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Research Paper

The Effect of Oral Selective Alpha 1 Blocker on the Intraocular Pressure in Rabbits

Medical Science

KEYWORDS : alpha 1 blocker, intraocular pressure,eye.

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ABSTRACT

Purpose:
To assess the effect of oral alpha 1 antagonists on the intraocular pressure (IOP) in rabbits eye.
Material and Methods:
Oral selective Alpha 1 blocker(doxasozin) was administered via an injector daily in rabbits (n=8) with an oral dose of0.08 mg/kg. Control rabbits (n=4) received equivalent oral doses of vehicle control of isotonic solution. The IOP of right and left eyes of both experimental and control rabbits were measured immediately before and 2 hours after therapy. Ten observationsfor each rabbit were recorded.
Results:
The mean values of IOP for the right eye before and after therapy were 13.6± 3.8 and 11.1±4.6mmHg respectively (P<0.002). The mean values of IOP of the left eye before and after therapy were 13.1±4.2 and 10.1±4.4 mmHg respectively (P<0.005). The mean values of IOP for right and left eye in control group were 15.5±3.8 and 15.4±3.1 respectively. The control group showed no significantvariation in the IOP neither in the right nor in the left eye, P<0.7, P<0.13, respectively.
Conclusion:
Oral alpha 1 adrenergic antagonistsresult in a significant reduction in IOP in rabbit's eye. The data may implicate potential therapeutic potential for alpha 1 blockers for treatment of patients with high IOP. Further in vitro and vivostudies are required in a large cohort to confirm our results.

Introduction

Selective alpha1 blocker is the most common used drugs for the treatment of patients with benign prostate hyperplasia (BPH). Three human alpha 1 receptors subtypes have been identified using binding and molecular cloning techniques; alpha 1a, alpha 1b and alpha 1d [1,2]. Their distribution varies among different human organs and approximately 70% of alpha 1 receptors in the human prostate are of the alpha 1a subtypes. The precise distribution of the alpha 1 receptors in the humans iris smooth muscle dilator is not known. There is substantial indirect evidence from animal studies that alpha 1a is the most dominant iris adrenoreceptors [2-7].

In 2005, Chang and Cample were the first to postulate that systemic alpha 1a antagonist (tamsulosin) blocks contraction of the iris dilator smooth muscle, and that deficient muscle tone leads to poor pupil dilation, iris floppy, floppiness and propensity to prolapse, such as intraoperative floppy iris syndrome (IFIS) [3]. Later, many studies have confirmed the association between IFIS and the use of systemic alpha 1 antagonists and tamsulosin, in particular [8,9]. This syndrome is associated with higher rate of cataract surgical complications [3]. Although, tamsulosin is the most highly drug associated with IFIS, there are many reports of IFIS syndrome occurring in patients taking nonselective alpha 1 antagonists. In a prospective study of 1968 cataract surgeries, Oshika et al found the incidence of IFIS to be 43% in patients taking tamsulosin compared with 19% in patients taking naftopidil [10]. Furthermore, Herd et al found an IFIS incidence of 37% in patients taking doxazosin and 83% in patients taking tamsulosin [9]. The aforementioned studies argue that alpha 1 adrenergic receptors have complex effects on ocular hydrodynamics, especially in regulating IOP and papillary diameters.

To our knowledge, today there is no study to investigate the therapeutic efficacy of oral selective alpha 1 blockers on the IOP. Herein we demonstrated the potential therapeutic benefits of oral selective alpha 1 blocker (doxasozin) on IOP in rabbits.

