The peripheral and central neural actions of clonidine in normal and glaucomatous eyes

G. K. Krieglstein,* Maurice E. Langham,** and W. Leydhecker*

The peripheral and central neural actions of clonidine on normal and glaucomatous eyes have been investigated. Threshold doses of clonidine applied topically induced a monotonic decrease of intraocular pressure in the treated eye and had no effect on the contralateral eye. With increased clonidine dose, a decrease of intraocular pressure occurred in the untreated eye, and there was a concomitant decrease of systemic arterial blood pressure. Analysis of aqueous humor dynamics showed that the ocular response to the peripheral and the central neural actions of clonidine were without effect on the tonographic coefficient of outflow facility. The episcleral venous pressure decreased in both the treated and the untreated eyes, but the changes were too small to account for the observed decrease of intraocular pressure. The results are consistent with the concept that both the peripheral and central ocular hypotensive actions of clonidine are mediated by an inhibition of adrenergic neurogenic vasoconstriction in the eye.

Key words: clonidine, intraocular pressure and aqueous-humor dynamics, ophthalmic arterial pressure

The peripheral and the central neural actions of clonidine (2-(2,6 dichlorophenylamino) 2-imidazoline hydrochloride; ST 155; Isoglaucan, Catapres, Glaucopres) on the mammalian eye have been characterized in studies on conscious rabbits. The peripheral action is twofold. First, an α-adrenoceptor-mediated vasoconstriction, mydriasis, and increase of intraocular pressure occur. These responses are of short duration and may be blocked by α-adrenoceptor antagonists. The second response is a prolonged decrease of intraocular pressure, which is associated with an inhibition of adrenergic tone. The central neural action on intraocular pressure results from a direct effect mediated by the sympathetic innervation of the eye. In man, it is well known that clonidine given orally, intravenously, or topically decreases intraocular pressure and that these responses are proportional to dose and to the initial intraocular pressure. It is also well established that therapeutic doses of clonidine applied to the eye are partially absorbed and may decrease systemic and ophthalmic arterial pressure.

The important physiological and clinical question remains unanswered as to whether there are both a direct peripheral action and a central ocular hypotensive action of clonidine.
Clonidine in man similar to those demonstrated in animals. This question has been answered in this study. A separation of the peripheral and central neural effects of clonidine on the intraocular pressure of normal and glaucomatous eyes has been demonstrated, and the mechanism of the two responses has been determined.

Methods

Intraocular pressures were either measured with a standard Goldmann applanation tonometer mounted on a Zeiss slit lamp or were recorded by the Alcon applanation Pneumatonograph (Alcon Laboratories, Fort Worth, Texas), developed jointly by Langham and Digilab, Inc. (Cambridge, Mass.). Episcleral and conjunctival venous pressures were recorded by the air-jet procedure of Krakau et al.9

The air-jet system and the Goldmann applanation tonometer were mounted on the same Haag-Streit slit lamp in order that the intraocular pressure and the episcleral venous pressure could be measured without movement of the patient. The air-jet pressure that decreased the width of the blood vessel by 50% was taken as the end point; a second reading was taken as the occluded vessel opened to approximately 50% of its normal diameter. Average readings of the ascending and descending values were recorded. The analysis of the aqueous humor dynamics was made by the pneumatonographic procedure described by Langham et al.9

The ophthalmic arterial pressure was derived from the pulse amplitude–pressure relationship by the methodology described by Langham and Tomney.10

Clinical procedures. The patients (41 to 66 years old) with open-angle glaucoma represented a

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**Fig. 1.** A, Time courses of the brachial arterial and intraocular pressure responses of 10 glaucoma patients to a unilateral application of 2 drops of 0.5% clonidine. The upper figure gives the mean of the systolic and diastolic pressures. The lower figure shows the mean pressures of the treated (•——•) and untreated eyes (○○○). The pressure decreases in the treated eyes, based on difference in pairs of eyes, were highly significant (p < 0.01) at 60, 90, 120, and 180 min. B, Corresponding episcleral venous pressure (EVP) and the conjunctival venous pressures (CVP). The vertical bars represent the standard errors of the arithmetic mean.
Fig. 2. Early vascular and ocular pressure responses of 10 glaucoma patients to a unilateral application of 2 drops of 0.25% clonidine. The open (o—o) and closed circles (••) represent the untreated and treated eyes. A, Arterial and intraocular responses. B, Corresponding EVP and CVP.

