Table IV. Comparison of inhibition of aqueous humor protein response to arachidonic acid (5 per cent OU) by various topical nonsteroidal anti-inflammatory agents

<table>
<thead>
<tr>
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<th>Mean aqueous humor protein ± S.E., control-drug at 30 min</th>
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<tbody>
<tr>
<td></td>
<td>mg./ml.</td>
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<tr>
<td>Indoxole (polysorbate)</td>
<td>11.4 ± 2.5*</td>
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<tr>
<td>Flurbiprofen</td>
<td>9.3 ± 2.3*</td>
</tr>
<tr>
<td>Medofenamic acid</td>
<td>8.8 ± 2.0*</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>7.5 ± 1.7*</td>
</tr>
<tr>
<td>Clonixin</td>
<td>4.8 ± 2.4</td>
</tr>
</tbody>
</table>

*Significant difference between the eyes treated with drug and those treated with diluent, paired t test, p < 0.01.

REFERENCES


In a total of 92 eyes in 46 individuals the outflow facilities obtained by weight tonography, C_in, correlated curvilinearly with those estimated by an acetazolamide test, C_acet. The presumed apathological pairs of eyes were those with C_acet above (or equal to) 0.15 and pressure symmetry (right/left). Twenty-one patients referred for glaucoma suspicion (and three normal test persons) showed these characteristics. The eyes appeared clinically healthy even if the pressure range reached 30 mm. Hg. Here C_acet averaged 0.32 but C_in only 0.16; the discrepancy is possibly caused by the outflow obstruction brought about by the high pressures during weight tonography. The presumed pathological eyes (33 from 20 individuals referred for glaucoma suspicion or manifest glaucoma) were those with C_acet below 0.15. They generally showed pressure asymmetry and in some cases pressure values above 30 mm. Hg, and there were in several cases other glaucomatous signs. In this group C_in and C_acet were similar; both averaged 0.09. The acetazolamide test is considered more informative than weight tonography because the test provides at the same time an estimate of the outflow facilities in the normal- or low-pressure range as well as an accurate comparison between the pressures and outflow facilities of the two eyes. The test is time-consuming, however (1 to 1½ hours).

In the acetazolamide test the rate of aqueous secretion is reduced to a new and lower (arbi-
Fig. 1. Acetazolamide test in 67-year-old man with simple glaucoma (bilateral visual field defects and excavated discs, untreated). Abscissa: time in minutes; ordinate: intraocular pressures measured by applanation tonometry (mm. Hg). At -17 minutes alternating readings begin ("first pressures"). In the control period the pressures stabilize on "initial pressure levels." Following the acetazolamide injection the pressures decay and stabilize again. Calculated reference curves for estimation of the outflow facilities are traced as illustrated. A "break" is seen in the pressure decay of the left eye. Estimated outflow facilities: 0.08/0.04; by weight tonography: 0.07/0.03 (right/left). The test shows abnormality of the aqueous circulation because of too high initial pressure levels, too low outflow facilities, unidentical curves, and a break.

Fig. 3. Outflow facilities estimated by the acetazolamide test (Cac.) correlate curvilinearly with those obtained by weight tonography (Cton) (Fig. 3). On the basis of the Cac values the eyes may as previously be distributed into two categories (A and B).

Material and methods.

Selection of patients. Forty-three out of a total of 46 patients were referred to the out-patient clinic by practicing eye specialists because of glaucoma or glaucoma suspicion. The clinical grouping is listed in Fig. 2. In three patients there was no suspicion of glaucoma or ocular hypertension. In 10 cases treatment (pilocarpine or adrenaline drops) was discontinued some 40 hours prior to the tests. Thirty-six patients were not in antiglaucoma therapy at all.

Tests. The weight tonographic test was carried out with a micrometer-calibrated Mueller instrument with a plunger weight normally of 7.5 grams for pressures between 20 and 30 mm. Hg. The acetazolamide test (Fig. 1) was done with a Goldmann applanation tonometer which was checked with the enclosed metal rod and connected electrically to a recorder (tonometer and slit lamp: Haag-Streit T 900 and 900). The reference curves had been calculated on the basis of the laws mentioned above by a summation procedure (0.1 mm. Hg pressure intervals).

The clinical examination was carried out as described earlier, apart from the use of Goldmann perimetry in addition to the examination on the tangent screen.

