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Effects of dipivefrin and pilocarpine on pupil diameter, automated perimetry and LogMAR acuity

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Abstract ● Background: A study was carried out to ascertain, in ophthalmologically normal subjects, the short-term effects of dipivefrin hydrochloride 0.1% on visual performance and make comparisons with pilocarpine. ● Methods: Twelve normal volunteers aged 20–26 years attended on three occasions. One eye, randomly selected, received one drop of either pilocarpine 2%, dipivefrin or saline 0.9%. High- and low-contrast LogMAR acuity at 6 m and pupil diameter (measured by infra-red pupillometry) were recorded at baseline (T0) and at intervals up to 90 min following instillation of drops. Program 30-2 of the Humphrey Visual Field Analyzer (HFA) was run at T0 and at 60 min after treatment instillation (T60). Saline was always instilled at visit 1, to allow for learning effects. On visits 2 and 3 either pilocarpine or dipivefrin was randomly instilled into the treated eye.
● Results: Pilocarpine significantly worsened the field global indices mean deviation ($P<0.001$) and pattern standard deviation ($P<0.01$) compared with T0. There was no significant change with dipivefrin. A significant ($P=0.01$) pupil dilation from 5.44 mm (SD 0.79) at T0 to 6.19 mm (SD 1.09) at T90 occurred with dipivefrin. Pilocarpine caused significant miosis. No significant changes in LogMAR values were found with dipivefrin. Pilocarpine significantly ($P<0.01$) increased LogMAR values (i.e. reduced acuity) compared with dipivefrin. At T30 the mean increase in LogMAR was 0.76 (SD 0.30) for high and 0.83 (SD 0.11) for low contrast. By T90 recovery of acuity was virtually complete.
● Conclusions: In normals dipivefrin causes mydriasis but does not affect the central visual field global indices (as assessed by STATPAC), or high- and low-contrast LogMAR acuity. Pilocarpine adversely affects the visual field and both measures of acuity. Knowledge of these effects is of value in glaucoma therapy and when monitoring the progression of visual loss.

Introduction

Pilocarpine and dipivefrin are two of the alternatives to, and concomitant treatments with, beta-adrenoceptor blockade in the medical management of open-angle glaucoma. Although no longer in the first line of glaucoma agents, both pilocarpine and dipivefrin are still used in the treatment of open-angle glaucoma. Also, patients on long-term follow-up for glaucoma may well have changed their medication from pilocarpine or dipivefrin to a current first-line drug, and the knowledge of any effect of the former drug on visual fields is of significance when monitoring progress of the disease. Furthermore, the short-term effects of dipivefrin and the comparative effects of the two agents on visual performance have not been thoroughly investigated.

For pilocarpine alone, the short-term effects on visual performance are well known. It is generally agreed that the miosis produced by pilocarpine adversely affects the visual field as evaluated by both kinetic perimetry [7, 22] and automated static perimetry [19, 24]. This can have important implications when serial fields are used to monitor the effect of therapy in open-angle glaucoma. Transitory reductions in visual acuity caused by ciliary spasm following the instillation of pilocarpine are well documented [8, 10] and may prevent the use of the drug in younger patients.

Dipivefrin, a prodrug of epinephrine, has been reported to cause mydriasis in several long-term clinical trials involving patients with glaucoma and/or ocular hypertension [3, 5, 15–18, 21]. However, the short-term effects of dipivefrin on pupil diameter are less well known, nor have the effects on automated visual fields and visual acuity been investigated. Mydriasis has been reported in animal studies, with the maximum mydriatic effect occurring 1 h after instillation in normotensive rabbits [9] and in both glaucomatous and normotensive beagles [11]. In a single-dose study in ten patients with ocular hypertension, mydriasis with 0.1% dipivefrin was found to be maximal at 2 h after instillation, with a change in mean pupil diameter of 1.6 mm (SD 1.0) [15]. Therefore, we designed a randomised, double-blind crossover study of 12 normal volunteers to compare the short-term effects of pilocarpine 2% and dipivefrin 0.1% on automated perimetry, pupil diameter and distance visual acuity.

