolateral nonpigmented epithelium of the ciliary processes, where aqueous production takes place [11]. Interaction of these receptors with melatonin may result in decreased aqueous inflow which could be another feasible explanation for intraocular pressure reductions. We cannot prove this in our clinical practice, and further studies are required to confirm the mechanism.

Our study is the first to show the hypotensive effect of agomelatine in non-glaucomatous depressive patients. Our pilot study shows that oral agomelatine may cause a reduction of 9% in normotensive patients, of which the clinical importance might be doubted. Pressure control is fundamental in glaucoma management, and even a pressure reduction of 1 mm-Hg may be of clinical significance to preserve visual field deterioration. Therefore, any amount of pressure decline should be seen as additional support.

Our study also carries some drawbacks which need to be clarified. A potential pitfall of our study is that we did not check serum melatonin levels. It might have been better to measure the hormone level, but it should not be a necessity since oral melatonin therapy obviously increases receptor activation and an effect on ocular pressure was apparent.

Another potential flaw is related to the method and the sequence of ocular pressure measurements. Both measurement methods used herein are prone to subjective faults, especially the Goldmann applanation tonometer. To overcome the weakness of the method, we chose to measure intraocular pressure using two different devices to confirm our readings independently. Additionally, we allowed a 5 min interval between IOP measurements with different devices in order for the effects we created to normalize. This waiting time was arbitrarily decided and may be argued. We do not know whether this 5 min waiting time is sufficient for the cornea to regain its elasticity. However, that time can be seen sufficient for the cornea to return to its original biomechanics as the Tono-Pen distorts cornea minimally. Thus, we assume that our applanation tonometers readings were accurate and were not influenced by the distortion created by the Tono-Pen. In this study, we did not compare measurements obtained by the two devices since our study design, study power and sample size were not sufficient to reveal this issue.

In conclusion, agomelatine reduced intraocular pressure in depressive patients in our study. Whether decreasing eye pressure in normal conditions is helpful requires further clinical trials. New studies investigating the role of the drug in larger glaucoma patient cohorts will elucidate the potential of the drug.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Zhdanova IV. Melatonin as a hypnotic: Pro. Sleep Med Rev 2005;9:51–65.
2. Tosini G, Baba K, Hwang CK, Iuvone PM. Melatonin. An underappreciated player in retinal physiology and pathophysiology. Exp Eye Res 2012;103:82-9.
3. Martinez-Aguila A, Fonseca B, Bergua A, Pintor J. Melatonin analogue agomelatine reduces rabbit's intraocular pressure in normotensive and hypertensive conditions. Eur J Pharmacol 2013;701:213–7.
4. Hung H, Wang Z, Weng SJ, Sun XH, Yang XL. Neuromodulatory role of melatonin in retinal information processing. Prog Retin Eye Res 2013;32:64-87.
5. Pandi-Perumal SR, Trakht I, Srinivasan V, Spence

DW, Maestroni GJ, Zisapel N, et al. Physiological effects of melatonin: Role of melatonin receptors and signal transduction pathways. Prog Neurobiol 2008;85:335–53.
6. Pescosolido N, Gatto V, Stefanucci A, Rusciano D. Oral treatment with the melatonin agonist agomelatine lowers the intraocular pressure of glaucoma patients. Ophthalmic Physiol Opt 2015;35:201–5.
7. Salido EM, Bordone M, De Laurentiis A, Chianelli M, Keller Sarmiento MI, Dorfman D, et al. Therapeutic efficacy of melatonin in reducing retinal damage in an experimental model of early type 2 diabetes in rats. J Pineal Res 2013;54:179-89.
8. Jiang T, Chang Q, Zhao Z, Yan S, Wang L, Cai J, et al. Melatonin mediated cytoprotection against hyperglycemic injury in Müller cells. PloS One 2012;7:e50661.
9. Lundmark PO, Pandi-Perumal SR, Srinivasan V, Cardinali DP, Rosenstein RE, et al. Melatonin in the eye: Implications for glaucoma. Exp Eye Res 2007;84:1021-30.
10. Bendel RE, Juzych MS. Principles and Complications of medical therapy of glaucoma. In: Zimmermann TJ, Kooner KS (eds.) Clinical Pathways in Glaucoma. Thieme, New York, USA, 2001:427-56.
11. Alarma-Estrany P, Crooke A, Mediero A, Peláez T, Pintor J. Sympathetic nervous system modulates the ocular hypotensive action of MT2-melatonin receptors in normotensive rabbits. J Pineal Res 2008;45:468-75.