Material and Methods

The cohort of the experimental group consisted of healthy Palamino rabbits (n=8) weighing 3-3.5kg. Rabbits (n=4) from the same family were used as a control group. Oral selective alpha 1 blocker (doxasozin;Pfizer,USA) was given at an oral dose of 0.08 mg /kg. One tablet of doxasozin (2mg) was dissolved in 10cc of isotonic solution, and each rabbit was given the appropriate dose via an injector in the mouth. The control group received a vehicle control(10cc of isotonicsolution) orally. The IOP of the left and the right eyes was measured using Schiotez Tonometer (Germany). The IOP was measured immediately before giving therapy at 12 o'clock AM and 2 hours after therapy, for each rabbit (Table 1). Local anesthetic eye drops, oxybuprocaine hydrochloride 0.4% (Localin) was used before measuring IOP. The IOP of the rabbits in the control group was also measured twice a day at the same time similar to that of the study group without giving therapy. The IOP was measured over period of 3 months--thus total of 160 measurements were taken for each eye. All observations were done at intervals separated by one week to wash out the previous drug. The overall number of the IOP measurements, which was accomplished for the right and the left eyes for all rabbits were 320 measurements.

Statistical analysis: All data are expressed as mean ± standard deviation (SD). An independent sample t-test was used to compare IOP values between eyes before and after therapy administration. SPSS for windows 10.0 statistical packet was used in statistical analysis. Significance difference between control and experimental group was assessed at P<0.05.

Results

There were significant reductions in the IOP of both eyes after the doxasozin therapy. The IOP's of the right eye before and after therapy were 13.6±3.8 and 11.1±4.6 mmHg, respectively (P<0.002) (Figure 1). The IOP of the left eye before and after therapy were 13.1 ±4.2 and 10.1±4.4 mmHg, respectively (P<0.005) (Figure 1). While the average percentage in the reduction in IOP of the right eye and left eye were 34.49% and 39.29%, respectively, there

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was no significant difference between both eyes (P<0.31). The mean values of the overall IOP of the right and left eyes before and after therapy were 13.6±3.9 and 11.9±5.1 mmHg (p=0.009), respectively (Figure 2). Out of 80 observations of the IOP for the right eye, 54 (67%) of them had reduction in the IOP, 12 (15%) showed no change in IOP, and 14 (17.5%) revealed increments in the IOP. In contrast, out of 80 observations for the IOP of the left eye, 58 (73%) had showed reduction in the IOP, 6 (7.5%) showed no change, and 16 (20%) showed increment in IOP and. The control group showed no significant variation in the IOP neither in the right nor in the left eyes. The mean values of the IOP measurements in the control group for the right eyes were 15.5±3.8 and 16.4±1.2 mmHg, respectively (P<0.7), and those for the left eyes were 15.37±3.1 and 15.9±1.4 mmHg, respectively (P<0.13).

Discussion

The pharmacological effects of selective alpha 1 blockers on the prostate are well studied, however, the regulatory effects of adreneoreceptor on the IOP and iris smooth muscle remain elusive. Palea et al recently published the only experimental study of the pharmacological effects on the iris dilator muscle [11]. Tamsulosin was more effective than other oral selective alpha1 antagonists at blocking adrenergic receptor of the iris in the pigmented rabbits [11]. Both tamsulosin and other selective alpha 1 antagonists were found to be less potent in the iris than in the prostate. Therefore, the authors suggested additional receptors could be involved in the contraction of the iris dilator muscle. Several studies demonstrate the effect of alpha 1 adrenoreceptor on the IOP. Stimulation of these receptors by norepinephrin and nephrine has been shown to initially cause a rapid increase in the IOP followed by mydriasis [12]. Topical application of the alpha 1 antagonist, bunazosin, reduced IOP, however, it had little or no effect on the pupillary diameter [13]. This means that each one of these responses is linked to a different alpha 1 adrenergic subtypes.

