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TREATMENT OF OCULAR HYPERTENSION BY ADRENALIN AND DIVERSE SYMPATHOMIMETIC AMINES*

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Hamburger,[1] in 1923, noted that the instillation of two-percent adrenalin induced a reduction of tension in glaucoma simplex. Goldmann,[2] in 1951, attributed this effect to a prolonged reduction in the rate of aqueous formation.

In recent publications Weekers, Prijot, and Gustin[3,4] have shown by Grant's technique of tonography that adrenalin lowers the ocular tension in open-angle glaucoma without affecting however the pathologically increased resistance to aqueous flow. This result would seem to be occasioned by a lessened formation of aqueous. As the miotics lower ocular tension by augmenting the facility of flow, adrenalin and miotics play a complementary role. The former reduces the formation of aqueous, the latter facilitates its drainage. The two in association provide a local treatment particularly efficacious for glaucoma simplex (open-angle glaucoma).

The theoretic and practical importance of this tension-reducing action of adrenalin has stimulated further research on the mechanism involved. The present study consists of two parts: (1) The measurement of changes in the delivery of aqueous under the influence of adrenalin; (2) a similar study with diverse sympathomimetic amines.

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I. Modification of Aqueous Production under the Influence of Adrenalin

a. Method of Measurement

Our method, based on that of Langley and MacDonald,[5] measures the speed of the disappearance of fluorescein from the anterior chamber after a previous instillation over the cornea. The fluorometer and the details of procedure have been described by Weekers and Delmarcelle.[6] After fluorescein is dropped in the eye, the concentration of the dye in the anterior chamber increases first, then progressively decreases. At the feeble concentration presented in the anterior chamber the role of diffusion in the elimination of the dye is but slight. The reduction of the concentration of the dye in percentage per minute is calculated by the following formula:

$$C = \frac{2.3 \log. \frac{\text{conc.}t_1}{\text{conc.}t_2}}{t_2 - t_1}$$

Conc.t_1 and Conc.t_2 are respectively the concentrations of fluorescein in the anterior chamber at the beginning and end of a period of decoloration of the aqueous. In normal subjects C varies from 0.33 to 0.65, the average value being 0.48.

This method does not permit the calculation of aqueous flow in cu.mm. per minute as it does not take into account the volume of the anterior chamber. Though less precise than the fluorometric method of Goldmann, its simplicity has facilitated its clinical application in numerous cases (Weekers and Delmarcelle[6]). The information obtained by this fluorometric method on the intraocular current of aqueous is generally in accord with the tonographic calculations of aqueous flow.

b. Results

Fluorometric measurements of flow were made 24 hours after instillation of two-percent *l*-adrenalin on 15 normal subjects, 13 patients with glaucoma simplex (open-angle glaucoma), and three cases of glaucoma following flat chamber after cataract extraction. The data are compared with those of a previous study in which the aqueous flow was measured by the same method in 64 normal subjects, 20 patients with untreated open-angle glaucoma and six untreated cases of glaucoma following flat chamber after cataract extraction. The findings are summarized in Table 1.

The instillation of two-percent *l*evorotatory adrenalin induces a lasting diminution of aqueous production. This conclusion is supported both by direct fluorometric measurements of aqueous flow and by tonographic measurements published previously (Weekers, Prijot, and Gustin[3,4]).

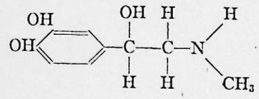
TABLE 1

Reduction of Aqueous Flow under the Influence of One Instillation of Levorotatory Adrenalin

	Without Treatment					24 Hr. after One Instillation of *l*-adrenalin				
	Number of Cases	Average Ocular Tension (mm. Hg)	Coefficient of Flow			Number of Cases	Average Ocular Tension (mm. Hg)	Coefficient of Flow		
			Min.	Mean	Max.			Min.	Mean	Max.
Normal subject	64	16	0.33	*0.48*	0.65	15	13	0.13	*0.34*	0.46
Open-angle glaucoma	20	28	0.30	*0.43*	0.55	13	17	0.28	*0.33*	0.45
Glaucoma of aphakic eye	6	High	0.44	*0.51*	0.60	3	17	0.21	*0.30*	0.40

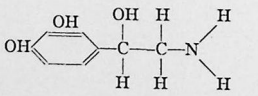
II. The effect on ocular tension of diverse sympathomimetic drugs

We have compared the effects on ocular tension of *l*-adrenalin, *d*-adrenalin, adrenalone, noradrenalin, and aleudrine.* These substances were chosen to facilitate insight into the tension-reducing mechanism. Levorotatory adrenalin, two-percent concentration, is the standard of comparison. It has this structural formula:

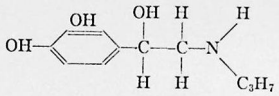


Dextrorotatory adrenalin was used to learn whether the effect on ocular tension was due to sympathetic stimulation or to some other factor, as the sympathomimetic action of *d*-adrenalin is very much less marked than that of *l*-adrenalin. Adrenalone served the same purpose. This substance results from the replacement of hydroxyl in the lateral chain by ketone. Its sympathomimetic activity is extremely feeble.

