Provocative test combining water drinking and homatropine eye drops

Appplanation versus tonography

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In a previous study (Leighton, Phillips, and Gibbs, 1970), a provocative outflow test using a combination of water drinking (20 ml./kg. body weight) and gutt. homatropine 2 per cent. in 24 open-angle glaucoma suspects caused a significantly greater fall in outflow facility and rise in outflow resistance than either water drinking alone or homatropine alone (0.02 < P < 0.05 in each case). When applanation tension was considered, water drinking combined with gutt. homatropine again gave the greatest rise; this was again significantly greater than the rise in applanation tension after either water alone or gutt. homatropine alone (P < 0.01 in each case). This less marked inter-test difference in change in outflow (i.e. 0.02 < P < 0.05) compared with change in applanation tension (i.e. P < 0.01) is likely to have been due to a wider scatter of tonographic than of tonometric readings. The difference between mean rise in applanation tension and mean rise in outflow resistance cannot unfortunately be compared statistically because they are expressed in different units.

Objectives of present study

I. As a preliminary, the timing of the peak applanation tension after water drinking and gutt. homatropine 2 per cent. was carried out in twenty subjects.

II. In order to assess the relative merits of a tonometry (applanation) test and an outflow (tonography) test, another twenty subjects each had a water-drinking homatropine applanation test and a water-drinking homatropine tonography test in randomized order.

III. The effect of some ocular dimensions on the results of the tests was studied.

Methods

I. Timing of peak applanation tension after water drinking and gutt. homatropine in twenty subjects

(1) Subjects

(a) Ten open-angle glaucoma suspects. These had “raised” ocular tension and/or discs considered to be symptomatic of glaucoma.

(b) Two cases of open-angle glaucoma.

(c) Eight first-degree relatives of patients with open-angle glaucoma.

All had open angles which were judged not to be liable to closure by mydriasis. There were ten males and ten females, and their average age was 50.6 yrs (range 20 to 85).
(2) **PROCEDURE** Only one eye chosen at random was used. Each subject was tested as follows in the course of a morning, having been instructed to have nothing by mouth from midnight on the previous day:

(a) Applanation tension.
(b) Water by mouth (20 ml./kg. body weight within 5 min.) and gutt. homatropine 2 per cent. to the test eye.
(c) Repeat applanation tensions 15, 30, 45, and 60 min. after the end of (b).

II. Water-drinking combined with gutt. homatropine. **Applanation test compared with tonography test in twenty subjects**

(1) **SUBJECTS**

(a) Fourteen open-angle glaucoma suspects who had "raised" ocular tensions and/or optic discs considered symptomatic of glaucoma.
(b) Five first-degree relatives of patients with open-angle glaucoma.
(c) One patient with unilateral open-angle glaucoma; the apparently normal eye was selected for investigation.

All had open angles which were judged not to be liable to closure by mydriasis. There were thirteen males and seven females and their average age was 57.4 yrs (range 35 to 79).

(2) **PROCEDURES**

(a) Water-drinking homatropine applanation test

(i) Applanation tension
(ii) Water (20 ml./kg. body weight) by mouth within 5 min. and gutt. homatropine 2 per cent. to the test eye
(iii) Applanation tension 45 min. after the end of (ii)

(b) Water-drinking homatropine tonography test

(i) Applanation tension
(ii) Schiötz tonometry
(iii) 4-min. tonography
(iv) Water (20 ml./kg. body weight) by mouth within 5 min. and gutt. homatropine 2 per cent. to the test eye
(v) Applanation tension 45 min. after the end of (iv)
(vi) Schiötz tonometry
(vii) 4-min. tonography

Only one (the same) eye was investigated on each occasion. Each test was done in the course of one morning by a technician who used the Goldmann applanation tonometer and Schwarzer electrotonometer, the 5.5 g. weight being used throughout. The order in which the tests were done was randomized so that, of the twenty patients investigated, ten had the applanation test first and ten the tonography test first. In these two groups of ten patients, five had the right eye tested and five the left. Patients were instructed to have nothing by mouth from midnight on the previous day.