Fig. 3. Early vascular and ocular pressure responses of 10 glaucoma patients to a unilateral application of 0.125% clonidine. The open and closed circles represent the untreated and treated eyes, respectively. A, Arterial and intraocular responses. B, Corresponding EVP and CVP.

random sample of patients attending the glaucoma clinic of the University Eye Hospital, Wurzburg. The diagnosis of glaucoma was based on sustained ocular hypertension (Goldmann applanation pressures exceeding 24 mm Hg), pathologic diurnal pressure curves, a glaucomatous field loss defined by the Goldman perimeter, and pathologic cupping of the disc. None of the patients had been under treatment with carbonic anhydrase inhibitors or with catecholamines, and miotic drugs were discontinued 48 hr prior to the studies. In the first series comprising 10 patients, the brachial blood pressure and ocular measurements were made at T = 0 and at 30, 60, 90, 120, and 180 min after topical application of 2 drops of 0.5% clonidine on the right eye (Isoglucon ½; Boeh-
Table I. Influence of a single unilateral application of clonidine on the intraocular pressure and systemic blood pressure in patients with open-angle glaucoma

<table>
<thead>
<tr>
<th>Clonidine dose (%)</th>
<th>Intraocular pressure of seated patients (mm Hg)</th>
<th>Treated eye</th>
<th>Untreated eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T = 0</td>
<td>120 min</td>
<td>T = 0</td>
</tr>
<tr>
<td>0.5</td>
<td>26.8 ± 1.6 (10)</td>
<td>14.0 ± 0.6 (10)*</td>
<td>28.0 ± 2.1 (10)</td>
</tr>
<tr>
<td>0.25</td>
<td>26.2 ± 0.5 (10)</td>
<td>19.0 ± 0.7 (10)*</td>
<td>24.8 ± 0.4 (10)</td>
</tr>
<tr>
<td>0.125</td>
<td>26.9 ± 0.8 (10)</td>
<td>20.0 ± 0.8 (10)*</td>
<td>24.8 ± 1.0 (10)</td>
</tr>
</tbody>
</table>

*Significant change (p < 0.01).

Table II. Influence of a single application of 0.25% clonidine unilaterally on the intraocular pressure and outflow facility coefficient in a group of normal subjects in supine position

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Intraocular pressure (mm Hg)</th>
<th>Control</th>
<th>Treated</th>
<th>Control − treated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19.8 ± 0.46 (12)</td>
<td>19.7 ± 0.37 (12)</td>
<td>0.1 ± 0.19 (12)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18.2 ± 0.43 (6)</td>
<td>15.5 ± 0.70 (6)</td>
<td>2.5 ± 0.43 (6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20.8 ± 0.58 (5)</td>
<td>16.4 ± 1.03 (5)</td>
<td>4.4 ± 0.75 (5)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19.4 ± 1.03 (5)</td>
<td>14.8 ± 0.73 (5)</td>
<td>4.6 ± 0.68 (5)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>19.7 ± 0.61 (6)</td>
<td>19.0 ± 0.61 (6)</td>
<td>0.7 ± 0.33 (6)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean difference in pairs of eyes of individual subjects.

The decreases in systolic and diastolic blood pressure induced by the unilateral application of 0.5% and 0.25% clonidine (Table I) were associated with significant decreases of the episcleral venous pressures in both eyes. The small decrease in conjunctival venous pressure in the same patients was not significant. In the series of glaucoma patients treated with 0.125% clonidine, a significant decrease of episcleral pressure developed in the treated but not the untreated eye.

The change in blood pressure seen in the first two series of patients was accompanied by a decrease in the pulse rate of approximately 10%. Thus, in those patients treated with 0.5% clonidine, the mean pulse rates before and 120 min after treatment were 85 ± 3/min and 77 ± 4/min, respectively.

