Experimental Studies

https://doi.org/10.31288/oftalmolzh202564247

Effect of the angiotensin-converting enzyme inhibitor zofenopril on ocular hydro- and hemodynamics in rabbits with experimental glaucoma

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Purpose: *To assess the effect of the angiotensin-converting enzyme (ACE) inhibitor zofenopril on the intraocular pressure (IOP), rheographic coefficient (RC) and tonographic parameters of the eye in a rabbit model of adrenaline-induced glaucoma (AIG).*

Methods: *In group 1 (12 animals), experimental glaucoma was induced by injecting 1:1000 adrenaline 0.1 ml through the auricle vein every other day for 3 months (40 injections totally). In group 2 (12 animals), glaucomatous animals received an aqueous suspension (1 ml) of zofenopril orally at a dose of 1 mg/kg daily for 3 months. The control group comprised 10 intact rabbits. Rabbit eyes were assessed by ophthalmoscopy and biomicroscopy. A Maklakoff tonometer was used for IOP measurements. Ocular hydro- and hemodynamics were assessed. The Kruskal-Wallis and Mann-Whitney tests were employed to assess group differences.*

Results: *In group 1, mean IOP statistically significantly increased by 28.3%, 34.2% and 46.7% at days 30, 60 and 90, respectively, compared to baseline ($p < 0.05$). Additionally, mean IOP statistically significantly increased at all time points compared to controls. In group 2, at day 60 and day 90, IOP was 19.6% and 29.6% lower, respectively, compared to group 1. In non-treated glaucomatous animals, at day 90, RC was decreased by 37.0%, tonographic aqueous humor (AH) outflow facility (C) was decreased by 36.8%, AH production was increased by 23.0% and tonographic IOP (P0) was increased by 61.4% compared to controls. In glaucomatous animals treated with zofenopril, at day 90, RC and C were 45.7% and 41.7%, respectively, higher, and AH production and P_0 were 24.1% and 22.4%, respectively, lower compared to non-treated glaucomatous animals.*

Conclusion: *In rabbits with AIG, ocular blood flow and ocular hydrodynamics parameters were impaired in the presence of elevated IOP. Zofenopril had a beneficial effect on the function of eyes with AIG (i.e., the IOP, parameters of ocular hemodynamics and AH circulation).*

Key words:

glaucoma, pathogenesis, ACE inhibitor zofenopril, intraocular pressure, ocular hydrodynamics, ocular hemodynamics, rheographic quotient, experiment

Introduction

Glaucoma is a common eye disorder and the leading cause of irreversible blindness worldwide. The disease causes vision loss due to neurodegeneration of the retinal ganglion cell (RGC) projection to the brain through the optic nerve [1, 2].

Elevated intraocular pressure (IOP) is a very consistent risk factor for the presence of glaucoma [3]. We have demonstrated a rise in IOP animals with experimental adrenaline-induced glaucoma (AIG) in animals [4], which is in general agreement with pathophysiological mechanisms of primary glaucoma.

Delivery of energy substances like glucose and oxygen to neurons is essential for enabling neuronal activities. Therefore, adequate blood flow in ocular vessels is important for ocular homeostasis [5, 6], whereas impaired ocular blood flow is critical in the pathogenesis of glaucoma [5, 7]. Additionally, studies have shown that an increase in systemic blood pressure is associated with an increased risk of open-angle glaucoma [3].

Studies demonstrated correlation of retinal vascular changes with the severity of POAG, suggesting that vascular dysfunction is present in POAG, even at a very early stage of glaucoma, and increases with the severity of the disease [8, 9]. These changes can eventually result in irreversible neurodegenerative disorder, not only in the retina, but also in the brain, with patients experiencing a heterogeneous set of visual and cognitive symptoms [1, 10].