(3) **OCULAR DIMENSIONS**

In eighteen of the twenty subjects mentioned in II (1) above, various ocular dimensions were taken from the eye which received provocation, *viz*:

(i) Corneal diameter (from a colour photograph)
(ii) Anterior chamber depth (by the No. II Haag-Streit depth-measuring attachment)
(iii) Keratometry (Zeiss apparatus)
(iv) Lens thickness and vitreous length by A-scan ultrasonography
(v) Axial length (=anterior chamber depth + lens thickness + vitreous length)
No patient had received eye drops (e.g. gutt. pilocarpine) before the above dimensions were measured.

Results and discussion

I. Timing of peak applanation tension after water drinking and gutt. homatropine in twenty subjects

Fig. 1 shows the mean applanation tension in twenty subjects immediately before, and 15, 30, 45, and 60 min. after water drinking and gutt. homatropine. The mean applanation tension at 30 and 45 min. was the same, so the peak probably occurred at one of these times or between the two. The rise in applanation tension after 45 min. was significantly greater than that after 15 min. (0.01 < P < 0.02: Wilcoxon test). Drance (1963), however, found in a water-drinking applanation test that the maximum rise in applanation tension occurred most frequently 10 min. after the water; he used water only, while our test adds gutt. homatropine. Armaly (1970) found a peak applanation tension 30 min. after water in normal subjects.

![Graph showing mean applanation tension over time](image)

A higher maximum applanation tension was reached significantly later than a lower maximum applanation tension; \( r_s = +0.455, 0.01 < P < 0.05 \) (Fig. 2, overleaf). Inspection of the Tables given by Drance (1963) suggested a similar finding.

The amount of the rise in applanation tension found after 45 min. correlated significantly with age \( (r_s = +0.526; 0.01 < P < 0.05) \), i.e. the higher rise occurred in older people, as Armaly (1970) also found. No significant correlation was found between the timing of the peak applanation tension and age \( (r_s = -0.059; P > 0.05) \).
II. Provocation using water drinking combined with gutt. homatropine: comparison of an applanation test and a tonography test in twenty subjects

(a) RISE IN APPLANATION TENSION AND RISE IN OUTFLOW RESISTANCE DUE TO WATER DRINKING AND HOMATROPINE

Table I shows that the rise in applanation tension in the applanation test and rise in outflow resistance in the tonography test (N.B. at different visits) had both been significant (Student's 't' = 7.47 and 3.98 respectively; P < 0.001 for each). The Wilcoxon test also showed that the rise in applanation tension and rise in outflow resistance had been significant (T = 0 and 12 respectively; P < 0.01 for each). Unfortunately, no statistical test is available to determine which is the more significant rise, or even which is the more significant proportionate rise, although t in the Student's 't' test and T in the Wilcoxon test both suggested that the rise in applanation tension had been slightly more significant.

Table I 20 subjects. Comparison of rise in applanation tension and rise in outflow resistance

<table>
<thead>
<tr>
<th>Provocative test</th>
<th>Water-drinking homatropine test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Applanation</td>
<td>Tonography</td>
</tr>
<tr>
<td></td>
<td>Wilcoxon</td>
<td>Student's t</td>
</tr>
<tr>
<td>Statistical test</td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>Rise in applanation tension</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rise in outflow resistance</td>
<td>12</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

T represents the Wilcoxon score for each t indicates that a Student's 't' test was used

**FIG. 2** Twenty subjects. Scattergram of maximum rise in applanation tension and its timing in a water-drinking homatropine applanation test. A significant correlation was present, i.e. the higher the rise, the later it occurred ($r_s = +0.455; 0.01 < P < 0.05$)
Provocative outflow tests

![Bar chart](image)

**FIG. 3** First column. Rise in applanation tension and standard error in water-drinking homatropine applanation test.

**Second column.** Rise in outflow resistance and standard error in water-drinking homatropine tonography test.

*Note the greater scatter in the second test.*

than the rise in outflow resistance. In Fig. 3 the rise in applanation tension and rise in outflow resistance are represented in bar charts with the standard error of the mean included for each. Scatter in the rise in outflow resistance is noticeably greater than it is for rise in applanation tension, but again no statistical test is available to compare these measurements.