Materials and methods

The subjects were 12 ophthalmologically normal volunteers (six men and six women) ranging from 20 to 26 years of age (mean 22 years). Written informed consent was given by each subject, and the study protocol was given approval by the university ethics committee. All subjects had Snellen visual acuity of 6/6 or better, mean refractive error not greater than ±3 D, and astigmatic error not greater than 1 D. Seven subjects (all Caucasian) had blue or blue-grey irides, one (Caucasian) had green irides, and four (three Asian, one Caucasian had brown irides. Each subject attended on three occasions at least 4 days apart. One eye of each subject was randomly assigned to receive the pilocarpine, dipivefrin, and saline 0.9% placebo drops. The two active preparations were instilled using a randomised, double-blind, crossover technique.

At visit 1, baseline measurements were taken prior to drug instillation. Automated perimetry was carried out using the Humphrey Full Threshold 30-2 program of the Humphrey Field Analyzer (HFA). This was performed on the treated eye only to reduce the confounding effects of fatigue on automated perimetry [14, 25], and to permit more frequent assessment of pupil diameter and visual acuity. Pupil diameter was measured by infra-red pupillometry (R and L) using the P-Scan 100 system [2]. Distance visual acuity was assessed by high-contrast LogMAR charts (R and L), and low-contrast letter recognition by low-contrast LogMAR charts (R and L).

One measured drop (35 µl) of saline 0.9% placebo was instilled into the treated eye using a micro-pipette. Post-instillation measurements were taken of automated perimetry, on the treated eye only, commencing 60 min after instillation, pupil diameter (R and L) at 15-min intervals up to 90 min, and high- and low-contrast LogMAR acuity (R and L) at 15-min íntervals up to 90 min.

The primary purpose of visit 1, not revealed to the subjects, was to allow for the effects of learning on automated perimetry [12, 27]. It is generally agreed that the main effects of learning can be accounted for by discarding each subject's first two automated fields, hence the HFA data for visit 1 have been ignored. Learning can also affect LogMAR results, and those from visit 1 are not presented here.

On visit 2, baseline measurements were repeated as on visit 1. This was followed by instillation of one drop (35 µl) of pilocarpine or dipivefrin (randomly allocated) into the treated eye. Post-instillation measurements were taken as on visit 1. Prior to post-instillation perimetry each subject's range of distinct vision was assessed to ensure that any pilocarpine-induced ciliary spasm did not result in blurring at 33 cm. Visit 3 followed the pattern of visit 2, with the instillation of one drop of the second active preparation into the treated eye.

Results

Automated perimetry

STATPAC global indices were used to compare perimetric performance at baseline (T0) and 60 min after instillation (T60; Table 1). With pilocarpine the mean deviation (MD) was significantly worsened (mean difference 2.01

Table 1 Comparison of mean STATPAC parameters at baseline (*T0*) and at 60 min after instillation (*T60*). *MD* Mean deviation, *PSD* pattern standard deviation. *SF* short-term fluctuation. All units in dB. Paired *t*-test used throughout

	MD	PSD	SF	PSD^2	SF^2
Pilocarpine					
Baseline (T0)	–2.35	2.06	1.17	4.67	1.50
T60	–4.36	2.78	1.47	9.18	2.64
Absolute mean difference	2.01	0.72	0.30	4.51	1.14
Standard deviation	1.21	0.85	0.53	6.02	2.27
	$P<0.001$	$P<0.01$	$P=0.11$	$P<0.01$	$P=0.14$
Dipivefrin					
Baseline (T0)	–2.49	2.27	1.20	6.10	1.50
T60	–2.67	2.24	1.39	6.00	2.05
Absolute mean difference	0.18	0.03	0.19	0.10	0.55
Standard deviation	0.45	0.43	0.34	2.71	0.94
	$P=0.20$	$P=0.77$	$P=0.09$	$P=0.89$	$P=0.08$

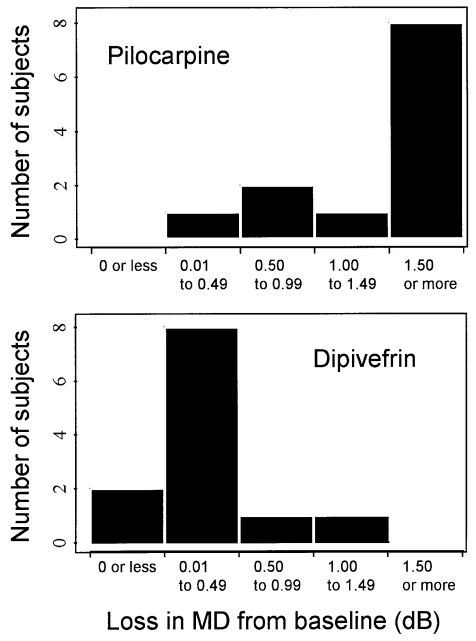

Fig. 1 Frequency distributions of change in mean deviation (dB) from baseline to 60 min after instillation for pilocarpine and dipivefrin