The utilization of noradrenalin was dictated by other considerations. Ahlquist and Gaddum classify the activities of adrenalin in two groups—alpha and beta. The alpha actions include all motor effects: enhancement of smooth muscle tone, augmentation of secretion, and so forth. The much more specific beta actions are tachycardia in mammals, inhibition of smooth muscle, and the influence on metabolism and the central nervous system. The alpha actions are markedly fortified by cocaine, but not the beta actions. Noradrenalin possesses the alpha actions of adrenalin but very little beta activity. Its structural formula is:



In aleudrine (isopropyl noradrenalin)* the alkyl radical is attached to nitrogen as shown in the formula below. This exaggerates the beta actions of *l*-adrenalin and diminishes the alpha effects (Bacq[7]).



a. Material and conditions of examination

This investigation was concerned almost exclusively with patients affected by open-angle glaucoma. Cases of narrow-angle glaucoma were eliminated by careful gonioscopic examinations since some of the amines used are mydriatic (*l*-adrenalin, noradrenalin) and mydriasis in narrow-angle glaucoma would provoke occlusion of the iridocorneal angle with a resulting increased resistance to aqueous flow and a consequent rise in ocular tension in spite of lessened flow of aqueous.

The tests of each drug were generally continued on the same patient for about two weeks, and the ocular tension was noted two to three times per week. The tests with aleudrine were of shorter duration for reasons explained later. The figures in the appended tables are averages of several tonometric measurements. All measurements were made 18 hours or more after the instillation of the drug in order to register the lasting effect on tension due to modification of aqueous production and not the immediate effect on tension which could be attributed to vasomotor changes. All solutions were instilled in the evening, one drop daily.

The solution of *l*-adrenalin was according to the following prescription:

l-adrenalin chlorhydrate equivalent to 2-percent *l*-adrenalin base	(gr.)
Sodium metabisulfite	.03
Chlorobutanol	.03
Sodium chloride	.02
Pontocaine	.05
Desogen (Geigy) (1:50,000)	
Sterile distilled water	10.00

* Translator's note. Isopropyl noradrenalin is marketed in America under the trade names Isuprel (Winthrop-Stearns), Norisodrine (Abbott), and Isonorin (Smith, Carrell, Dunham).

TABLE 2

OCULAR TENSION AS AFFECTED BY *l*-ADRENALIN AND *d*-ADRENALIN

Without Treatment (mm. Hg)	After *l*-adrenalin (mm. Hg)	Without Treatment (mm. Hg)	After *d*-adrenalin (mm. Hg)
25	15	26	23
26	15	26	25
26	20	26	25
27	20	26.5	25.5
27	22	27	27
27	20	27	29
28	20	27	24
34	20	27.5	24
35	16	36	31
36	15	39	35
45	18	44	36
AVERAGE *30.5*	*18.3*	*30.2*	*27.7*

The other sympathomimetic amines were prepared in a concentration equimolar to two-percent *l*-adrenalin. When racemic compounds had to be used, as with noradrenalin and aleudrine, the concentrations were doubled as investigation showed that *d*-adrenalin was almost totally ineffective.

b. RESULTS

Table 2 shows that *l*-adrenalin lowers the ocular tension much more than *d*-adrenalin in patients affected with glaucoma simplex (open-angle glaucoma). Occasionally the *d*-adrenalin solution on oxidizing is so altered as to become a mydriatic and acquire tension-reducing power. This occurs inconstantly and was not systematically studied.

TABLE 3

OCULAR TENSION AS AFFECTED BY *l*-ADRENALIN AND ADRENALONE

Without Treatment (mm. Hg)	After *l*-adrenalin (mm. Hg)	After Adrenalone (mm. Hg)	After *l*-adrenalin plus Adrenalone (mm. Hg)
23	20	26	19
24	18	31	20.5
27	22	24.5	21.5
27	24	30	21
28	18	23	18
29	21	32	21
30	19	28	19
30	20	27	18
32	20	30	20
39	23	39	21.5
AVERAGE *28.9*	*20.5*	*29.0*	*19.9*

Table 3 demonstrates that *l*-adrenalone is much less active than *l*-adrenalin. A mixture of two-percent *l*-adrenalone and two-percent *l*-adrenalin was no more effective than two-percent *l*-adrenalin alone. The "glaucosan" of Hamburger was such a mixture and in a previous study[3,4] we employed a similar pharmaceutical preparation. We use now the two-percent *l*-adrenalin prescription previously discussed.