That is why vascular dysregulation with chronic vasoconstriction is believed by some researchers to be the primary cause of POAG, limiting energy supply to retinal and brain neurons with subsequent hypo-metabolism or neuronal cell death. Understanding the details of these pathophysiological processes in glaucoma will enable the development of therapeutic means to combat not only elevated IOP, but also manifestations of vascular dysfunction for the prevention of neurodegenerative progression that can cause structural changes in the retina and optic nerve and neural cell apoptosis, leading to loss of sight [11].

Despite advances in the research of the pathogenesis of glaucoma, the mechanisms of the disease remain incompletely understood. Therefore, further research is warranted to acquire knowledge on the potential for developing effective means to prevent and treat this insidious disease. Numerous publications have discussed current glaucoma treatment strategies. The development and implementation of these strategies will support neurovascular function in the eye [7], and – with the impact on neuroregulatory mechanisms [12] and neuronal protection [2, 10] – will enable successful treatment, especially with combinations of these treatment options.

The intraocular renin-angiotensin system (RAS) produces effects on aqueous humor (AH) dynamics, whereas angiotensin-converting enzyme (ACE) inhibitors are associated with the function of the system [13]. Given the above facts and that glaucoma is a chronic disease involving particularly vascular neurodegenerative processes, our attention was drawn by this medication group. However, ACE inhibitors may exert potential antiglaucomatous effects not only at the level of ocular hydrodynamics, but also at the level of ocular vessels due to the capability of the inhibitors to induce relaxation of spastic vessels. These medications are widely used in cardiological practice.

Zofenopril contains two sulfhydryl groups and is an ACE inhibitor that we believe deserves special attention. It has a high restorative potential due to the presence of these groups in the molecule. Zofenopril significantly preserved ischemic zone endocardial blood flow at reperfusion in pigs after myocardial ischemia/reperfusion and significantly augmented plasma H2S levels in mice and pigs [14]. Zofenopril (but not enalapril that includes no thiol group) improved vascular function by potentiating the H_2S pathway in a model of spontaneous hypertension [15].

In our previous study, a negative Spearmen correlation was noted between the IOP and levels of endogenous H_2S in the eye drainage system (trabecular meshwork, Schlemm canal and collector channels), retina, optic nerve and AH in rabbits with AIG.

Daily treatment with the H_2S donor NaHS contributed to an increase in H_2S levels in the ocular tissues and IOP reduction [16].

Given the features of the ACE inhibitor zofenopril and its potential capacity to impact on the mechanisms of glaucomatous process, we aimed to examine experimentally the effect of this compound on the ocular functional parameters that change in glaucoma (IOP dynamics, ocular hydrodynamics and hemodynamics).

The purpose of the study was to assess the effect of the ACE inhibitor zofenopril on the IOP, rheographic coefficient (RC) and tonographic parameters of the eye in a rabbit model of AIG.

Material and Methods

Thirty-four rabbits > 2 years of age were included in the study. They were maintained under normal vivarium conditions and fed and watered ad libitum. All animal experiments were performed in compliance with the General Ethical Principles of Animal Experiments (approved by Third National Congress on Bioethics, Ukraine, Kyiv, 2007) and European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes from the European Treaty Series (Strasbourg, 1986). The study was approved by the Bioethics committee (Reference number: №3, Date of approval: April 14, 2021).

In group 1 (12 animals), experimental glaucoma was induced by injecting 1:1000 adrenaline 0.1 ml through the auricle vein every other day for 3 months (40 injections totally) [17].

In group 2 (12 animals), animals received an aqueous suspension (1 ml) of zofenopril orally at an active substance dose of 1 mg/kg daily for 3 months (with adrenaline introduced 20 minutes after zofenopril).

The control group comprised 10 intact rabbits that were not subjected to any effects.

Rabbit eyes were assessed by ophthalmoscopy and biomicroscopy throughout the experiment. A Maklakoff tonometer with a 7.5-g plunger load was used for IOP measurements after topical anesthesia with alkain 0.5%.

The tonograph TNS-100 was used to measure ocular hydrodynamic parameters. The computerized rheographic complex (Reocom, Ukraine, Kharkov) was used to measure hemodynamic parameters.