dB, SD 1.21; $P<0.001$, two-tailed paired *t*-test), as was pattern standard deviation (PSD) with a mean difference of 0.72 dB (SD 0.85, $P<0.01$, two-tailed paired *t*-test). However, short-term fluctuation (SF) was not significantly affected. With dipivefrin there were no significant changes in MD, PSD, or SF. Lindenmuth et al. [19] observed that PSD and SF are in effect weighted standard deviations that represent the square root of variance. It is statistically more correct to consider their squared values, and these have been included in Table 1 for completeness. Analysis of PSD^2 and SF^2 does not contradict the results obtained for PSD and SF.

Figure 1 illustrates the marked difference between the effects of pilocarpine and dipivefrin on sensitivity. Pilocarpine worsened MD by more than 1.5 dB in two thirds (67%) of subjects. For pilocarpine, a coarse indication of the spatial distribution of the sensitivity loss was obtained by dividing the 30-2 field into three zones, namely inner (24 locations within the central 15°), middle (28 locations) and outer (24 locations beyond 24°). For this sample the mean sensitivity loss increased with eccentricity from 1.43 dB (SD 1.06) in the inner zone to 2.37 dB (SD 1.28) in the middle zone and 2.89 dB (SD 1.97) in the outer zone. Analysis of STATPAC reliability parameters showed all subjects to be consistently reliable, with negligible changes in false-positive errors, false-negative errors or fixation losses between T0 and T60.

Pupil diameter

Figure 2 shows the change in pupil diameter from baseline for each subject for pilocarpine and dipivefrin. For each treatment there is general similarity in response between subjects. Pilocarpine produced the expected marked miosis. Dipivefrin-induced mydriasis is generally evident by 75 min after instillation. Mydriasis was usually maximal at 90 min and further dilation may have occurred in the post-study period. Subjects 2, 6 and 8, of Asian origin with dark brown irides, had a reduced response to pilocarpine compared with the remaining Caucasian subjects.

For each subject and treatment the 'pupil index' was calculated, being the area under the response curve in Fig. 2, calculated using the trapezoidal rule, and divided by time. This represents an appropriate method of analysis of serial measurements [1]. The pupil index is a summary measure, describing a cumulative effect. The mean pupil indices were 2.59 mm (SD 0.57) for pilocarpine, 5.71 mm (SD 0.94) for dipivefrin and 5.70 mm (SD 0.88) for saline. These were statistically compared using a two-factor ANOVA with repeated measures, and a significant difference was found: *F*-ratio (treatments)=32.8, $P<0.001$. Whilst pupil diameters with pilocarpine were significantly smaller than with dipivefrin or saline, there was no significant difference between dipivefrin and saline (Newman-Keuls) [6].

Mean pupil diameter at the end of each visit (T90) was compared with T0 (Table 2). A significant dipivefrin-induced mydriasis occurred ($P=0.010$), from a mean of 5.44 mm (SD 0.79) to 6.19 mm (SD 1.09). There were no significant changes in pupil diameter in the untreated eyes.

Table 2 Comparison of pupil diameter at baseline (*T0*) and at 90 min after instillation (*T90*)

	Mean pupil diameter (SD), mm		Paired comparison (*t*-test)
	T0	T90	
Dipivefrin	5.44 (0.79)	6.19 (1.09)	Pupil diameter significantly larger at T90 ($P=0.010$)
Pilocarpine	5.49 (1.06)	2.26 (0.49)	Pupil diameter significantly smaller at T90 ($P=0.002$)
Saline	5.56 (0.98)	5.62 (0.96)	No difference between T0 and T90 ($P=0.560$)