The rise in applanation tension in the applanation test did not correlate with age ($r_s = -0.130; P > 0.05$), but the rise in outflow resistance in the tonography test ($r_s = +0.402; 0.01 < P < 0.05$) was age-dependent.

**b** Rise in applanation tension during (I) the applanation test, and (II) the tonography test

In the applanation test itself the mean applanation tension at the end of 45 min. had risen by 4.5 mm. from its initial level of 18.5 mm. The mean applanation tension during the tonography test at the end of 45 min. had risen by 3.9 mm. from an initial 19.2 mm. ($t = 7.47$ and 6.53 respectively; $P < 0.001$ for each). Surprisingly, the applanation tension 45 min. after provocation seems to have been little influenced by the fall in ocular tension due to the initial tonography.

The rise in applanation tension during the tonography test correlated significantly with that in the applanation test itself at different visits ($r_s = +0.498; 0.01 < P < 0.05$) and also with the rise in outflow resistance at the same visit $r_s = +0.464; 0.01 < P < 0.05$.
However, it is an odd finding that the rise in applanation tension in the applanation test and rise in outflow resistance in the tonography test \textit{i.e., AT DIFFERENT VISITS}, did not correlate significantly \((r_s = +0.248; 0.2 < P < 0.3)\).

Two factors may account for this:

\(a\) The tonography test measures a different characteristic from the applanation test (but at the \textit{SAME} visit the tonometry and tonography results correlated!)

\(b\) A test result depends to some extent on the patient's general state of hydration, etc., at the time of the test (but the applanation results at \textit{DIFFERENT} times correlated!)

\section*{III. Ocular dimensions and effects of tests}

Table II (opposite) shows correlations between ocular dimensions and rise in applanation tension in both the applanation and tonography tests, and rise in outflow resistance in the tonography test (for further details, see Leighton and Tomlinson, 1971). However, relevant to a comparison between an applanation test and a tonography test are:

\textbf{(A) WATER-DRINKING HOMATROPINE APPLANATION TEST}

A significant correlation between corneal astigmatism and rise in applanation tension was found in that "with-the-rule" astigmatism, \textit{i.e.,} smaller vertical than horizontal corneal radius, was associated with a high rise in applanation tension. The direction of the trend is opposite to that between corneal astigmatism and age (Marin-Amat, 1956) and may indicate an unreliable feature of the test because "with-the-rule" corneal astigmatism is unlikely to be a special characteristic of the eye in open-angle glaucoma. An inverse correlation between axial length and rise in applanation tension did not quite reach significance.

\textbf{(B) WATER-DRINKING HOMATROPINE TONOGRAPHY TEST}

\(i\) \textit{Rise in applanation tension}

The correlation with corneal astigmatism was significant \((r_s = -0.490; 0.01 < P < 0.05)\) as it had been in \(a\), the water-drinking homatropine applanation test.

The following correlations were also significant \((r_s = -0.632; -0.604 \text{ respectively}; P < 0.01\) each):

\(a\) between shallow anterior chamber and a high rise in applanation tension

\(b\) between great axial length and a small rise in applanation tension.

These last two correlations were not significant in the water-drinking homatropine applanation test (although the same trends were present), probably because the 4-min. tonography expresses fluid and this magnifies the effect on the rise in applanation tension of the surface area of the corneo-scleral envelope.