JASP software (version 0.95.3; the JASP Team, Amsterdam, the Netherlands) was used for statistical analysis [18]. The Kruskal-Wallis and Mann-Whitney tests were employed to measure differences in groups.

Results

Table 1 presents mean IOP values at baseline and days 30, 60 and 90 after the initiation of the experiment in study groups.

Table 1. Intraocular pressure (measured in mmHg) in control rabbits and rabbits with adrenaline-induced glaucoma untreated or treated with ACE inhibitor zofenopril

Group of rabbits	Statistics	Time points			
		Baseline	30 days	60 days	90 days
Controls (n=20)	Mean ± SEM	14.6 ± 0.8	15.1 ± 0.7	14.3 ± 0.9	14.7 ± 0.7
	p	-	>0.05	>0.05	>0.05
	%	100.0	103.4	97.9	100.7
	p_1	-	-	-	-
	$\%_1$	100.0	100.0	100.0	100.0
Untreated glaucoma (n=24)	Mean ± SEM	15.2 ± 0.9	19.5 ± 1.2	20.4 ± 1.3	22.3 ± 0.9
	p	-	<0.01	<0.01	<0.01
	%	100.0	128.3	134.2	146.7
	p_1	>0.05	<0.01	<0.01	<0.001
	$\%_1$	104.1	129.1	142.7	151.7
	p_2	-	-	-	-
	$\%_2$	100.0	100.0	100.0	100.0
Glaucoma treated with zofenopril (n=24)	Mean ± SEM	14.9 ± 0.7	17.5 ± 0.9	16.4 ± 0.8	15.7 ± 1.2
	p	-	<0.05	>0.05	>0.05
	%	100.0	117.4	110.1	105.4
	p_1	>0.05	>0.05	>0.05	>0.05
	$\%_1$	102.1	115.9	114.7	106.8
	p_2	>0.05	>0.05	<0.05	<0.001
	$\%_2$	98.0	89.7	80.4	70.4

Notes: n, number of eyes; p, P-value for difference compared to baseline; p_1, P-value for difference compared to controls; p_2, P-value for difference compared to animals with untreated glaucoma; AIG, adrenaline-induced glaucoma; ACE, angiotensin-converting enzyme; SEM, standard error of mean

Baseline IOP errors in experimental groups and IOP variations throughout the experiment in the control group were within the range of statistical error.

In group 1, mean IOP statistically significantly increased by 28.3%, 34.2% and 46.7% at days 30, 60 and 90, respectively, compared to baseline. Additionally, mean IOP statistically significantly increased by 29.1%, 42.7% and 51.7% at days 30, 60 and 90, respectively, compared to controls.

In eyes of rabbits treated with zofenopril in the presence of AIG, mean IOP was found to be increased by 17.4% at day 30 ($p < 0.05$), and by 10.1% and 5.4% and days 60 and 90, respectively, compared to baseline. At each time point, there was no significant difference in IOP between glaucomatous animals treated with zofenopril and controls.

There was a significant difference in IOP between glaucomatous animals treated with zofenopril and non-treated glaucomatous animals, with IOP being 19.6% and 29.6% higher in the latter group at day 60 ($p < 0.05$) and day 90 ($p < 0.001$), respectively. At day 90, ocular blood flow was found to be substantially decreased in non-treated AIG animals, with the RC being 37.0% decreased compared to controls (Table 2). Additionally, in non-treated glaucomatous animals, tonographic AH outflow facility (C) was decreased by 36.8%, AH production was increased by 23.0%, tonographic IOP (P_0) was increased by 61.4% compared to controls (Table 2).

Treatment with zofenopril in the presence of AIG substantially improved ocular hydrodynamics and hemodynamics, with RC and C values approaching those seen in eyes of the control group. Moreover, in glaucomatous animals treated with zofenopril, P_0 was increased by 25.2%, and F was decreased by 6.6% compared to controls (Table 2).

