Mechanisms in open-angle glaucoma

R. MAPSTONE
From St. Paul's Eye Hospital, Liverpool

SUMMARY. One hundred and nineteen eyes from 68 patients with open-angle glaucoma were provoked by means of a pilocarpine phenylephrine provocative test. In 22% the response was the same as that seen in normal eyes. In 78% the response was the same as that seen in contralateral eyes at risk to the development of closed-angle glaucoma, which do not develop a positive provocative test.

The 68 patients were randomised and 34 submitted to a 'dummy' provocative test. No significant change in pressure or outflow occurred.

Fifty-two of the 93 eyes with an abnormal provocative test were selected for a peripheral iridectomy and reprovoked at least 6 months after operation. The results were significantly different from those obtained before operation. It was concluded that partial-angle closure could be demonstrated in some eyes with apparent open-angle glaucoma.

The mechanisms involved in the production of partial-angle closure in eyes with apparent open-angle glaucoma are discussed.

In some patients with ocular hypertension partial-angle closure can be demonstrated by means of a pilocarpine phenylephrine provocative test (Mapstone, in preparation). If open-angle glaucoma is preceded by a variable period by ocular hypertension, then it would seem reasonable to suppose that a pilocarpine phenylephrine provocative test would show partial-angle closure here too. This paper investigates that hypothesis.

Material and methods

One hundred and nineteen eyes from 68 unselected patients with open-angle glaucoma (that is, disc cupping, a glaucomatous field defect, pressure before treatment greater than 21 mmHg, a gonioscopically normal angle, and no history suggestive of closed-angle glaucoma) were provoked with pilocarpine and phenylephrine drops as follows:

At zero hour intraocular pressure was measured, facility of outflow recorded, and pilocarpine drops 2% plus phenylephrine drops 10% instilled. Approximately ½ hour later an additional drop of phenylephrine 10% was instilled and pressure recorded. One-and-a-half hours from the start of the test the intraocular pressure was recorded, tonography was repeated, and another dose of pilocarpine and phenylephrine instilled. Finally, 1 hour later (that is, 2½ hours from the start of the test) pressure was recorded and tonography repeated.

Fifty-two eyes from 30 of the 68 patients were treated with a peripheral iridectomy. The maximum period of follow-up is 20 months, the minimum 12 months. At least 6 months after operation they were reprovoked as described above with pilocarpine and phenylephrine, and the results were recorded. The method of selection for operation was not random. No patient with a normal provocative test result, before operation, was asked. Of the remainder, the patients chosen were the first 30 who agreed to an iridectomy after an explanation that no benefit could be assured.

Finally, the 68 patients were randomised, and 34 eyes from 34 patients had a 'dummy' provocative test, that is, the procedure was as described above but no autonomic drugs were instilled.

All patients receiving pilocarpine and/or adrenaline drops (Eppy) were instructed to instil no drops on the morning of the test. Oral acetazolamide was not stopped.

Results

(1) Provocative test in 119 eyes

Fig. 1 records the result of provoking 119 eyes with simultaneous pilocarpine and phenylephrine. The first dose produced a fall in pressure from a mean of 23-4, to 20-2 mmHg \( (t = 5-74, \ P < 0-001) \) and an increase in outflow from a mean of 0-12 to mean of
0·14 μl/mmHg per min (t = 3·39, P < 0·001). The second dose produced an increase in pressure from a mean of 20·2 to 22·0 mmHg (t = 4·92, P < 0·001) and a decrease in C from a mean of 0·14 to 0·13 (t = 1·54, not significant). The overall effect was to decrease pressure by 1·4 mmHg (t = 2·3, P < 0·05) and increase outflow by 0·01 (t = 1·92, not significant). Finally, there is a significant negative linear correlation between the changes in outflow and pressure (r = -0·51; P < 0·001).

This analysis, however, hides the fact that, as in contralateral eyes at risk to the development of closed-angle glaucoma, and ocular hypertensives (Mapstone, 1977b, c, in preparation)—there were 4 separate patterns of response, details of which are as follows.

(a) 26 eyes. Fig. 2 shows that 26 eyes developed a normal provocative test result. The first dose produced a fall in pressure from a mean of 24·6 to 19 mmHg (t = 7·08, P < 0·001) and an increase in outflow from a mean of 0·10 to 0·16 (t = 6·04, P < 0·001). The second dose produced a fall in pressure from a mean of 19 to 18·8 mmHg (t = 0·48, not significant) and an increase in outflow from a mean of 0·16 to 0·21 (t = 6·5, P < 0·001). Both the overall decrease in pressure and increase in outflow are statistically significant (for pressure t = 8·27, for outflow t = 7·95, P < 0·001).