In this present study we gave oral doxasozin as alpha 1 antagonist to rabbits and we measured the pre-therapeutic IOP and the post-immediate therapeutic IOP. The IOP of both eyes were significantly reduced after administration of alpha 1 blocker, however, no significant change was observed in the IOP of the control group. Since the effect of alpha blocker are poorly understood, further studies are required to unravel the underlying mechanism(s) involved in drug-mediated reduction of IOP. However, current evidence exists for the presence alpha 1 receptors in the iris muscle [2-7]. Indeed, activation or inhibition of these receptors has been associated with development of complex effects on ocular hydrodynamics pertaining to changes in the aqueous fluid, either in production or flow. Contraction of the iris muscle by alpha agonists leads to open pupil and closing of the angle, thus decreasing the circulation of the aqueous fluid. Conversely, blockade of these receptor by alpha 1 antagonists leads to dilation of the iris, opening the angle, and an increase in the aqueous out flow, thus reducing the IOP. Beside this mechanism, activation of alpha receptors leads to vasodilation, which affects the ciliary blood flow and the production of the aqueous blood flow. Keil et al investigated the paradoxical effect of acute systemic nonselective alpha-adrenergic blockade on the aqueous flow [14]. The study concluded that these drugs have complex effect on the ocular hydrodynamics and it is too difficult to explain the reduction in IOP by aqueous dynamics or ocular rigidity. It thought that the drug effects are most likely resulting from the disgorgement of choroidal blood volume caused by decrease venous pressure outside the eye. The study also suggested that a decrease in aqueous flow and, perhaps, in episcleral venous pressure or inhibition of aqueous production are among the expected mechanisms [14]. Topical application of prozasin (alpha 1 antiagonist) significantly reduced the circadian IOP elevation [15]. John et al reported that topical administration of 0.1% prazosin could reduce the circadian elevation of IOP [15]. Although they could not define the exact mechanism by which alpha 1 blocker reduce IOP, many explanations were introduced; alpha-1-adrenergic antagonism probably directly blocked the signaling pathway of norepinephrine for the IOP elevation; release of norepinephrine activates alpha 1 adrenergic and cause an increase of outflow resistance; and alpha-1-adrenergic antagonism indirectly modified the circadian IOP elevation. Another study suggest that the ability of alpha adrenergic antagonists to lower IOP in the rabbit did not correlate with single alpha-receptor subtype and appears to involve at least two separate mechanisms [16].

The mean reduction in the IOP in the right and left eyes were 34.49% and 39.29% respectively. Herd et al reported similar percentage of IFIS syndrome (37%) in patients taking doxasozin [9]. This finding may suggest that the patients with IFIS syndrome are susceptible to reduction in the IOP. Pupil constriction, which is one of the characteristics of IFIS syndrome, may allow opening of the angle --thus aqueous flow increases and IOP decreases. However, further studies are needed to prove this claim. Out of 80 observations for the IOP of the left eye 58 of them showed reduction in the IOP. The reduction IOP was more than 15% in all those patients. Thus, it is difficult to attribute this reduction in IOP by diurnal fluctuation of IOP, which is usually occurs in the morning (highest) and the early afternoon (lowest) with average of 4.4 mmHg in glaucoma patients [17]. Some other studies showed that during diurnal IOP measurements in an upright position there were no statistically significant differences in IOP changes [18]. Nonetheless, in a supine position the IOP was significantly higher than in a sitting position and increased more in the glaucoma patients than in healthy controls [18]. In the right eye out of 80 measurements, 54(67.5%) measurements showed reduction in IOP. Only 6 of them (7%) had reduction in IOP less than 15% . This also confirm that the reduction in the IOP is not consequent to diurnal change in the IOP but rather to the therapy, which was given to the rabbits. Similarly the control group showed no such reduction of IOP, which were measured at the same times of the study groups. This findings further support that the reduction in IOP is not attributed to diurnal fluctuation or machine error.