Table 4 shows that racemic noradrenalin lowers ocular tension but less consistently than *l*-adrenalin.

The tests with aleudrine ran into difficulties. Instillation of the aleudrine solution provoked almost immediately a brief though marked tachycardia. For this reason and because the solutions rapidly become inert, the observations with aleudrine were generally of short duration. It is evident, how-

TABLE 4

OCULAR TENSION AS AFFECTED BY *l*-ADRENALIN AND NORADRENALIN

Without treatment (mm. Hg)	After *l*-adrenalin (mm. Hg)	After Noradrenalin (mm. Hg)
24	21	25.5
24.5	21	22.5
25	25	29
25	20	24
25	19.5	20.5
26	19	22
26	19	22
26	19	19
26	18	18
26	21	22
26.5	24	24
27	21.5	29
28	19	20.5
28	—	19
29	21	26
29	24.5	25
30	19	19
30	19	22
30	19	20
31	18	24
32	20	21.5
32	19	22
34	22	35
39	23	36.5
AVERAGE *28.2*	*20.2*	*23.7*

TABLE 5

OCULAR TENSION AS AFFECTED BY *l*-ADRENALIN AND ALEUDRINE

Without Treatment	After *l*-adrenalin	After Aleudrine
45.5	—	29
45	21	22
39	21.5	24
39	18	20
37	—	22
32	20	26
32	24.5	15
30	19	14
30	20	22
30	19	17
29	25	21
27.5	—	19.5
26	18	20
28	—	20
25	20	21
25	—	19.8
24.5	20	20
24	17.5	17.5
24	17.5	17.5
24	20.5	18
25	17	18
AVERAGE *30.9*	*19.9*	*20.2*

ever, that aleudrine lowers the tension in open-angle glaucoma (table 5). Though aleudrine is neither a mydriatic nor a vasoconstrictor, its action is comparable to that of *l*-adrenalin. In the present study we were unable to quantitatively assess the comparative tension-lowering effect of the two drugs. The graphs (figs. 1 and 2) suggest that, though their effects are approximately of the same order, *l*-adrenalin has an apparently more lasting action than aleudrine.

COMMENT

The tonographic measurements previously published[3,4] and the fluorometric measurements of flow in the present study definitely establish that the tension-lowering action of *l*-adrenalin in open-angle glaucoma results from a reduction of aqueous formation and not from an improvement of drainage conditions. The comparison of the tension-reducing action of diverse sympathomimetic amines clarifies the mechanism through which *l*-adrenalin inhibits the formation of aqueous. Drugs without appreciable sympathomimetic activity like *d*-adrenalin and adrenalone likewise lack a tension-reducing effect. The reduced tension apparently results then from sympathetic stimulation.

The hypothesis that the reduction of the formation of aqueous is determined by vasoconstriction and the lessened blood flow in the ciliary body that follows should hence be abandoned. The reduction in tension after the instillation of *l*-adrenalin is much more prolonged than the vasoconstriction visible in the conjunctiva; moreover aleudrine, which is not a vasoconstrictor, possesses like *l*-adrenalin the same property of lowering ocular tension. A plausible hypothesis according to which *l*-adrenalin and aleudrine alter the metabolic processes required for the formation of aqueous is proposed.

This concept is of practical clinical importance. In many cases of ocular hypertension the obstacle to the drainage of aqueous is so extensive that miotics cannot ameliorate drainage nor consequently reduce ocular tension. In this contingency an adjuvant that reduces the formation of aqueous may retard the necessity of surgical intervention.

Various therapeutic measures recently proposed reduce the formation of aqueous, such as retrociliary diathermy, Diamox, and some sympathomimetic amines. Each of these therapies has its advantages and deficiencies. Retrociliary diathermy acts by altering the circulation of the ciliary body. When properly performed it is harmless and reduces the formation of aqueous to approximately half its initial value. The indications of the procedure have been defined by L. and R. Weekers.[8] Diamox inhibits markedly the formation of aqueous but the required dosage can seldom be tolerated over a long period (Becker,[9] Grant and Trotter,[10] Weekers and Watillon[11]).

