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ANASTROZOL EFFECTS ON THE HISTOMORPHOLOGY OF RABBIT LENS

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ABSTRACT

Objective: To evaluate the effects of prolonged use of anastrozole as an endocrine treatment of breast cancer on the lens in an animal model.

Study Design: Randomized control trial.

Place and Duration of Study: Department of Anatomy Army Medical College, Rawalpindi in collaboration with National Institute of Health Islamabad, 6 months from Jun 2012 to Nov 2012.

Material and Methods: Twenty adult female NewZealand white rabbits were taken. Ten rabbits were placed in control group A and 10 placed in group B and were given anastrozole orally in the normal dose. After the completion of the study, both eyes of each animal were enucleated and lenses removed and grossly examined. The specimens were fixed and processed and slides prepared for histological examination. The lenses were carefully examined for any opacities. Thickness and diameter of the lenses were measured for each eye. The results were compared between the groups for statistical significance by using SPSS version 21.

Results: The lenses in the experimental group were found to be transparent with no opacities. In the experimental group B, the mean diameter of lenses was 10.42 ± 0.51 µm for the right eye and 10.43 ± 0.49 µm in the left eye. Mean thickness of the lenses in group B was 6.48 ± 0.43 µm and 6.46 ± 0.44 µm for the right and left eye, respectively. The *p*-values in the comparison between the control and the experimental group was statistically insignificant.

Conclusion: Ocular side effects are quite common even in systemically administered cancer medication. Long term administration of Anastrozole has no effect on the histomorphology of the lenses of the eye.

Keywords: Anastrozole, Dry eye syndrome, Eye, Lens, Tamoxifen.

INTRODUCTION

The lens is a transparent, biconvex, elastic structure which lies between the iris and the vitreous body. It is not a part of the coats of eyeball and is suspended in the path of light by the zonular ligaments. The lens can change its diameter to help focus the image on the retina. This ability of accommodation is achievable only because of the elasticity of the lens and its capsule[1]. The lens is a completely avascular structure and has 3 principle components; the lens capsule, the subcapsular epithelium and the lens fibers.

The rabbit lens is much more spherical than a human lens and differs markedly in size, being much larger. The diameter of lens in situ is 9.95 ± 0.24 mm in rabbits as compared to 9.53 ± 0.31 mm in humans. It increases markedly after excision and on an average measures 10.47 ± 0.31 mm and 9.58 ± 0.27 mm in rabbits and humans, respectively. The thickness of lens in situ is 4.24 ± 0.46 mm in humans and 6.36 ± 0.13 mm in rabbits due to their more spherical shape[2]. Unlike human lens, the nucleus is not sharply marked off to be easily distinguishable. In older rabbits, the nucleus tends to be harder than human lens[2].

The eye has a rich blood supply and relatively small mass and drugs can distribute from the systemic blood circulation to the choroid through the fenestrated choroidal blood vessels, but further penetration into the eye is limited by the blood-retinal barrier[3]. Due to the various ocular barriers only less than five percent of the administered drug reaches intraocular structures[4]. Systemic medication can have ocular side effects. The small size of the eye in relation to

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its extensive blood supply makes it susceptible to side effects caused by systemic drugs. Many drugs are related to the discoloration of lens and formation of lens opacities.

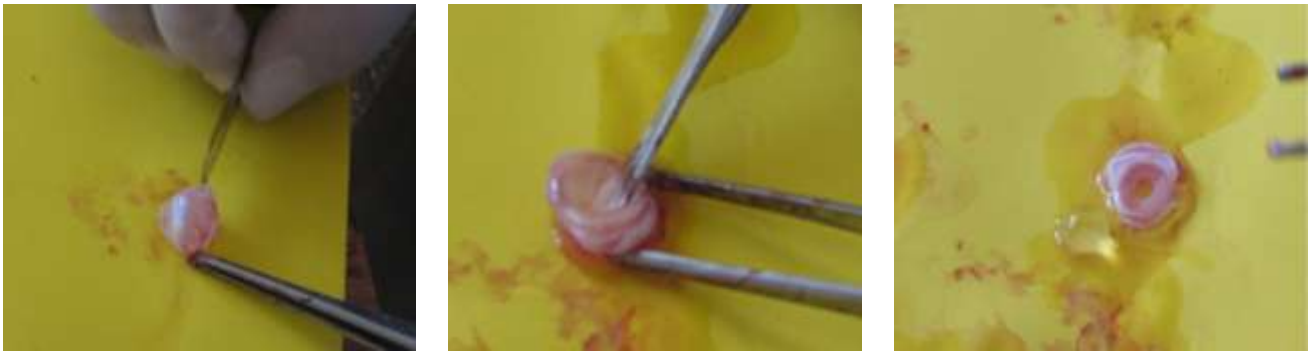
Anastrozole was the first aromatase inhibitor to be approved by the US Food and Drug Administration (FDA) as an adjuvant hormonal therapy in early stage breast cancer in 2002. Anastrozole is currently being used as first line therapy in postmenopausal women with hormone- receptor-positive advanced breast cancer. The efficacy and tolerability of anastrozole was found to be superior to tamoxifen in postmenopausal patients with breast cancer[5].

