THE EFFECT OF TOPICAL ALISKIREN ON OCULAR HYPERTENSION INDUCED BY WATER LOADING IN RABBITS

Hussain Saad H*, Zalzala Munaf H

Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

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* Hussain Saad A., Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq E-mail: saad_alzaidi@yahoo.com

ABSTRACT

The aim of this work was to assess the effect of topical instillation of aliskiren on the ocular hypertension induced by water loading in rabbits. The effect of three different concentrations of aliskiren (7.5, 15 and 30mg/ml) on the intraocular pressure rise produced by oral administration of tap water (60 ml/kg) was tested in groups of six rabbits each. When applied at the utilized concentrations studied, topical aliskiren was found to decrease the intraocular pressure rise after water loading within a certain intervals of time. This effect was found to be dose-dependent when compared with that reported in control group at the same corresponding time. Although aliskiren, and probably other rennin inhibitors, may be useful in the management of ocular hypertension, the data obtained suggest that these drugs may have complex actions on aqueous humor dynamics; therefore further studies in animal models of glaucoma should be carried out before their clinical evaluation in humans.

KEY WORDS: aliskiren; renin inhibitor, intraocular pressure, glaucoma

INTRODUCTION

Renin-angiotensin system (RAS) is an important regulator of blood pressure and body fluid homeostatic balance. Evidence is accumulating to indicate its importance also for local intraocular regulating systems. The presence and functional role of RAS, including ACE activities, the concentration of angiotensinogen and angiotensin II (Ang II), and the density of Angiotensin II AT1 receptor in the ocular tissues and fluids have been demonstrated in several species, including humans. These findings indicate that the eye contains a local RAS which may be involved in the regulation of IOP. Also the importance of the angiotensin type 1 (AT1)-receptors in the microcirculation in the ocular tissues has been reported. However, the mechanism of action for the ACE inhibitors in lowering IOP has not been definitely known. Topical administration of various ACE inhibitors, enalaprilat, ramiprilat, and fosinopril, reduces IOP in rabbits. These compounds reduce IOP by inhibition of ACE in aqueous humor and in ocular tissue, resulting in decrease of Ang II formation within the eye. In rabbits, CS-088 (an angiotensin AT1 receptor antagonist) reduces IOP with a 17% increase in uveoscleral outflow, but without changes in outflow facility and in rates of aqueous humor flow. Aliskiren represents the first in a novel class of renin inhibitors with the approved potential for treatment of hypertension and related cardiovascular diseases. Aliskiren received Food and Drug Administration approval for the treatment of hypertension in March of 2007 and considered as a potent and selective inhibitor of human renin at sub-nanomolar concentrations. Although the IOP lowering effects of the rennin inhibitor enalkiren (ABBOTT-64662) was previously reported in normotensive animal and for mechanistic study approach, no data available for evaluating such class of compounds in experimental models of glaucoma. So, the present study was designed to evaluate the IOP lowering effect of aliskiren, the direct rennin inhibitor, after corneal instillation in rabbit model of acute glaucoma.

Aim of the study

The purpose of this study was to evaluate the effect of topically instilled aliskiren on ocular hypertension induced by water overload in rabbits.