A comparison of the ocular and systemic pressure responses of these three groups of glaucoma patients to increased concentrations of clonidine is shown in Figs. 1 to 3. In all three series, the decrease of intraocular pressure in the treated eyes exceeded that in the untreated eyes (p < 0.01). The intraocular pressure of the untreated eyes decreased significantly (p < 0.01) for both the 0.5% and 0.25% concentrations of clonidine but not for the 0.125% clonidine.

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A comparison of the ocular and systemic pressure responses of these three groups of glaucoma patients to increased concentrations of clonidine is shown in Fig. 4. The mean values were evaluated from pressure measurements made prior to and 120 minutes after unilateral application of the drug.

Ocular response of normal eyes to clonidine. The time courses of the intraocular
pressure and systemic arterial pressure responses to a single unilateral application of 0.25% clonidine are summarized in Fig. 5. All pressure measurements were made on seated subjects. The brachial arterial pressure decreased during the first hour but returned to predrug levels within 3 hr. This was associated with a decrease of approximately 10% in the pulse rate. At this time, the intraocular pressures of the treated eyes showed a maximal response. A partial recovery of intraocular pressure was present at 5 hr, and full recovery was seen at 24 hr.

Intraocular pressures were recorded on subjects in both seated and supine positions. Qualitatively, the responses in the two positions appeared similar, but quantitatively the pressure response was greatest in the supine position in six of the 12 subjects.

Larger hypotensive intraocular and arterial pressure responses followed the unilateral application of 0.5% clonidine. In three normal subjects, the mean brachial blood pressure decreased from a mean value of 105 ± 3 mm Hg to 80 ± 5 at 90 min. The initial intraocular pressures of 18, 21, and 17 mm Hg in the treated eyes decreased to 14, 13, and 12 mm Hg, respectively, at 90 min. Significant but smaller decrease of intraocular pressure was seen in the untreated eyes.

Topical unilateral application of 0.125% clonidine to six normal subjects induced pressure decreases in the treated but not in the untreated eyes. Initially, the mean intraocular pressures of the treated and the untreated eyes were 17.4 ± 0.3 and 17.4 ± 0.3 mm Hg, and at 60 min the corresponding pressures were 13.8 ± 0.5 and 17.6 ± 0.4 mm Hg. The brachial blood pressure remained unchanged during this period.

**Aqueous humor dynamics in normal and glaucomatous subjects treated with clonidine.**

The outflow facility coefficients in normal subjects treated with a single application of 0.25% clonidine are summarized in Table II. No demonstrable change in the mean outflow facilities was seen in pairs of treated and untreated eyes over the 24 hr period. A random fluctuation in values over the time course was seen in individual cases, but no clear-cut pattern emerged. Similarly, no changes in the outflow coefficient were found in four subjects treated unilaterally with 1 drop of 0.5% clonidine. This lack of response in the out-

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>T = 0</td>
<td>120 min</td>
<td>T = 0</td>
</tr>
<tr>
<td>145 ± 18 (10)</td>
<td>90 ± 3 (10)*</td>
<td>102 ± 4 (10)</td>
</tr>
<tr>
<td>144 ± 12 (10)</td>
<td>110 ± 8 (10)*</td>
<td>92 ± 4 (10)</td>
</tr>
<tr>
<td>146 ± 11 (10)</td>
<td>140 ± 9 (10)</td>
<td>94 ± 3 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outflow facility coefficient (μl min⁻¹ mm Hg⁻¹)</th>
<th>Control</th>
<th>Treated</th>
<th>Control – treated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.29 ± 0.02 (12)</td>
<td>0.31 ± 0.02 (12)</td>
<td>-0.02 ± 0.01 (12)</td>
<td></td>
</tr>
<tr>
<td>0.26 ± 0.02 (5)</td>
<td>0.23 ± 0.04 (5)</td>
<td>0.03 ± 0.03 (5)</td>
<td></td>
</tr>
<tr>
<td>0.30 ± 0.03 (5)</td>
<td>0.27 ± 0.03 (5)</td>
<td>0.02 ± 0.03 (5)</td>
<td></td>
</tr>
<tr>
<td>0.37 ± 0.03 (5)</td>
<td>0.37 ± 0.05 (5)</td>
<td>-0.01 ± 0.03 (5)</td>
<td></td>
</tr>
<tr>
<td>0.33 ± 0.02 (6)</td>
<td>0.31 ± 0.02 (6)</td>
<td>0.01 ± 0.02 (6)</td>
<td></td>
</tr>
</tbody>
</table>
flow facility was in contrast to the increased outflow facility in normal subjects treated with epinephrine and measured by the same technique.\textsuperscript{12, 13}