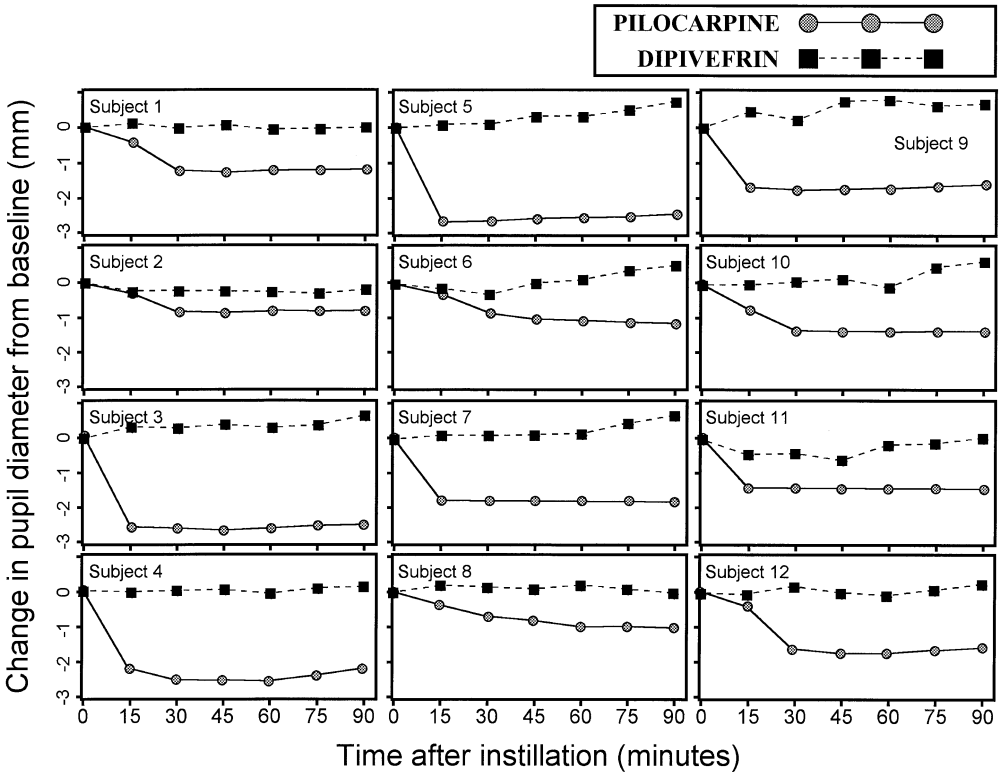

Fig. 2 Change in pupil diameter from baseline over 90 min for each subject for pilocarpine and dipivefrin

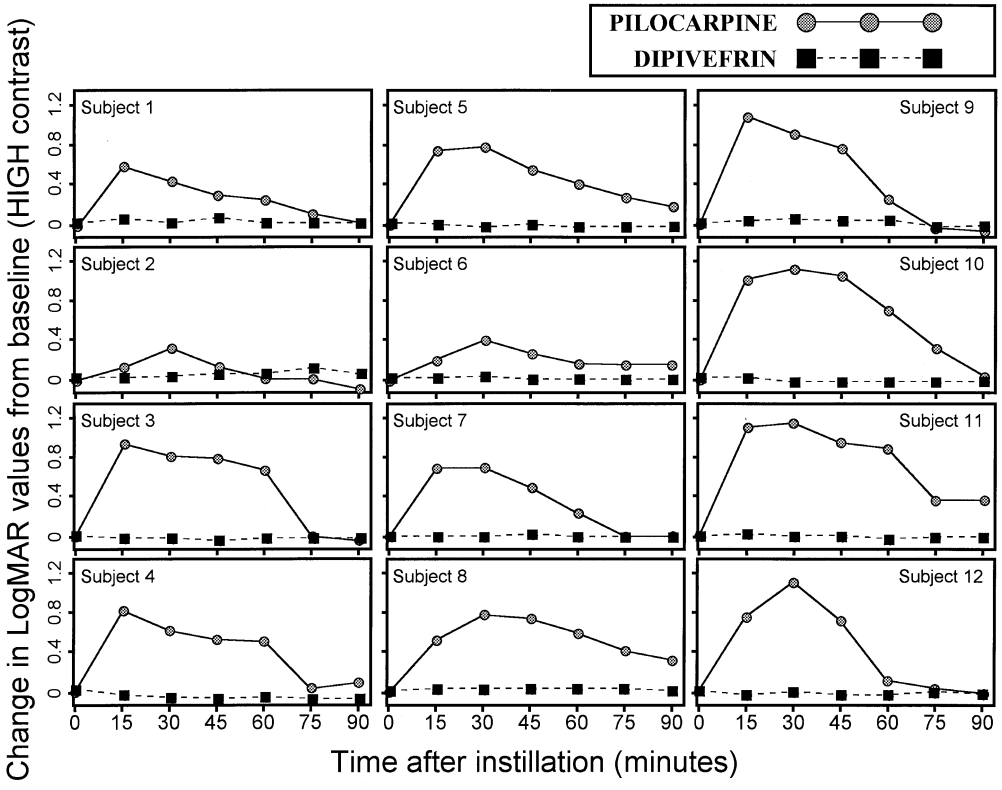

Fig. 3 Change in high-contrast LogMAR values from baseline for each subject for pilocarpine and dipivefrin