As an association between shallow anterior chamber and short axial length nearly reached significance \((r_s = +0.375; P > 0.05; r_s \text{ for } P = 0.05 \text{ is } 0.399)\), it may well be that shallow anterior chamber was less important than short axial length (Leighton and Tomlinson, 1971) or, more directly, surface area of the corneo-scleral envelope (see Phillips and Shaw, 1970) in determining the effect of the provocation. A greater rise in applanation tension tended to be found in eyes with a small corneal diameter but this trend did not approach significance \((r_s = -0.111; P > 0.05)\). However, as shallow anterior chamber was associated with small corneal diameter \((r_s = +0.519; 0.01 < P < 0.05)\).
Table II  18 Subjects. Correlations between (1) Ocular dimensions and age and (2) effects of water drinking and gutt. homatropine on applanation tension and outflow resistance

<table>
<thead>
<tr>
<th>Test</th>
<th>Rise in</th>
<th>Corneal diameter</th>
<th>Horizontal corneal radius</th>
<th>Astigmatism (corneal radii: horizontal minus vertical)</th>
<th>Anterior chamber depth</th>
<th>Lens thickness</th>
<th>Vitreous length</th>
<th>Axial length</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-drinking</td>
<td>Applanation tension</td>
<td>NS</td>
<td>NS</td>
<td>S*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>(a) Homatropine applanation</td>
<td>NS</td>
<td>NS</td>
<td>S*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Water-drinking</td>
<td>Applanation tension</td>
<td>-0.369</td>
<td>+0.150</td>
<td>-0.482</td>
<td>-0.150</td>
<td>-0.232</td>
<td>-0.031</td>
<td>-0.232</td>
<td>-0.276</td>
</tr>
<tr>
<td>(b) (i) Homatropine tonography</td>
<td>NS</td>
<td>NS</td>
<td>S*</td>
<td><em>S</em></td>
<td>NS</td>
<td>NS</td>
<td><em>S</em></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Water-drinking</td>
<td>Outflow resistance</td>
<td>-0.088</td>
<td>-0.190</td>
<td>-0.084</td>
<td>-0.112</td>
<td>+0.503</td>
<td>-0.296</td>
<td>-0.250</td>
<td>+0.309</td>
</tr>
<tr>
<td>(b) (ii) Homatropine tonography</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>S*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*S* = Significant at $P < 0.01$
S* = Significant at $0.01 < P < 0.05$
NS = Not significant $P > 0.05$

Correlation coefficient for $P = 0.05$ is 0.399 and for $P = 0.01$ is 0.564

The rise in applanation tension in (a) is the difference between applanation tensions taken immediately before and 45 min. after provocation.

The rise in applanation tension in (b)(i) and rise in outflow resistance in (b)(ii) are the differences between tonometric and tonographic readings taken immediately before and 45 min. after provocation. (b)(i) and (b)(ii) relate to the same visit.
0.05), the latter could also have contributed to the correlation found between shallow anterior chamber and a high rise in applanation tension after the provocation. Presumably the high rise in applanation tension after provocation in an eye with a small corneal diameter and circumference is due to the relatively small cross-sectional area of outflow channels available for escape of aqueous in such eyes.

Correlation between a small rise in applanation tension and high axial length seems an unfortunate trend in a test to diagnose glaucoma, because large eyeballs have significantly greater applanation tensions than small eyeballs (Tomlinson and Phillips, 1970), which is consistent with the observations that myopic eyes are probably unduly prone to open-angle glaucoma (Weekers, Lavergne, and Prigot, 1958; Perkins and Jay, 1960). Probably the small surface area of corneo-scleral envelope in an eye with a short axial length is less able to accommodate the increased volume of aqueous humour formed after water drinking.

(ii) **Rise in outflow resistance**

The only significant correlation was with lens thickness, the explanation for which (Leighton and Tomlinson, 1971) is presumably an indirect one, e.g. correlation of both rise in outflow resistance and lens thickness with age, although it may be due to the association of a thick lens and a shallow anterior chamber and hence a narrow angle, which may be correlated with high outflow resistance (François, Rabae, Neetens, and Evens, 1958).