(b) 27 eyes. Fig. 3 shows that in 27 eyes the first dose produced an increase in pressure from a mean of 21·3 to 22·0 mmHg (t = 0·51, not significant) and a decrease in outflow from a mean of 0·13 to 0·10 (t = 5·74, P < 0·001). The second dose produced an increase in pressure from a mean of 22·0 to 26·1 mmHg (t = 4·77, P < 0·001) and a decrease in outflow from a mean of 0·10 to 0·07 (t = 5·18, P < 0·001). Both the overall increase in pressure and decrease in outflow are statistically significant (for pressure t = 4·21, for outflow t = 8·95, P < 0·001).

(c) 44 eyes. Fig. 4 shows that in 44 eyes the first dose produced a decrease in pressure from a mean of 25·4 to 20·0 mmHg (t = 5·95, P < 0·001) and an increase in outflow from a mean of 0·10 to 0·17 (t = 6·38, P < 0·001). The second dose then produced an increase in pressure from a mean of 20·0 to 22·1 mmHg (t = 3·39, P < 0·001) and a decrease in...
outflow from a mean of 0·17 to 0·11 (t = 5·08, P < 0·001). Overall, the decrease in pressure was statistically significant (t = 3·64, P < 0·001), but the increase in outflow was not (t = 1·39).

(d) 22 eyes. Fig. 5 shows that in 22 eyes the first dose produced a fall in pressure from a mean of 20·4 to 19·8 mmHg (t = 0·66, not significant) and a decrease in outflow from a mean of 0·15 to 0·10 (t = 7·9, P < 0·001). The second dose produced an increase in pressure from a mean of 19·8 to 20·5 mmHg (t = 0·95, not significant) and an increase in outflow from a mean of 0·10 to 0·15 (t = 8·5, P < 0·001). Neither the overall change in pressure nor in outflow was statistically significant (for pressure t = 0·1, for outflow t = 0·27).

**Fig. 4** Response of 44 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

**Fig. 5** Response of 22 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

(2) Response of 55 eyes to provocative testing with pilocarpine and phenylephrine before and after a peripheral iridectomy

The 55 eyes can be regarded as forming 2 groups, 1 before and 1 after iridectomy; there are therefore 2 analyses.

**Within groups.**—Fig. 6 shows that before an iridectomy the first dose of pilocarpine and phenylephrine produced a decrease in pressure from a mean of 24·2 to 21·1 mmHg (t = 3·17, P < 0·01) and an increase in C from a mean of 0·12 to 0·13 (t = 1·2, not significant). The second dose of pilocarpine and phenylephrine produced an increase in pressure from a mean of 21·1 to 25·0 mmHg (t = 6·2, P < 0·001) and a decrease in C from a mean of 0·13 to 0·10 (t = 2·92, P < 0·01). The overall change in pressure was not statistically significant (t = 0·76) but the overall decrease in outflow probably was (t = 2·33, P < 0·05).

Fig. 6 also shows that after an iridectomy the first dose of pilocarpine and phenylephrine produced a decrease in pressure from a mean of 22·8 to 17·3 mmHg (t = 8·64, P < 0·001) and an increase in C from a mean of 0·11 to 0·17 (t = 6·85, P < 0·001). The second dose of pilocarpine and phenylephrine produced a further decrease in pressure from a mean of 17·3 to 17·0 mmHg (t = 0·95, not significant) and an increase in outflow from 0·17 to 0·18 (t = 2·3, P < 0·05). Both the overall decrease in pressure and increase in outflow are statistically significant (for pressure t = 9·5, for outflow t = 6·93, P < 0·001).

**Between groups.**—There was no significant change
in mean outflow or pressure of the 55 eyes after an iridectomy (for pressure \( t = 0.94 \), for outflow \( t = 0.33 \)). At the time of instillation of the second dose of pilocarpine and phenylephrine pressure in the eyes after an iridectomy was significantly lower \( (t = 5.12, P < 0.001) \) and outflow significantly higher \( (t = 4.1, P < 0.001) \) than before. At the termination of the test the same difference was present \( (t = 7.4, \text{ for outflow } t = 6.19) \), that is, a peripheral iridectomy had a highly significant effect on the mean response of these eyes to a provocative test.

Of the 52 eyes after an iridectomy the outflow response in 39 eyes to pilocarpine and phenylephrine was as in normal eyes. In 13 eyes an abnormal outflow response was still present.

Finally, if the 52 eyes in this group are divided into those with and those without narrow angles, a chi-squared test leads to a rejection of the null hypothesis that there is no association between a positive test and narrow angles \( (\chi^2 = 4.67, P < 0.005) \).

3) Dummy provocative test in 34 eyes

Fig. 7 records the result of a dummy provocative test in 34 eyes. The initial pressure was 22.5 mmHg and outflow 0.13. At the time of the second measurement pressure had increased to 23.4 mmHg (not significant) and outflow decreased to 0.12 (not significant). At the end of the test pressure was 23.3 mmHg and outflow 0.12. Neither the overall change in pressure nor in outflow was significant.