Results. Considering the material as a whole, the outflow facilities estimated by the acetazolamide test (Cac.) correlate curvilinearly with those obtained by weight tonography (Cton) (Fig. 3). On the basis of the Cac values the eyes may as previously be distributed into two categories (A and B).

Category A. Cac. \( \geq \) 0.15 was found in 59 eyes from 33 patients. As before we find that the eyes in this group appear to be clinically healthy even if, after repeated explanations, the pressures ("initial levels") are rather high in some eyes, up to
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*diff

89 mm Hg.

12

0.15 O

referred for intraocular hyp. (33)

chronic angle closure (1)

juvenile glauc. (gon. changes) (2)

pigment glaucoma (1)

steroid treatment (kidney transpl.) (1)

excessive myopia (2)

glau. scotomas (3)

normotensive (3)

Fig. 2. Low outflow facilities are associated with pressure asymmetry. Total subjects, 46; numbers in parentheses in key indicate individuals. One point per pair of eyes. Abscissa: the outflow facility of the two eyes (acetazolamide test); the lowest if they differ. Ordinate: the difference between the initial pressure levels (see Fig. 1) of the two eyes (used as an indicator for asymmetry). Medians: 2.8 mm Hg for Caret <0.15; 0.2 mm Hg for Caret > 0.15; significantly different, p <0.001 by Mann-Whitney U test. Asymmetry was not correlated to initial pressure levels; thus, if the ordinate were the difference between the initial pressure levels in per cent of the average of the two initial pressure levels, the graph would almost appear the same and the level of significance be unchanged.

27 mm Hg (Fig. 4) (first pressures up to 30 mm Hg). And it is confirmed that in the majority of the patients (21 referred for intraocular hypertension plus three without sign of ocular hypertension) the curves of the two eyes are virtually identical (in Fig. 2, demonstrated by the small or lacking difference between the initial pressure levels as an indicator for the pressure symmetry). In these patients, considered to have an apathological aqueous circulation even if hypertensive, Caret averages 0.32 and Cton 0.16 (significantly different for p <0.001, Sign test on single eyes, Fig. 3); eight eyes had Cton values below 0.12 (often considered to be the lower limit of normality in weight tonography), showing that the two methods do not always agree (Fig. 4). In group A as a whole Caret was 0.31 and Cton 0.15 (different for p <0.001).

Category B. Caret <0.15 was found in 33 eyes from 20 patients. This category incorporated the eyes with abnormal gonioscopic findings, visual field defects, or intraocular pressures above 30 mm. Hg. Nearly all initial pressure levels were above 20 mm. Hg (Fig. 4), and most of the eye pairs showed pressure asymmetry (Fig. 2). Here Caret and Cton were similar, the average of each of them being 0.09.

In the example of an acetazolamide test in a glaucoma patient shown in Fig. 1, a "break" is seen in the pressure decay of the left eye. The possible nature of this phenomenon was discussed earlier. In four cases, breaks were observed with the present selection of patients. They originated in category B.

Discussion. The curvilinearity of the relationship between the two measures of outflow facility (Fig. 3) raises the central question: Why is Caret generally larger than Cton in the eyes with high outflow facilities (Caret >0.15), but close to Cton in the remaining eyes? The possible errors of the acetazolamide test have been discussed earlier, and we find it improbable that any of them can explain the curvilinearity. A clue to the question may be that Cton is determined at a relatively high pressure due to the weight of the Schiötz tonometer (e.g., p0 = 42 mm. Hg for p0 = 25 mm. Hg with a 7.5 gram plunger weight) but Caret at a lower pressure due to the effect of the acetazolamide (around 20 mm. Hg in most cases), since it seems from other studies that the outflow facility of an eye is lower the higher the intraocular pressure. Like the present material Thorburn's included, beside normotensive individuals, cases of symmetrical ocular hypertension without other signs of glaucoma.

Moses suggested that the phenomenon was due to a compression of the trabeculae or of Schlemm's canal and in fact morphological changes, which might be obstructive, have been observed in the Schlemm system as a response to elevation of the intraocular pressure.