MATERIALS AND METHODS

Experiments were carried out in male albino New Zealand rabbits, weighing 2.5–3.5 kg, that had previously been trained to be handled and restrained in boxes in the laboratory environment. Animals were housed in individual cages under a 12-hours light-dark cycle (lights on 7.0 a.m. to 7.0 p.m.), and maintained conventionally during the study with regulated air temperature (15-21°C), relative humidity (40-70%) and ventilation (air volume change 20 times/h). They had...
free access to a standard laboratory diet and tap water. Animals were deprived of water and food for 24 hours before each experiment. Intraocular pressure was measured with Icare tonovet® (Icare Co, Finland), which based on the new patented induction based method, which allows IOP to be measured accurately, rapidly and without a local anesthetic; the instrument was calibrated by direct manometry in anesthetized rabbits. Immediately before each study, calibration was checked according to the instructions of the manufacturer. To induce water loading, rabbits were administered 60 ml of tap water (at 37°C) per kilogram of body weight by orogastric intubation with the use of a needle catheter. Aliskiren (Novartis, Switzerland) was dissolved in distilled water at different concentrations, 7.5mg/ml, 15mg/ml and 30mg/ml. After the baseline intraocular pressure (pretreatment pressure) was recorded, six groups of six rabbits each received one 50 µl drop of each aliskiren concentration instilled in the middle of the inferior cul-de-sac of the left eye. In three of the previously mentioned animal groups, the aliskiren drop was instilled 2 hours before water loading; while in the other groups aliskiren was instilled at time of water loading. One 50 µl drop of the drug vehicle (distilled water) was administered to an additional group of six rabbits (control group). Intraocular pressure was measured at 15, 30, 45, 60, 90, and 120 min after water loading. Results are expressed as mean ± SD. Data analyzed by one-way analysis of variance by using the Bonferroni multi comparisons post-test. Values of P<0.05 were considered to be statistically significant.

RESULTS

In the present study, aliskiren was instilled in two manners, either at the time of water loading or two hours before water to explore the duration of aliskiren effect. In control group, there was significant elevation in intraocular pressure between 15 and 120 minutes after water load, and the maximum change in IOP was achieved after 45 minutes in both approaches (16.2±3.6 and 16.4±4.09 mmHg; figures 1 and 3). In the animal group instilled with 7.5 mg/ml aliskiren, water loading increases IOP significantly between 15 and 90 minutes, then IOP became non-significantly different compared to baseline after 120 minutes; these results were observed in both approaches of using aliskiren (figures 1 and 3). Compared to control group, aliskiren (7.5mg/ml) significantly decreases IOP between 30 and 120 minutes when instilled 2 hours before water loading; aliskiren decreases IOP significantly between 45 and 120 minutes (figures 2 and 4). Increasing the concentration of aliskiren to 15 mg/ml, IOP was significantly elevated after water loading between 15 and 60 minutes when aliskiren instill at time of water load, while IOP was significantly increased between 15 and 90 minutes when aliskiren instilled 2 hours before water load (with respect to baseline) (figures 1 and 3). When compared with data of control group, aliskiren (15mg/ml) significantly decreased the IOP between 30 and 120 minutes in both approaches (figures 2 and 4). With regard to 30mg/ml aliskiren, a significant ocular hypertension was reported just between 15 and 60 minutes after water loading when aliskiren instilled at that time, but the IOP was significantly elevated between 15 and 90 when aliskiren instilled 2 hours before water loading compared with baseline of corresponding group (figures 1 and 3). When compared with data of control group, aliskiren (30mg/ml) significantly decreases the IOP between 30 and 120 minutes when instilled at time of water load, but in 2 hours gap approach, aliskiren decreases IOP significantly only within the interval between 15 and 120 minutes (figures 2 and 4).