Discussion

The pilocarpine phenylephrine provocative test consists of 2 separate experiments. Assume, initially, an anterior segment incapable of developing any degree of angle closure, with a normal outflow system. At zero hour (1, Fig. 8) the average pupil is miosed (rather than mid- or widely dilated); intraocular pressure is recorded, facility of outflow measured, and pilocarpine plus phenylephrine drops are instilled. During the following 45 minutes to 1 hour the pupil moves up to mid-dilatation and there it remains, with the help of phenylephrine, changing little in diameter over the next half hour. At 2 (Fig. 8) pressure has decreased and outflow increased by a significant amount (Mapstone, 1977a) and more pilocarpine plus phenylephrine is instilled. The second dose retains the pupil at mid-dilatation, although during the next hour there is usually a small decrease in diameter. In addition there is a further significant increase in outflow, but pressure is little affected. At the end of 21/2 hours, therefore, in a normal eye pressure has decreased and outflow increased by a significant amount.

If now, a group of normal eyes is treated in the same fashion, except that no autonomic drug is instilled (Fig. 9), then pressure and outflow facility show no significant change at any stage during the 21/2-hour period (although individual eyes vary).

The first event that can complicate this simple picture is closure of most of the angle during the test, producing 3 separate patterns of response (Mapstone, 1977b). Firstly, closure can occur as the pupil moves up to mid-dilatation (Fig. 10), so that only 1 dose of pilocarpine and phenylephrine is
Mechanisms in open-angle glaucoma

necessary. In this instance pressure has increased and outflow decreased sufficiently within 1 hour to produce an acute closed-angle glaucoma. Secondly (Fig. 11, line a), partial-angle closure can occur as the pupil moves up to mid-dilatation, decreasing outflow and increasing pressure on the way, but the pressure increase is less than 8 mmHg. The instillation of a second dose of pilocarpine and phenylephrine at this point then closes more of the angle at mid-dilatation and produces a positive test.

Fig. 9 Diagram to illustrate the response of a sample of normal eyes to a 'dummy' provocative test. No autonomic drugs are instilled but pressure and outflow are measured at intervals 1, 2, and 3. Analysed as a group, no significant change in pressure or outflow occurs at any stage.

Thirdly (Fig. 12), the first dose of pilocarpine and phenylephrine moves the pupil up to mid-dilatation, and on the way pressure decreases and outflow increases. The instillation of a second dose of pilocarpine and phenylephrine at mid-dilatation then closes the angle and produces an acute attack. If eyes showing one of these patterns have a peripheral iridectomy and are then reprovoked after an interval, the response is the same as that seen in normal eyes (Fig. 8) (Mapstone, 1977c).

The second event that can complicate the picture shown in Fig. 8 is the development of partial-angle closure in eyes at risk that do not develop positive provocative tests. Three abnormal patterns of response are produced (Mapstone, 1977c). Firstly (Fig. 11), partial-angle closure occurs as the pupil moves up to mid-dilatation, outflow is reduced, but pressure is little affected at this stage. The instillation of a second dose of pilocarpine and phenylephrine at mid-dilatation can then either decrease outflow still more and increase pressure (Fig. 11, line a) or open the angle, increasing outflow and decreasing pressure (Fig. 11, line b).

The third pattern is shown in Fig. 12, as the pupil moves up to mid-dilatation outflow increases and pressure falls, the instillation of a second dose of pilocarpine and phenylephrine at mid-dilatation
Fig. 12 Diagram to illustrate an abnormal response to provocative testing with pilocarpine (P) and phenylephrine (F). During interval 1, pressure and facility of outflow are measured, and pilocarpine + phenylephrine are instilled. Over the next 1½ hours the pupil moves up to mid-dilatation, outflow increases, and pressure decreases. During interval 2 pressure and outflow facility are again measured, and more pilocarpine and phenylephrine are instilled. Over the next 1 hour outflow decreases and pressure increases. Finally, during interval 3, outflow and pressure are measured.

Closes part of the angle, reducing outflow and increasing pressure. But at no point in these 3 situations is sufficient of the angle closed for a sufficient period of time to produce a positive test result (Mapstone, 1977c). If a peripheral iridectomy is done in eyes giving one of these responses, and the eye is reprovoked after an interval, the test result is now converted to that seen in normal eyes (Fig. 8) (Mapstone, 1977c).

Eyes with ocular hypertension (Mapstone, in preparation) during provocative testing with pilocarpine and phenylephrine also develop the 4 patterns of response shown in Figs. 8, 11, and 12. After a peripheral iridectomy the abnormal responses are converted to the normal one shown in Fig. 8 (14 of the 16 eyes).