The flow equation \( F = C (P_o - P_v) \), where \( F \) is the rate of aqueous humor formation (\( \mu l \) \( \text{min}^{-1} \)), \( C \) the outflow facility (\( \mu l \) \( \text{min}^{-1} \) mm Hg\(^{-1} \)), and \( P_o \) and \( P_v \) the intraocular and episcleral venous pressures, was used to evaluate the influence of clonidine on the rate of aqueous humor formation. The mean values of \( F \) in pairs of eyes of five normal subjects prior to treatment were 2.1 ± 0.2 and 2.2 \( \mu l \) \( \text{min}^{-1} \), and at 60 to 120 min after the unilateral application of 1 drop of 0.25% clonidine, the mean values of \( F \) in the treated and untreated eyes were 1.0 ± 0.21 \( \mu l \) \( \text{min}^{-1} \) and 1.8 ± 0.34, respectively. The mean rate of flow in the treated eyes of individual subjects was 58% ± 6 of that of the control eyes.

### Influence of clonidine on the ophthalmic arterial and the ocular perfusion pressures

Table III summarizes the results in six normal subjects treated unilaterally with 1 drop of 0.25% clonidine. The intraocular pressures of the treated but not the untreated eyes decreased significantly by 90 min. There was a significant decrease of the mean brachial and ophthalmic arterial pressures over the same time period. The mean ocular perfusion pressure did not decrease in the treated eyes but fell by 10% in the untreated eyes.

### Discussion

In both normal and glaucomatous eyes, threshold doses of clonidine applied unilaterally caused a prolonged decrease of intraocular pressure in the treated but not the untreated eyes. At higher dosage, the intraocular pressure response increased and was accompanied by a significant but smaller response in the contralateral eye and by a decrease of systemic blood pressure. Both the direct peripheral and the central mediated ocular pressure responses occurred without significant change in the tonographic outflow facility. In the assessing of the mechanism and characteristics of these peripheral and central actions of clonidine, it is
Fig. 5. Time courses of the brachial arterial and intraocular pressure responses of 12 normal adult subjects to a unilateral application of 1 drop of 0.25% clonidine. The pressure decrease in the treated eyes, based on difference in pairs of eyes, was highly significant (p < 0.001) at 1, 3, and 5 hr.

Pertinent to point out that clonidine acts as an α-adrenergic agonist. In this respect α-adrenoceptor antagonists have been shown to block both the peripheral and the central actions of clonidine.

Peripheral ocular response to clonidine. There were both qualitative and quantitative differences between the ocular responses to clonidine and to the adrenergic transmitter agonist, norepinephrine. The pupil dilatation was small and transient with concentrations of clonidine that caused rapid and significant decrease of intraocular pressure in both normal and glaucomatous eyes. In contrast, the dose response for pupil dilatation and decreased intraocular pressure to norepinephrine in human eyes is identical. A more striking difference between the two α-adrenoceptor agonists was seen in the time course of the pressure response. The onset of the pressure response to norepinephrine has a delay of 2 to 3 hr, at which time the maximal pupillary response is well past. Clonidine induced a rapid decrease of intraocular pressure which was maximal within 1 to 2 hr. The qualitative difference in responses between the two agonists was seen in their effect on the outflow facility. Clonidine induced no significant change in the outflow facility, whereas the pressure response induced by norepinephrine in both normal and glaucomatous eyes is associated with increase of the outflow facility.
to be dependent on two $\alpha$-adrenoceptor mechanisms. The first is due to stimulation of postsynaptic adrenergic receptors. These responses persist after surgical denervation of the adrenergic neuronal innervation of the eye but are blocked by $\alpha$-adrenoceptor antagonists.