DISCUSSION

Studies in dogs and men have revealed that the sequence of events that results in the intraocular pressure rise after water loading is precipitated by a reduction in blood osmolality9. This reduction would create an osmotic gradient between blood and aqueous humor and thus a passive flow of water into the eye. As well as, a decrease in the outflow facility of the aqueous humor, likely due to a mechanical obstruction of the outflow by hydration of the trabecular meshwork cells10 or to an increase in the episcleral venous pressure in response to hydremia11, may play a role in the intraocular pressure rise after water loading. It is clear that the ocular hypertension induced by water loading is mainly produced by passive mechanisms resulting from blood hypo-osmolality. The renin-angiotensin-aldosterone system is known to play an essential role in controlling sodium balance and body fluid volumes, and thus blood pressure. Many recognized RAS components have also been identified in the human eye12,6; expression of intraocular RAS has been demonstrated in a number of studies and it is involved in the regulation of IOP, being probably more activated in glaucomatous eyes, the exact mechanism of action is remaining however unclear. Evidence is accumulating to suggest that the widely used antihypertensive drugs acting on the renin-angiotensin system (RAS) can also lower IOP. In recent human studies, orally administered losartan (angiotensin type 1 receptor blocker)13 and captopril (ACE inhibitor)14 are able to lower IOP in both normotensive and glaucomatous subjects, although blood pressure is reduced in only arterial hypertensive patients.
Topical application of olmesartan (ARB)\textsuperscript{15,16}, ACE inhibitors\textsuperscript{17,18} and renin inhibitors\textsuperscript{19} has been reported to lower IOP in animal studies; however, the exact mechanism of this action is yet unclear. In the present study, aliskiren significantly decreased the intraocular pressure in dose dependent manner; this ocular hypotensive effects could be attributed to the inhibition of RAS with subsequent reduction in angiotensin II production. Aliskiren decreases the extent and duration of IOP elevation after water loading; also in two hours gap manner, aliskiren significantly decreased the zero time IOP relative to the baseline value. The exact function of the RAS in the eye has not yet been clarified; however, RAS activity has been shown in cultured non-pigmented human ciliary epithelial cells, which are responsible for aqueous humor formation\textsuperscript{20,21}. Ang II has been reported to activate a Ca\textsuperscript{2+} signaling system which increases potassium ion channel activity and triggers aldosterone production\textsuperscript{22}. These effects are accompanied by cell volume loss, indicating that Ang II acts as an operated secretogogue in the non-pigmented ciliary cells\textsuperscript{20}. Ang II has also been found to cause an increase in cytoplasmic sodium concentration due to activation of Na\textsuperscript{+}/H\textsuperscript{+} exchange\textsuperscript{23}. It has been previously reported that blockade of the AT1 receptor by losartan potassium reduces the rates of aqueous humor flow with a subsequent reduction in IOP\textsuperscript{1}. Meanwhile, topical administration of various ACE inhibitors, enalaprilat, ramiprilat, and fosinopril, reduces IOP in rabbits. These compounds reduce IOP by inhibition of ACE in aqueous humor and in other ocular tissue, resulting in decrease of Ang II formation within the eye\textsuperscript{24,25}. Indomethacin blocks the IOP-lowering effect of enalaprilat, indicating that prostaglandins may mediate, at least in part, the ocular hypotensive effect of enalaprilat\textsuperscript{17}. In rabbits, CS-088 (an angiotensin AT1 receptor antagonist), reduces IOP with a 17% increase in uveoscleral outflow, but without changes in outflow facility and in rates of aqueous humor flow. Although there is a small increase in uveoscleral outflow, the mechanism for the significant IOP lowering by CS-088 is not understood in the rabbit and is unknown in the monkey eye\textsuperscript{16}. In conclusion, topically instilled aliskiren reduce the elevated IOP due to water over load in rabbits, which may be due to either decreasing aqueous humor production and/or increase its drainage.

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**REFERENCES**


Figure 1. Changes in IOP induced by water loading in the different experimental animal groups instilled with different concentrations of aliskiren at the time of loading. In each plot, IOP after water loading was compared with its own pre-treatment value. Values statistically significant: * P<0.05; **P<0.01, *** P<0.001.
Figure 2. Comparison of IOP changes reported after water loading in each aliskiren-treated (at time of loading) group with the control group at the corresponding time point. Values statistically significant: *P<0.05; **P<0.01; ***P<0.001.

Figure 3. Changes in IOP induced by water loading in the different animal groups instilled with different concentrations of aliskiren 2 hrs before loading. In each plot, IOP after water loading was compared with its own pre-treatment value. Values statistically significant: *P<0.05; **P<0.01; ***P<0.001.
Figure 4: Comparison of IOP changes reported after water loading in each aliskiren-treated (2 hrs before loading) group with the control group at the corresponding time point, where aliskiren instilled 2 hour before water load. Values statistically significant: *P<0.05; **P<0.01; ***P<0.001.

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