Finally, this paper, too, shows that eyes with open-angle glaucoma, before operation, behave in a similar fashion. After an iridectomy 75% of the provocative test results are converted to a normal response. The results also show that during a dummy provocative test the amount of 'spontaneous' variation in 34 eyes is insignificant (although individual eyes vary); the overall pattern of response is the same as in normal eyes (Fig. 9). It is improbable, therefore, that the pattern of response shown in Fig. 1 is a chance observation.

At first sight, therefore, it would seem that partial-angle closure does occur in some eyes with ocular hypertension and apparent open-angle glaucoma. But there is an additional complication in interpreting the outflow patterns in these eyes. The eyes at risk to the development of closed-angle glaucoma had—as apart from an increased probability of developing angle closure—a normal outflow system. The eyes with ocular hypertension and open-angle glaucoma have—to a varying degree—a damaged outflow system, and this creates difficulties.

Consider first an anterior segment incapable of producing any degree of angle closure but with a reduced outflow facility (Fig. 13). The first dose of pilocarpine and phenylephrine decreases pressure and increases outflow. This may be the maximum response that that system can produce, so that the second dose now has no significant effect on true outflow and its dependent pressure change. Consequently, when outflow and pressure are measured at the end of the test, random errors alone will be as likely to show an increase as a decrease—mimicking the patterns shown in Figs. 8 and 12. Again, the outflow system may be totally unresponsive to instilled drugs. Random errors (Fig. 14) may then produce all the patterns shown in Figs. 8, 11, and 12.

It therefore necessarily follows that, in a particular eye, the fact that it develops an abnormal response to provocative testing is not sufficient reason to assert that the cause was partial-angle closure. There are 3 options.

Firstly, it could be argued that all abnormal
outflow patterns (the emphasis is on outflow and not pressure change, since the former is related to the latter as cause to effect—in this particular set of conditions) are due to a lack of response by a damaged outflow system. If this were so, there is no reason to suppose that a peripheral iridectomy would make any significant difference to a provocative test. That it did so (Fig. 6) can only mean that this explanation is not sufficient. Secondly, it could be argued that all the abnormal patterns are due to the development of partial-angle closure. If this were so, there is reason to suppose that a peripheral iridectomy would make a significant difference to a provocative test. That it did not in all 52 eyes (25% still had an abnormal test after operation) can mean only that this explanation is insufficient too.

The reality, therefore, lies somewhere in between. That is, some of the abnormal patterns are due to partial-angle closure and some to an abnormal response by a damaged outflow system. But how can they be differentiated?

**Example 1.** Male, aged 73. Open-angle glaucoma. Treated with pilocarpine drops 4%, 4 times a day for 7 years. Before a peripheral iridectomy (Fig. 15) the first dose of pilocarpine and phenylephrine produced a fall in pressure from 24 to 18 mmHg and an increase in outflow from 0.08 to 0.11. The second dose increased pressure from 18 to 28 mmHg and decreased outflow from 0.11 to 0.09. After an iridectomy the first dose produced a fall in pressure from 26 to 15 mmHg and an increase in outflow from 0.08 to 0.20. The second dose produced an increase in pressure from 15 to 16 mmHg and no change in outflow.

In this patient, therefore, a peripheral iridectomy made a significant difference to the provocative test response.

**Example 2.** Female aged 56. Family history of open-angle glaucoma. Treated with pilocarpine...
drops 4% 4 times a day and 1% adrenaline drops twice a day for 8 months (Fig. 16). Although the outflow pattern of response is different from that in Example 1, a peripheral iridectomy makes a significant difference to the effects of a provocative test (Fig. 16).

Example 3. Male aged 68. Open-angle glaucoma. Treated with pilocarpine drops 2% 4 times a day for 2 years. Here the preoperative outflow pattern was the same as that in Example 1 although there was no associated pressure increase. Postoperatively the pattern of response was the same, and there is no evidence to suggest that a peripheral iridectomy had any significant effect (Fig. 17).

Of the 52 eyes that had an iridectomy 75% showed an abnormal preoperative response converted to a normal one, but in 25% this did not happen. It is clearly necessary to explain this and establish why it occurs. These points are explored in subsequent papers, together with the clinical implications of partial-angle closure for the aetiology and treatment of ocular hypertension and open-angle glaucoma.

Finally, if random errors plus a damaged outflow system account for an abnormal pattern before iridectomy, they will produce the same result after operation. Consequently, the mean statistics of a sample of eyes before operation will not be significantly different from those obtained after operation. The results described above show that a peripheral iridectomy made a highly significant difference to the sample means. The available evidence suggests that this was because it prevented partial-angle closure in eyes with apparent open-angle glaucoma.

I thank colleagues who referred patients for study and Mrs E. Tubb for secretarial help.

References