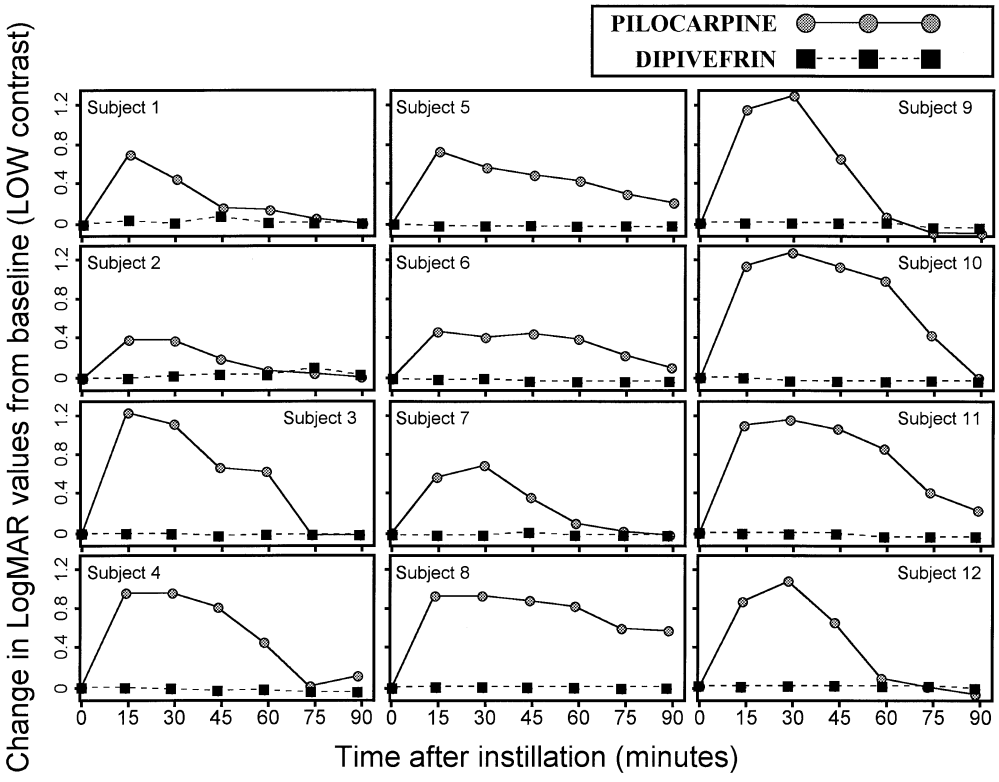

Fig. 4 Change in low-contrast LogMAR values from baseline for each subject for pilocarpine

Distance visual acuity

Figure 3 shows the change in high-contrast LogMAR values from baseline for each subject for pilocarpine and dipivefrin. Figure 4 shows the equivalent data for low-contrast LogMAR values.

With pilocarpine the rapidity and extent of the reduction in acuity are illustrated by the increase in mean LogMAR (decrease in acuity) for all 12 subjects at 30 min after instillation. For high contrast this was 0.76 (SD 0.30) and for low contrast 0.83 (SD 0.11), equivalent in both cases to approximately 8 lines of the chart. Comparisons between Fig. 3 and Fig. 4 reveal striking similarities between the effects on high- and low-contrast LogMAR values. The mean time to reach maximum reduction in acuity for all 12 subjects was 21 min (SD 8) for low-contrast and 24 min (SD 8) for high-contrast letters. There was no significant difference between low- and high-contrast letters (paired *t*-test; P=0.44), further demonstrating the similarity between their responses. By 90 min LogMAR values approach baseline levels for both high and low contrast. A paired comparison of the responses at T90 and baseline showed no significant difference for either low contrast [mean difference=0.06 (SD 0.20); P=0.37] or high contrast [mean difference=0.09 (SD 0.17); P=0.11].