After oral administration, anastrozole takes two to three hours to reach maximum concentration. It is extensively metabolized in the liver to produce three major metabolites, triazole, glucoronide conjugate of hydroxyanastrozole and a glucoronide of anastrozole. Anastrozole is generally well tolerated in the majority of the patients. Most commonly seen adverse effects are hot flushes, arthralgia, fatigue, mood disturbances, nausea and vomiting, bone fractures, cardiovascular disturbances and vaginal bleeding. The specific effect of anastrozole on lens opacification has not been studied exclusively. More recently, anastrozole administration has been associated with dry eye syndrome in a clinical retrospective study carried out by Turaka[6].

The purpose of this study was to assess the effect of anastrozole use on the transparency of the lenses and to observe for the thickness and diameter of all the lenses.

MATERIAL AND METHODS

The study was conducted in the Department of Anatomy Army Medical College Rawalpindi in collaboration with National Institute of Health, Islamabad. Permission was taken from ethical committee on animal experiments of the Army Medical College, Rawalpindi. The study design was an experimental randomized controlled trial. Twenty adult female New Zealand white rabbits weighing 1.2-2 kg were used for the experiment. Healthy, active, non-pregnant female animals with ages between six months and two years were taken. They were kept at room temperature for about 6 months in separate cages and were given normal animal house diet.

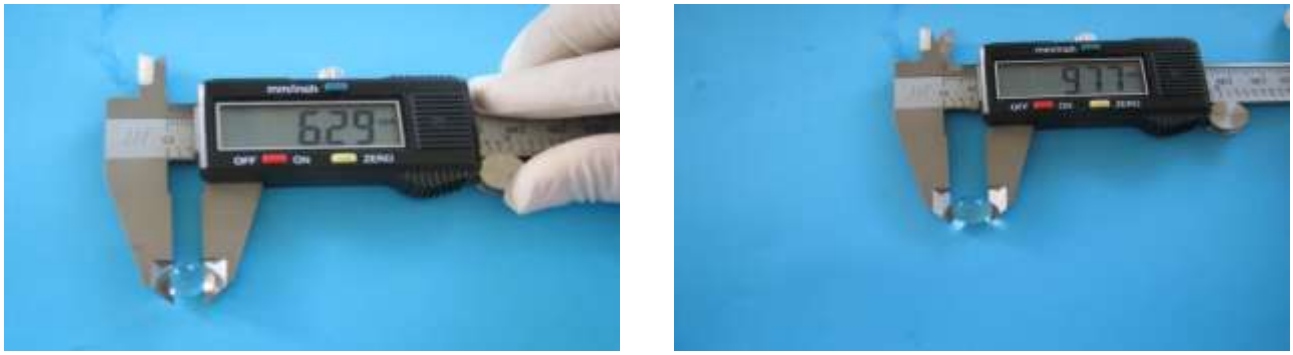


(A) (B) (C)

Figure-1: Photographs showing dissection of eyeball. A) The eyeball being cut open at the equator. B) Cutting of the suspensory ligaments of lens using scissors. C) Lens being taken out for gross measurements.

The animals were randomly divided into two groups. Group A was the control group comprising 10 animals. Group B included 10 rabbits that received anastrozole orally at a dose of 0.02 mg/kg/day for 6 months. After completion of study, the animals were anaesthetized by giving chloroform inhalation in a glass jar. The eyeballs were dissected away from the surrounding structures in the anaesthetized rabbits. The eyeball was bisected at the equator and the posterior half of the globe removed (fig-1a). The suspensory ligaments of

lens were cut with a dissecting scissors (fig-1b) and the lens removed from the eyeball (fig-1c). It was observed grossly for appearance and measurements taken from the fresh specimen. The freshly dissected lenses were blotted dry and then examined for their transparency. The diameter and thickness of each lens was recorded using a digital vernier caliper up to 1µm (fig-2).