In glaucomatous animals treated with zofenopril, ocular blood flow and hydrodynamics were substantially improved compared to non-treated glaucomatous animals. Particularly, RC and C were 45.7% and 41.7%, respectively, higher, and AH production and P_0 were 24.1% and 22.4%, respectively, lower in the former animals than in the latter.

Therefore, in rabbits with AIG, treatment with an aqueous suspension of the ACE inhibitor zofenopril orally daily throughout the experiment contributed to IOP reduction to the values close to those of the control group, and to substantial improvements in ocular blood flow and AH circulation.

Discussion

Previous failures to achieve a positive final treatment outcome in medication-only treatment for glaucoma can be accounted for the prolonged use of hypotensive therapy only. Later, the multifactorial nature of the glaucomatous process was established, in which the microenvironment of the ganglion cell and its axon is disrupted as a result of

Table 2. Effect of the angiotensin-converting enzyme (ACE) inhibitor zofenopril on the rheographic coefficient (RQ) and parameters of ocular hydrodynamics in rabbits with adrenaline-induced glaucoma

Group of rabbits	Statistics	Parameters examined			
		RC, $^0/_{00}$	Hydrodynamics parameters		
			C, mm³/min	F, mm³/min	P_0, mmHg
Controls (n=20)	Mean ± SEM	2.92 ± 0.21	0.19 ± 0.01	1.52 ± 0.13	9.20 ± 0.46
	p	-	-	-	-
	%	100.0	100.0	100.0	100.0
	p_1	-	-	-	-
	$\%_1$	-	-	-	-
Untreated glaucoma (n=24)	Mean ± SEM	1.84 ± 0.15	0.12 ± 0.02	1.87 ± 0.06	14.85 ± 0.92
	p	<0.001	<0.01	<0.05	<0.001
	%	63.0	63.2	123.0	161.4
	p_1	-	-	-	-
	$\%_1$	100.0	100.0	100.0	100.0
Glaucoma treated with zofenopril (n=24)	Mean ± SEM	2.68 ± 0.23	0.17 ± 0.01	1.42 ± 0.08	11.52 ± 0.78
	p	>0.05	>0.05	>0.05	<0.05
	%	91.8	89.5	93.4	125.2
	p_1	<0.01	<0.05	<0.001	<0.05
	$\%_1$	145.7	141.7	75.9	77.6

Notes: n, number of eyes; p, P-value for difference compared to baseline; p_1, P-value for difference compared to controls; p_2, P-value for difference compared to animals with untreated glaucoma; ACE, angiotensin-converting enzyme; AIG, adrenaline-induced glaucoma; C, aqueous humor outflow facility; F, aqueous humor production; P_0, tonographic IOP; RC, rheographic coefficient; SEM, standard error of mean

metabolic and biomechanical disturbances, impairments of neurovascular coupling and autoregulation, ultimately leading to vascular dysfunction in glaucoma [19].

Successful therapy for functional improvement in patients with glaucoma should take into account not only the initial cause (involving molecular mechanisms of pathophysiological sequelae, reduced blood flow, impaired autoregulation, neurovascular coupling dysfunction, and blood-retina/brain-barrier breakdown, etc.) but also all potential pathways for disease progression and complication development [7, 19].

Several biomarkers of glaucoma progression from a vascular perspective, including endothelin-1 (ET-1), , vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs), nitric oxide and hydrogen sulfide have been identified [8, 16, 20]. Consequently, they may be considered for their potential as pharmacological intervention targets.

It has been reported that H_2S-producing donors can reduce IOP in normotensive rabbits [21] and elevated IOP in animals with experimental glaucoma [16].

We have reported previously [22] that zofenopril substantially increased the level of H_2S gas transmitter and was helpful in the normalization of control of constitutive NO-synthases and endogenous nitrite and nitrate (NO_3^- and NO_2^-) ions. Therefore, zofenopril may be considered as a potential component of comprehensive conservative treatment for primary glaucoma [22].