The second local adrenergic mechanism mediates the prolonged decrease of intraocular pressure. The anatomic basis of this response differs from the former in that it is dependent on an intact adrenergic innervation of the eye. It is suggested, but not yet proven, that the response results from stimulation of presynaptic $\alpha$-adrenoceptors by clonidine. This explanation is in keeping with experimental evidence that clonidine acts in such a manner in other organs of the body. Clonidine decreased the heart rate in dogs with spinal cord section at the level of the second cervical vertebra and blocked the cardiac acceleration caused by low-frequency electrical stimulation of the right postganglionic cardiac sympathetic nerves in dogs. In isolated rabbit hearts, clonidine also antagonized the release of norepinephrine caused by stimulation of intact sympathetic nerves.

In related investigations it has been shown that presynaptic $\alpha$-adrenoceptors mediate a negative feedback control of norepinephrine release and that the inhibitory action of clonidine results from competition with norepinephrine for the presynaptic sites. Central nervous system's response to clonidine. The stimulation of $\alpha$-adrenoceptors in the vasomotor centers of the medulla oblongata by clonidine causes a general decrease of efferent sympathetic nerve activity to the peripheral organs. In normal and glaucomatous eyes the importance of the central neural effect was reflected in the decrease of intraocular pressure in the contralateral untreated eyes. This was approximately 50% of the total pressure response in the treated eyes of both normal and glaucomatous patients.

The mechanism of the central neural action on the eye has been studied in rabbits and was found to be dependent on an intact adrenergic innervation. This finding is in keeping with much evidence that clonidine modifies the peripheral circulation through a decrease of efferent sympathetic nerve activity, i.e., an inhibition of adrenergic and vasoconstrictor tone.

The results on man are consistent with the view that the central neural action of clonidine in decreasing intraocular pressure is also mediated by the adrenergic nerves innervating the eye. The alternate explanation that the intraocular pressure decrement is a consequence of the decrease of general blood pressure appears most unlikely. Thus it is well known that the influence of systemic blood pressure on the level of the intraocular pressure of animals and man is disproportionately small. Moreover, as pointed out above, this mechanism was disproved as the cause of the ocular hypotensive response in rabbits. Finally, it is known that in glaucoma patients on sustained treatment with topical clonidine, the ocular response is sustained, whereas the blood pressure response decreases and may even disappear completely (ref. 24 and unpublished observations of the authors).

Vascular responses to clonidine. The circulatory responses to clonidine are complex in that it causes both vasoconstriction, through its stimulation of postsynaptic $\alpha$-adrenoceptors, and vasodilatation, by stimulation of inhibitory presynaptic $\alpha$-adrenoceptors and through inhibition of efferent neurogenic vasoconstrictor activity. It is evident, however, that the vasoconstrictor response is weak and that the vasodilator response dominates. Thus a decrease of peripheral vascular resistance is associated with the decrease of arterial pressure in systemic hypertensive patients treated with clonidine. A similar situation probably exists in the eye, for the transient vasoconstrictor response yields to a prolonged intraocular hypotensive response resulting from a decrease of aqueous humor formation, a response typical of the vasodilator adrenergic agonists.
episcleral venous pressure induced by local application of clonidine throws no light on the local microcirculatory changes, for it has been reported that both vasoconstrictor and vasodilator drugs applied topically to man increase episcleral venous pressure. 25

The significance and possible danger to the glaucomatous eye resulting from a decrease of arterial blood pressure induced by clonidine remains to be clarified. 26, 27 Thus, although intraocular pressure decrement in glaucoma patients can be induced by clonidine without effect on the systemic blood pressure, it is evident that a maximal ocular pressure response is associated with a decrease of systemic blood pressure. It remains, however, to be elucidated whether the decrease in intraocular pressure in the patients treated chronically with clonidine is accompanied by a decrease in the ocular perfusion pressure (the ophthalmic arterial pressure minus the intraocular pressure).

REFERENCES


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