A LogMAR index was calculated from the area under the response curve divided by time. With high-contrast letters the mean LogMAR indices were 0.36 (SD 0.20) for pilocarpine and −0.09 (SD 0.11) for dipivefrin, while for low-contrast letters they were 0.57 (SD 0.21) for pilocarpine and 0.07 (SD 0.12) for dipivefrin. For both high and low contrast a paired comparison showed a significant difference between pilocarpine and dipivefrin (high contrast P=0.003, low contrast P=0.002).

Dipivefrin had no effect on acuity at either contrast level. There were no changes in the untreated eyes.

Discussion

A single instillation of dipivefrin does not affect the visual field, as assessed by STATPAC global indices. Tropicamide-induced mydriasis has been found to significantly worsen MD [20], but for pupillary dilations having a mean of 3.0 mm, far greater than those produced by dipivefrin in this study (mean increase 0.75 mm).

The significant worsening of MD following pilocarpine instillation confirms the results of Lindenmuth et al. in normal volunteers [19]. However, the extent of the worsening was greater (2.01 dB, SD 1.21), and is more likely to be clinically significant, in the current study than in that of Lindenmuth et al. (0.67 dB, SD 0.67), who were equivocal as to the clinical significance of their findings. These differences may be due, at least in part, to their decision to re-refract subjects prior to post-instillation perimetry and to correct any myopic shift resulting from cil-

iary spasm. No refraction was performed in the current study, provided subjects demonstrated the ability to read N5 print at 33 cm, N5 being the smallest print on our Faculty of Ophthalmologists near vision chart and 33 cm the radius of the Humphrey bowl. All 12 subjects achieved this standard of near acuity despite the presence of varying amounts of ciliary spasm, so no refractions were performed. In the clinical environment, patients on pilocarpine therapy are not always refracted prior to automated perimetry. If they are refracted, and subsequently wear a correction for ciliary spasm, this may provoke further spasm. Furthermore, a marked improvement in visual acuity between 55 min and 75 min after pilocarpine instillation, the result of the gradual lessening of ciliary spasm over time, is clearly seen in Fig. 3. Hence, any refractive correction given prior to perimetry, commencing at 60 min in this study, is unlikely to be accurate by the completion of the test. There is much to be said for the procedure followed in some clinics, in which a wash-out period of 24 h is allowed prior to visual field testing in patients on pilocarpine therapy.

Most of the subjects in Lindenmuth et al.'s study were naive to automated perimetry, and it is possible that the effects of learning may have masked a greater worsening of MD [19].

The deterioration in MD became more pronounced with increasing eccentricity, a finding in accord with other studies [19, 26]. The asymmetrical nature of this deterioration is highlighted by the significant decline in PSD compared with baseline. If such a decline in PSD were present in glaucomatous patients following pilocarpine instillation this could have important implications when monitoring serial fields. However, Webster et al. found an improvement in PSD, which was not statistically significant, in their glaucomatous sample [24]. Lindenmuth et al., who subdivided their 30-2 field in a manner similar to that in the current study, found the effect of eccentricity to be much less dramatic [19].

Webster et al. found a worsening of MD, having a mean of 1.49 dB, in a sample of 20 eyes with a range of glaucomatous field defects, following the instillation of one drop of pilocarpine 2% [24]. This worsening approaches the magnitude of that in the current study, but their subject sample, with a mean age of 70.6 years, differed greatly. Also, four HFA 30-2 field tests were performed in each subject on the same day, so fatigue effects cannot be ruled out.

This worsening of MD with a miotic pupil has been attributed to two possible causes, decreased retinal illumination and diffraction. The combination of small pupil diameters and the relatively low background illumination level of the HFA (31.6 apostilb) may cause retinal illumination to be reduced to a level at which Weber's law is no longer applicable. Weber's law predicts that the differential light threshold remains unaltered when pupil size is varied, but this is only valid for retinal illumination levels within the mesopic range. Wood et al. found that mean retinal sensitivity increased with increasing pupil diameter, and the sensitivity increase became more marked with increasing eccentricity [26]. The effect of changing pupil diameters on sensitivity was similar at adaptation levels from 10 to 45 apostilbs, and Wood et al. concluded that Weber's law applied over this range of adaptation levels. However, this was for pupil diameters ranging from a mean of 2.5 mm to a mean of 6.85 mm. This conclusion was supported by Herse for pupil diameters from 3 mm to 8 mm [13].