**Further discussion and conclusions**

The noticeably greater variance of the rise in outflow resistance compared with the rise in applanation tension (Fig. 3) is likely to be a disadvantageous feature of a water-drinking homatropine tonography test if used in the diagnosis of open-angle glaucoma. On the other hand, the high variance of the rise in outflow resistance may merely have revealed more effectively the heterogeneity of the sample, some of which may be due to attributes of the eye in open-angle glaucoma, although all the test subjects lacked pathological cupping of the optic discs and field defects typical of glaucoma.

The correlations between rise in applanation tension and rise in outflow resistance and (a) shallowness of the anterior chamber (probably due to) (b) small axial length (an unreliable trend?) were not noticeably different: see Table II. (None was significant.)

A significant correlation was found between (i) a high rise in applanation tension in the water-drinking homatropine tonography test and (ii) short axial length. This trend was not significant in the water-drinking homatropine applanation test. This discrepancy probably indicated that the squeezing-out effect of the initial tonography had magnified a tendency for the effect of the provocation to be dependent on surface area of corneo-scleral envelope (Phillips and Shaw, 1970).

Mainly because of the greater scatter of the tonography readings, it seems reasonable to conclude that a water-drinking homatropine applanation test is marginally better than a water-drinking homatropine tonography test. An applanation test is easier to perform. However, in the final analysis, the relative ability of these two tests to discriminate between normal subjects and patients predisposed to open-angle glaucoma would have to be assessed by a protracted long-term study of cohorts. Nevertheless it seems practical to avoid provocative tests involving tonography, which is an inconsistent test even in the same individual (Gloster, 1966), in open-angle glaucoma and to proceed in a future study to compare the normal and glaucomatous response to the water-drinking homatropine applanation test.
Summary

In twenty subjects (ten open-angle glaucoma suspects, two cases of open-angle glaucoma, and eight first-degree relatives of patients with open-angle glaucoma), the rise in applanation tension after water drinking (20 ml./kg. body-weight) combined with gutt. homatropine 2 per cent. was significantly greater after 45 than after 15 min. (0·01 < P < 0·02). The maximum rise occurred at or between 30 and 45 min. after the provocation. A high maximum applanation reading tended to occur significantly later than a low maximum (0·01 < P < 0·05).

Another twenty subjects (fourteen open-angle glaucoma suspects, five first-degree relatives of patients with open-angle glaucoma, and one patient with “unilateral” open-angle glaucoma) each had a water-drinking homatropine applanation test and a water-drinking homatropine tonography test in random order on one eye. The effects of the provocation were measured by a second applanation or tonography reading 45 min. after the provocation. The applanation test was considered marginally better than the tonography test because the rise in applanation tension in the former was slightly more significant than the rise in outflow resistance, and the scatter of the rise in applanation tension was noticeably smaller than the scatter of the rise in outflow resistance. It is therefore planned to compare the effects of a water-drinking homatropine applanation test on normal subjects and patients with open-angle glaucoma.

The older the patient the higher the rise in applanation tension in response to water drinking plus homatropine (significant at 0·01 < P < 0·05).

The rise in applanation tension in the water-drinking homatropine tonography test, i.e. when a 4-min. tonography had been done after the initial applanation tension (before provocation), tended to be higher if the axial length was short (significant correlation P < 0·01), probably because the squeezing-out effect of the initial tonography magnified a tendency for the effect of provocation to be dependent on the surface area of the corneo-scleral envelope.

References

DRANCE, S. M. (1963) Ibid., 69, 39
——— and TOMLINSON, A. (1971) Ibid., 55, 607
PERKINS, E. S., and JAY, B. S. (1960) Trans. ophthal. Soc. U.K., 80, 153