(A) (B)

Figure-2: Photographs showing gross measurement of lens of right eye of animal A1 with digital vernier caliper. A) Measurement of lens diameter. B) Measurement of lens thickness.

transparency of the lenses graded by using criteria adopted by Mehra and Minassian[7]. All the lenses were clear and transparent with no opacities. Thickness and diameter of all the lenses were recorded with digital vernier caliper. In the control group, the mean diameter of right eye lens was 10.47 ± 0.48 µm and left eye lens was 10.47 ± 0.47 µm (table-I). Mean thickness of lens in the control group was 6.45 ± 0.37 µm in the right eye and 6.43 ± 0.36 µm in lefteye. In the experimental group B, the mean diameter of lenses was 10.42 ± 0.51 µm for the right eye and 10.43 ± 0.49 µm in the left eye (table-I). Mean thickness of the lenses in group B was 6.48 ± 0.43 µm and 6.46 ± 0.44 µm for the right and left eye, respectively (table-II). The *p*-values in all the comparisons between the control and the experimental group were insignificant.

Table-I: Showing comparison of diameters of lens among groups.

Parameter	Group A Mean ± SD (n=10)	Group B Mean ± SD (n=10)	*p*-value
Lens diameter of right eye (mm)	10.47 ± 0.48	10.42 ± 0.51	0.970
Lens diameter of left eye (mm)	10.47 ± 0.47	10.43 ± 0.49	0.986

p-value ≤0.05 is statistically significant.

Table-II: Showing comparison of lens thickness among groups.

Parameter	Group A Mean ± SD (n=10)	Group B Mean ± SD (n=10)	*p*-value
Thickness of lens of right eye (mm)	6.45 ± 0.37	6.48 ± 0.43	0.980
Thickness of lens of left eye (mm)	6.43 ± 0.36	6.46 ± 0.44	0.983

p-value ≤0.05 is statistically significant.

Statistical Analysis

The data was entered and analyzed by using SPSS version 17. Independent sample t-tests was used to assess the significance of the results between the control and experimental groups. Results were considered statistically significant at $p<0.05$.

RESULTS

At the end of the experiment, the eyes were examined by an ophthalmoscope and the

DISCUSSION

The objective of this study was to see the effects of orally administered anastrozole on the histomorphology of the lens in adult female rabbits. High incidence of dry eye among postmenopausal women that may be related to the hormonal treatment. Anastrozole had no effect on optic nerve head topography, retinal-hemorrhages, hemicentral retinal artery occlusion and vitreo-retinal traction, while corneal intraepithelial cysts have been described in a female patient, using exemestane[8]. As far as the anterior segment is concerned, Turaka et al[6] found that patients receiving anastrozole presented dry eye syndrome and ocular surface disease more frequently and severely than controls[9].

The ocular anatomy of the rabbit is quite similar to that in humans and it continues to be one of the most commonly used animal models for ophthalmic research[10]. In our study, the lens was not affected by the use of anastrozole. There was no discoloration or opacification of lens seen in any group. There is an increased risk of posterior sub-capsular cataract formation with long term use of tamoxifen[11]. Tamoxifen is used in chemo- prevention of breast cancer because of its action on the estrogen receptors. However, when the changes in lens produced by tamoxifen were studied in detail, it was found that the mechanism is related to the ability of the drug to block chloride channels in the lens leading to lens opacification and cataract formation[12]. Rifabutin, an antibiotic primarily used in the treatment of tuberculosis, reduces both rod and cone function in rabbit's retina and causes a discoloration of the lens, but does not alter the retinal morphology. The use of Tamoxifen is related with the development of keratopathy and retinopathy[13]. Tamoxifen, like several other ampiphilic cationic drugs, may interfere with intralysosomal catabolism of polar lipids. It is evident that, although a drug is designed to act on the tissues in a specific mechanism to alleviate disease process, it can cause effects by many other undiscovered methods.

The aromatase inhibitors are the new development in the endocrine treatment of breast cancer. Examestane is a selective steroidal aromatase inhibitor taken orally in such patients to lower the circulating estrogen levels[8]. In a case report, administration of Exemestane caused the formation of intraepithelial cysts in the corneal epithelium[14]. Anastrozole selectively targets the aromatase enzyme in tissues and lowers the serum estrogen levels. In postmenopausal women with breast cancer, it is now the first line of endocrine treatment preferred over the previously used Tamoxifen[15].

Side effects of aromatase inhibitors resemble those of tamoxifen to some extent but little is known about the effects of aromatase inhibitors on visual system[16].

CONCLUSION

Ocular side effects are quite common even in systemically administered cancer medication. Long term administration of Anastrozole has no effect on the histomorphology of the lenses of the eye.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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