Double-blind cross-over comparison of aceclidine and pilocarpine in open-angle glaucoma

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Aceclidine hydrochloride (3-acetoxyquinuclidine, "Glaucostat": Chibret) used topically in a strength of 2 per cent. is a parasympathomimetic drug acting directly on the motor end-plate (cholinergic nerve-endings). It is suitable for administration as eye drops, penetrating rapidly into the anterior chamber. It is a synthetic substance and was first prepared in Russia by Rubitzov and Miklina (1960). The name "Aceclidine" was coined by Mashkovski and Zaitzeva (1960), who studied its pharmacological aspects. It was also described by Sharts and Shulpina (1961).

Numerous clinical trials in Russia, France, and Italy and in other countries have led to its widespread use on the continent of Europe, including the U.S.S.R. In several centres it is used routinely as an alternative to pilocarpine or when pilocarpine fails.

The drug has also been investigated in the United States of America by Lieberman and Leopold (1967), who described a definite lowering of intraocular pressure with no corresponding increase in facility of outflow. Aceclidine is not in clinical use in the U.S.A.

Our interest was stimulated by these early reports. No fully satisfactory topical direct-acting parasympathomimetic drug is available as an alternative to pilocarpine if for any reason this is or becomes unsuitable. In such cases resort is usually made to cholinesterase-inhibiting substances—eserine, prostigmine (neostigmine), or one of the "irreversible" cholinesterase inhibitors, di-isopropylfluorophosphonate (DFP), phospholine iodide, demecarium bromide, etc.

The use of the latter group of drugs is not without its disadvantages or dangers. Of the available direct parasympathetic stimulating drops, acetylcholine itself is too unstable to remain in solution for more than a few minutes. Carbachol (carbachol, Doryl, carbamylcholine chloride, a synthetic drug) 0.75 to 3 per cent. has poor corneal penetration, being hydrophilic, and must be used with a wetting agent in methyl cellulose (Shaffer, 1967), or as a dry suspension in anhydrous vehicles (Swan, 1959). Methacholine (Mecholyl) 10 to 20 per cent. is unstable and short-acting and must be used every 5 to 10 minutes. Arecoline, the alkaloid of the betel nut, was tried in ophthalmology in 1895 but never used in practice. Its formula is similar to that of aceclidine. Furfurmethide (furfuryl methyl ammonium iodide) and urecholine (urethane of beta-methyl choline) have also been abandoned.

Among the obvious advantages that aceclidine appears to offer over the preceding drugs are its stability, penetration, and long shelf-life.

Pharmacology

Aceclidine is 3-acetoxyquinuclidine (cf. molecular structure. Figure).

FIGURE Structural formula of aceclidine hydrochloride

It is available as:

- (i) The salicylate (molecular weight 308.34, a 2 per cent. concentration corresponding to an 0.065 molar solution). This is the preparation used by Lieberman and Leopold (1967). A 2 per cent. solution of aceclidine salicylate is only 0.79 times as concentrated a molar solution as 2 per cent. pilocarpine nitrate.
- (ii) Aceclidine hydrochloride (Glaucostat) with a molecular weight of 205.5. A 2 per cent. solution of the hydrochloride corresponds to an 0.097 molar solution. It is interesting that pilocarpine HCl has a molecular weight of 244.71, a 2 per cent. solution corresponding to an 0.82 molar solution, *i.e.* intermediate between the two forms of aceclidine (Table I).

Table I Formula of 2 per cent. aceclidine hydrochloride eye drops

3-acetoxyquinuclidine hydrochloride	2.0 g.
Boric acid	1.8 g.
Sodium borate	0.13 g.
Distilled water	100 ml.

Aceclidine has a potent parasympathomimetic action in man and experimental animals and a very weak anticholinesterase activity. This action is accordingly abolished or greatly weakened by atropine but almost unaffected by cholinesterase (Mashkovski and Zaitzeva, 1960). In experimental animals it possesses a parasympathomimetic action superior to that of a similar dose of pilocarpine. It is less toxic than pilocarpine, the L.D.₅₀ being 0.116 g./kg. (in mouse intraperitoneally) and 0.105 g./kg. (in rat)—approximately twice that of pilocarpine. No tachyphylaxis has been noted after repeated doses in contrast to that seen with pilocarpine (Yankelowitz, 1965).

It is prepared in a lyophilized form and is mixed at the time of dispensing. In powder form it undergoes only a 5 per cent. loss of activity after 3 months at 37°C. and can be used for up to 3 years. In solution a similar loss of activity occurs after 30 days at 22°C. (Tarrerias and Vassallo, 1967). The pH of the hydrochloride before bottling is 6.60. That of a 2 per cent. pilocarpine HCl solution is 4.8. On storing, aceclidine undergoes a slight fall in pH to 6.43, whereas pilocarpine tends to become more acidic.