The majority of the studies regarding the ocular effect of adrenergic receptors failed to identify the underlying mechanisms and effect of alpha 1 antagonists on the IOP. This can be consider as one of the limitation for such kinds of studies as in our study too. The optimal dose of the drug can be considered another limitation for such studies. It is well known that the effect of alpha 1 antagonists is dose dependent, thus variations in doses of the drug may result in a different effects. Therefore, we recommend further studies with different doses to find out the exact effect of the drug. The third limitation is the long term effect of the drug, which may change with prolonged treatment. Thus, it is difficult to predict the exact effect of long term user of alpha 1 blocker on the IOP in patients with BPH. Despite all of these limitations, our study provides novel therapeutic potential for alpha 1 blockers. This is not unexpected advantage of alpha 1 blockers, which are already proved to have many valuable benefits besides its main usage as antihypertensive drug and in symptomatic treatment for patients with BPH. Alpha 1 antagonists have been reported to have beneficial effects in cholesterol and lipid profiles [19]. Spontaneous passage of lower and upper ureter stones as well as in improving the outcomes after extracorporeal shock waves lithotripsy [20,21].

Conclusion

Selective oral alpha 1 blocker results in acute reduction in the post-immediate therapeutic IOP in a rabbit model. While alpha adrenoreceptors have complex effect on the ocular hydrodynamics, an increase aqueous out flow, reduce production of aqueous and presence of additional receptors were speculated in mediating IOP reduction by alpha 1 blockers. However, further studies

should be carried out to corroborate our findings. Importantly, the fundamental mechanisms that govern the drug-induced reduction in the IOP certainly warrant further investigation.

We have no conflict of inertest to declare

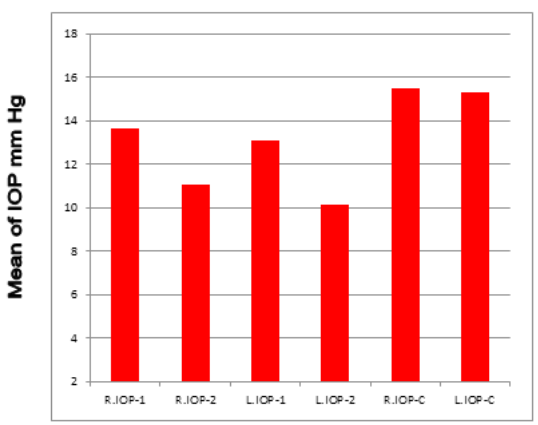
Table 1: The values of IOP for right and left eyes before and after therapy in the study and control groups.

	Before therapy	After therapy	P value
IOP of right eye mmHg	13.62±3.82	11.08±4.59	0.002
IOP of Left eye mmHg	13.08±4.15	10.13±4.40	0.005
IOP of right eye (control group)*	15.11±3.7	16.36±1.18	0.7
IOP of left eye (control group)*	15.30±3.22	15.95±1.37	0.13

IOP; intraocular pressure.

*No therapy was given to the rabbits in the control group.

Figure 1: Shows the mean IOP for right and left eyes before and after therapy with right and left mean IOP for control group.



R.IOP-1; right eye intraocular pressure before therapy.

R.IOP-2; right eye intraocular pressure after therapy.

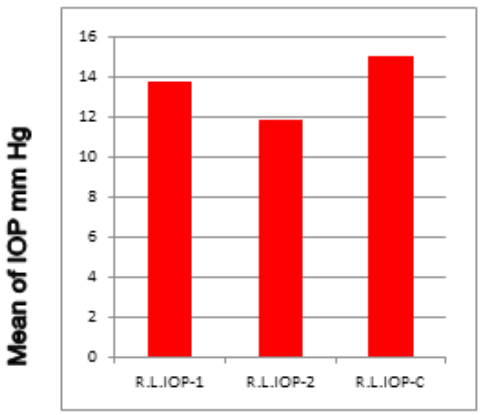
L.IOP-1; left eye intraocular pressure before therapy.

L.IOP-2; left eye intraocular pressure after therapy.

R.IOP-C; right eye intraocular pressure for the control group.

L.IOP-C; left eye intraocular pressure for the control group.

Figure 2: Shows the mean IOP of the right and left eyes before and after therapy with mean IOP for control group in all observations.



R.L.IOP-1; right and left eyes intraocular pressure in all observations before therapy.

R.L.IOP-2; right and left eyes intraocular pressure in all observations after therapy.

R.L.IOP-C; right and left intraocular pressure in all observations for control group

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