We would stress the advantages of *l*-adrenalin in the treatment of open-angle glaucoma. It rarely produces intolerance and can be used for months.[3,4] Levorotatory adrenalin is definitely contraindicated in narrow-angle glaucoma as the accompanying mydriasis closes the angle, increases re-

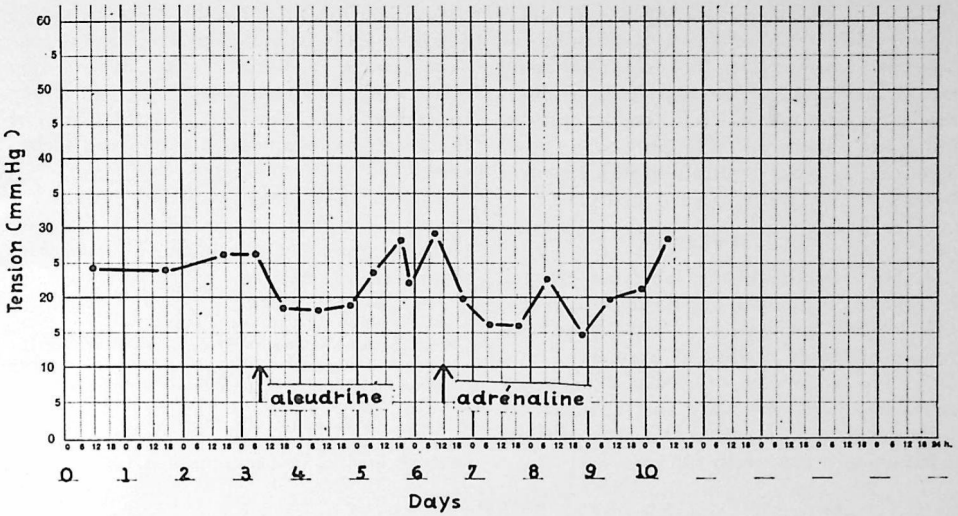


Fig. 1 (Weekers, Delmarcelle, and Gustin). The effect on ocular tension of a single instillation of aleudrine and of a single instillation of *l*-adrenalin in the same patient.

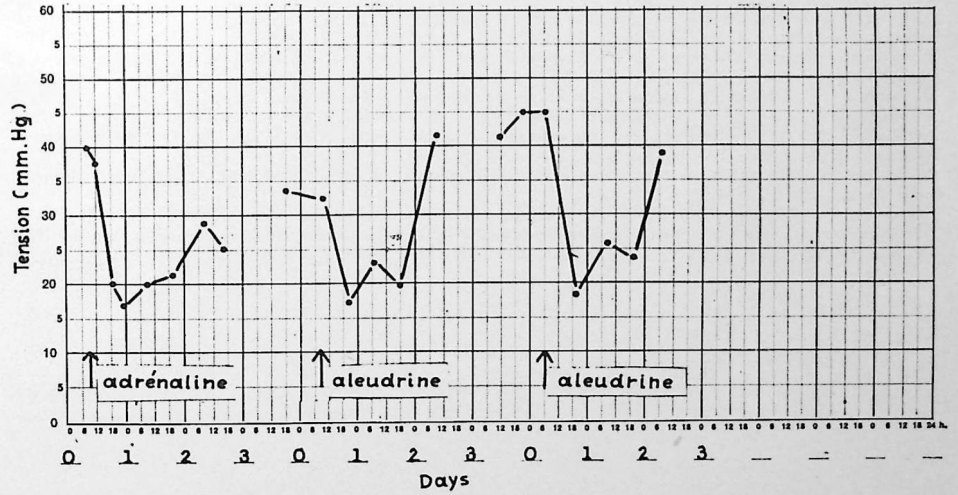


Fig. 2 (Weekers, Delmarcelle, and Gustin). The effect on ocular tension of *l*-adrenalin and aleudrine in the same patient.

sistance to drainage, and raises the ocular tension despite a lessened production of aqueous. This accounts for our special interest in aleudrine, which apparently inhibits the formation of aqueous like *l*-adrenalin but is not a mydriatic. The prolonged use of aleudrine appears contraindicated however because of the tachycardia it provokes.

Summary

1. The reduction of ocular tension effected by *l*-adrenalin in open-angle glaucoma is due to a lessened production of aqueous and not to any increased facility of drainage.

2. The reduction of ocular tension by noradrenalin is less than that achieved by *l*-adrenalin, and the action of *d*-adrenalin and adrenalone is practically nil.

3. Aleudrine, though not a vasoconstrictor, acts like *l*-adrenalin in reducing ocular tension. Since aleudrine also induces no mydriasis it may be eventually of some value in narrow-angle glaucoma, but the drug has the great disadvantage of provoking tachycardia.

4. The advantages accruing from the simultaneous use of remedies facilitating aqueous drainage and reducing aqueous formation are emphasized.

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