Accordingly, the occurrence of a relatively low
Fig. 3. The curvilinear relationship between outflow facilities obtained by weight tonography (ordinate) and acetazolamide test (abscissa) in 43 patients referred for suspected glaucoma and 3 normotensive individuals (total material, 92 eyes). Each point represents the results of one eye. The Spearman rank correlation coefficient, $r_s$, is 0.64. The probability that this is due to chance alone is less than 0.001.

Fig. 4. The highest intraocular pressures are associated with the lowest outflow facilities (estimated from $C_{acet}$ or from $C_{ton}$). Total material. Each point represents the results of one eye. Abscissa: outflow facility (acetazolamide test); ordinate: initial pressure level (defined in Fig. 1).

Outflow facility with weight tonography in eyes with $C_{acet}$ values above 0.15 could then be explained by the "outflow obstruction effect" of an elevated pressure.

In the eyes with $C_{acet}$ values below 0.15 (the presumed pathological eyes) $C_{acet}$ and $C_{ton}$ were about equal. Apparently, in this group there was no distinct effect on the outflow resistance of an ocular pressure elevated during weight tonography. The underlying pathological mechanism might be that a compression and fusion of the walls of Schlemm's canal are already widespread at the pressures prevailing in the acetazolamide test. In that case a further compression by the Schiotz tonometer would not reduce the outflow facility much. (In a few eyes the outflow system might still be able to unfold sporadically during the marked decompression produced by the acetazolamide and give rise to increases in the outflow facility registered as "breaks" [Fig. 1] or a high pressure-reducing effect of acetazolamide.)

The reasonably good correlation between $C_{acet}$ and $C_{ton}$ supports our belief that the acetazolamide test mirrors the pressure-buffering capacity of the aqueous circulation and can detect abnormalities in the outflow system. On the other hand,
in our opinion, it should be used with some reservation as a prognostic test for the later appearance of glaucomatous visual field defects since the individual pressure vulnerability of the optical nerve head may vary—in this respect, even if more informative, it shares the fate of other tests for aqueous humor dynamics.

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Key words: acetazolamide test, facility of aqueous outflow, glaucoma test, intraocular hypertension, pathological and apathological aqueous circulation, weight tonography.

REFERENCES


The intraocular pressure of conscious, unsedated owl monkeys (Aotus trivirgatus) was measured with an applanation tonometer. Untreated eyes of the conscious animals were found to have higher values than those reported for owl monkeys anesthetized with pentobarbitone. Locally applied pilocarpine, carbachol, and oxotremorine gave concentration-related reductions in pressure, oxotremorine being the most potent and having longer duration of effect than the other compounds. Slight reductions were also observed with aceticholine and R.S. 86. These results are discussed in relation to the effects of miotics in man.

In studies on monkeys anesthetized with pentobarbitone, it was reported that locally administered pilocarpine increased the outflow facility. However, no significant reduction in intraocular pressure was induced by pilocarpine, but it is notable that under the anesthetic, the basal pressure was low even in untreated eyes. Possibly the observation of Cavarol and Macri that pentobarbitone apparently reduces aqueous inflow in rhesus monkeys is significant, since pilocarpine might be unable to induce further reductions if the intraocular pressure is approaching that of the recipient veins.

The present study reports the effects of several parasympathomimetic drugs on the eyes of fully conscious owl monkeys, and it has been shown that consistent reductions in intraocular pressure can be obtained under appropriate experimental conditions.

Methods. Male owl monkeys (Aotus trivirgatus) weighing 0.8 to 1.5 kilograms were used in groups of five to seven. During tonometry each animal was loosely restrained in a cloth bag which enveloped the trunk and limbs. After thorough training, the animals accepted the experimental procedures without apparent anxiety. The pneumatic tonometer using a Digilab, Inc. (Cambridge, Mass.) floating probe was constructed in this laboratory. Oxygen was admitted to the probe at a pressure of 34.5 kPa. (5 p.s.i.) and the recordings were made using a Bell & Howell (Pasadena, Calif.) transducer (4-421-001) and transducer indicator (1-176) and an Omniscribe pen recorder (Houston Instrument Div., Bausch & Lomb, Inc., Bellaire, Texas). Open-stopcock manometric calibration was carried out on five eyes of anesthetized owl monkeys.

The parasympathomimetic drugs were dissolved in sterile physiological saline, and 10 or 20 μl of a given solution was administered topically to each eye.

*Pentobarbitone = pentobarbital.