It is difficult to apply these conclusions with any certainty to the present study, in which the mean pupil diameter was 2.06 mm just prior to automated perimetry at 60 min after drug instillation, and seven subjects had pupil diameters below 2.0 mm during perimetry. A breakdown of Weber's law must remain a possible explanation for the worsening of MD. As the pupil diameter is reduced to 2.4 mm, the quality of the retinal image improves in the normal eye as the eye's aberrations are reduced. Reductions below 2.4 mm cause image quality to deteriorate as the effects of diffraction increasingly outweigh the reduction in aberrations [4]. Pupil diameters were below 2.4 mm during perimetry in 11 of the 12 subjects (subject 6 was the exception), and it is likely that diffraction made a major contribution to the decreases found in MD.

A Spearman's rank correlation non-parametric test was used to investigate any possible association between the worsening of MD and the degree of miosis. There was some evidence to support such a relationship, $\rho=0.61$, $P=0.04$), although any suggestion of a cause and effect nature must be treated with caution. Webster et al. found a similar level of association with their complete sample ($r=0.62$; $P=0.004$) [24].

Baseline values for MD, at −2.35 dB and −2.49 dB, are lower than expected for normal subjects. However, other studies on young normal subjects using the HFA have also found lower values; for a more complete discussion of this topic, see Rudnicka and Edgar [23].

Dipivefrin produced a mean increase in pupil diameter of 0.75 mm over 90 min, a figure comparable with that of 0.70 mm (SD 0.70) found 60 min after instillation by Kaback et al. in a single-dose study using ocular hypertensives taking no other medications [15]. Kaback et al. measured pupil diameters for 240 min after instillation, and mydriasis, as recorded by a millimetre rule, was maximal at 120 min, with a mean increase of 1.6 mm (SD 1.0). It is possible that further pupillary dilation may have occurred beyond the 90-min duration of the present study. In a long-term study the mydriatic effect of dipivefrin, with a mean of 0.65 mm, was comparable to that of epinephrine 2% [18]. As a result of these short- and long-term mydriatic effects, dipivefrin, like epinephrine, is contraindicated in closed-angle glaucoma.

The significant increase in mean pupil diameter from T0 to T90 produced by dipivefrin did not, in the short

term, affect either high- or low-contrast LogMAR acuity. A decrease in acuity is theoretically possible, resulting from the increased effects of aberrations in dilated pupils. In two long-term studies involving dipivefrin, Kohn et al. [18] and Kass et al. [16] recorded acuity at irregular intervals and found no measurable reduction. Two other long-term studies, which relied on self-reporting by patients of adverse reactions, reported 2 out of 57 and 5 out of 287 subjects experiencing significantly blurred vision [5, 17].

While the accommodative spasm accompanying pilocarpine-induced miosis has been quantified in terms of change in refractive error [8, 10], it is less often expressed in terms of the reduction in visual acuity. The rapidity of the fall in acuity in these young subjects is striking (Fig. 3). The subjects in this study were all aged in their 20s, and as such are much more susceptible to pilocarpine-induced spasm of accommodation than older potentially glaucomatous subjects. Recovery of acuity had begun by T45 in all subjects and was almost complete by T90. The rapidity of the fall in acuity runs parallel to the reduction in pupil diameter (Fig. 2), but recovery of acuity was much more rapid than pupillary redilation. By 90 min after instillation, LogMAR values in some subjects have improved compared with baseline levels for both high and low contrast. By T90 pupil diameter is often no longer at its minimum, resulting in diminished diffraction effects, and ciliary spasm is much reduced. This allows the reduction in blurring of the retinal image caused by the miotic pupil to dominate, which may lead to an improvement in acuity. The remarkable similarity between the effects on high- and low-contrast letter recognition (Figs. 3, 4) is notable, and the poor low-contrast performance is consistent with the subjective reports from patients on miotic therapy of difficulties with visual tasks performed in conditions of reduced contrast.

This study reveals a single instillation of dipivefrin in normals to cause mydriasis, but to leave the central visual field (as assessed by STATPAC) unaffected, and high- and low-contrast LogMAR acuity unchanged. Pilocarpine adversely affects the field and both measures of acuity. Knowledge of these visual effects is of value when selecting the most appropriate form of medical management of open-angle glaucoma, when advising patients of possible adverse reactions to their medication and when monitoring the progression of visual loss.

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