Therefore, although the exact mechanism of action of zofenopril on the control of aqueous humor dynamics remains elusive, the physiological effects of zofenopril are due to its antioxidative and vascular protective properties, which is associated with the release of H_2S. Our experiment demonstrated that IOP can be normalized in AIG treated with zofenopril. It is likely that the hypotensive effect of zofenopril is due to an increased level of H_2S in the eye drainage system in AIG [22]; effects of H_2S on sympathetic neurotransmission from isolated porcine iris-ciliary bodies [23] and the pool of neuromediators in the anterior segment of the eye [24] have been reported.

Effects of H_2S on the AH outflow pathways may be associated with its ability to relax vascular smooth muscle, resulting in vasodilation [25]. This H_2S activity is caused by its effects on adenosine triphosphate (ATP)-sensitive K+ channels [26].

Zofenopril protects against myocardial ischemia-reperfusion injury by increasing nitric oxide and hydrogen sulfide bioavailability and has been shown to exert vasculoprotective and cardioprotective actions [14, 27]. The involvement of deficiency of H_2S and NO-dependent processes in the pathogenesis of glaucoma makes it reasonable to assess the effects of zofenopril on ocular hemodynamics and hydrodynamics in animal models of glaucoma.

ACE inhibitors can affect IOP levels through their actions on AH dynamics. These inhibitors can decrease angiotensin II levels in AH, thus affecting the uveoscleral outflow, and slow down AH formation by lowering blood flow in the ciliary body [13].

We have experimentally demonstrated that the ACE inhibitor zofenopril can be used to normalize the ocular blood flow and AH circulation in rabbits with AIG.

The effects of zofenopril on the blood volume of choriociliary vessels appear to be caused by its capacity to increase plasma and heart tissue levels of nitric oxide [14] that plays an important role in supporting vascular homeostasis. Nitric oxide deficiency is a pathogenetic factor of endothelial dysfunction [28].

In turn, the beneficial effect of zofenopril on the parameters of ocular hydrodynamics in rabbits with AIG is also likely to be caused by nitric oxide deficiency in ocular tissues, causing relaxation of the trabecular meshwork and improving AH outflow [29].

Therefore, our study on AIG in rabbits demonstrated impaired ocular blood flow and ocular hydrodynamics in the presence of elevated IOP, and beneficial effect of the ACE inhibitor zofenopril on the eye function (i.e., the IOP, and parameters of ocular hemodynamics and hemodynamics). Further research is needed to confirm the results clinically.

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Disclosures

Received: 04.06.2025

Accepted: 25.09.2025

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Author Contributions: *: IMM: Conceptualization, Methodology, Writing – review and editing; NIK: Investigation, Data Analysis and Interpretation; Writing - original draft preparation; SGK: Investigation, Data Analysis and Interpretation, Writing - original draft preparation; TIS: Investigation, Data Analysis; AM: Investigation, Data Analysis. All authors reviewed the results and approved the final version of the manuscript.*

Conflict of interest: *The authors state that they have no conflicts of interest that could influence their views on the subject matter or material described or discussed in this manuscript.*

This paper is part of the research project "To investigate the role of gaseous neurotransmitters hydrogen sulfide and nitric oxide in the glaucomatous process and the effect of the angiotensin-converting enzyme inhibitor zofenopril on the mechanisms of this process in an animal model" 2022–2024 (State register No. 0122U001487).

Disclaimer: *The views presented in this article are those of the authors and do not necessarily represent those of their institutions or funding entities.*

Data Availability Statement: *All the data obtained or analyzed during this study are reported in the article.*

Abbreviations: *ACE, angiotensin-converting enzyme; AIG, adrenaline-induced glaucoma; C, aqueous humor outflow facility; F, aqueous humor production; IOP, intraocular pressure; P_0, tonographic IOP; RC, rheographic coefficient; SEM, standard error of mean.*