No irritation in human subjects is recorded with a 2 to 4 per cent. solution, or in the rabbit eye with a 20 per cent. solution (Yankelowitz, 1965). The drug penetrates rapidly into the anterior chamber (Rouher, 1966).

Description of the trial

The object of the trial was a direct comparison of the effect on the same eyes and under identical conditions of gutt. pilocarpine 2 per cent. and gutt. aceclidine HCl 2 per cent., both used three times a day. One eye received pilocarpine and the other aceclidine. The eyes were examined at the end of one week of therapy, and after a fixed interval, $1\frac{1}{2}$ hours, from the last instillation. The following conditions were thought to be desirable:

- (a) Double-blind conditions to ensure lack of bias on the part of the patient in describing the symptoms, and greater objectivity on the part of the observer.
- (b) Use of a placebo for one week to each eye to eliminate the effect of previous medication; it is claimed that 32 hours are sufficient for this purpose (Agugini and Stecchi, 1968).
- (c) Cross-over after a further week of placebo.

MATERIAL AND METHODS

The trial covered a total of 54 eyes (27 cases). All were established cases of open-angle (chronic simple) glaucoma undergoing medical treatment (with pilocarpine: 36 eyes; pilocarpine and eserine: 3 eyes; pilocarpine and neutral adrenaline: 16 eyes; phospholine iodide and neutral adrenaline: 1 eye; adrenaline alone: 2 eyes).

SUITABILITY OF CASES

- (1) No patient undergoing therapy with a carbonic anhydrase inhibitor and only one eye previously on a powerful anticholinesterase drug was included in the test. (In two eyes neutral adrenaline was continued during the trial.)
- (2) Visual acuity had to be at least 1/60 in each eye to allow tonography to be performed in both eyes.
- (3) Patients fulfilling the above requirements were considered suitable for the "full trial" (see later) only if their anterior chamber depth and configuration were such that angle closure was considered unlikely to occur when miotic therapy was interrupted for a week. Patients with a previously-recorded high level of intraocular pressure (greater than 28–30 mm. Hg) were also considered unsuitable for the full trial.

In Groups 2 and 3, the non-placebo or shorter trial was carried out.

A. Full Trial (34 eyes) (Table IIA, opposite)

- (1) *First visit*: Nature of trial explained: whatever the frequency of previous medication, drops to be used three times a day during trial (7.0 a.m., 2.0 p.m., and 10.0 p.m. whenever possible).

On day of attendance at clinic, however, mid-day instillation set at a specified hour (usually 1.30 or 2.0 p.m.) so that a constant interval should elapse before tonometry. Patient requested to observe and note various symptoms (see later) following use of drops, with special attention to comparison of the two eyes.

Two bottles dispensed marked Right and Left containing placebo (physiological saline) to enable patients to practise adhering to new routine of treatment.

- (2) *Second visit* (after 7 days).

- (a) Questionnaire: contrasting and comparing effects on the two eyes as regards: pain/

Table II Clinical particulars of 17 full trial cases (34 eyes)

Case no.	Eye	Po	P pilo	P acec	Co	C pilo	C acec	Po/Co	Po/C pilo	Po/C acec
1	R	29	20	26	0.15	0.24	0.18	193	83	144
	L	32	27	26	0.11	0.20	0.18	290	130	144
2	R	23	14	23	0.13	0.27	0.12	176	51	191
	L	24	20	17	0.20	0.15	0.17	120	133	100
3	R	24	14	18	0.19	0.33	0.20	105	42	90
	L	24.5	16	17	0.20	0.22	0.24	100	72	70
4	R	22	16	20.66	0.13	0.23	0.20	176	52	150
	L	22	21.33	18	0.12	0.26	0.15	250	80	140
5	R	30	22	21.66	0.07	0.25	0.16	430	88	137
	L	36	20.33	26	0.07	0.19	0.21	514	105	123
6	R	26	13.0	18	0.13	0.25	0.27	200	52	96
	L	29.66	18.50	18	0.20	0.25	0.27	150	112	66
7	R	20.33	18	10	0.30	0.41	0.41	66	43	37
	L	17.33	9	16	0.40	0.45	0.45	42	22	34
8	R	26.5	17.33	19.66	0.06	0.20	0.18	450	85	111
	L	29.5	16.33	16.66	0.06	0.16	0.26	500	100	64
9	R	18	24.66	33.66	0.05	0.11	0.10	360	218	300
	L	20	22	20.33	0.15	0.12	0.20	133	183	100
10	R	26	21.66	19.66	0.16	0.13	0.13	162	154	154
	L	22	18.66	18.33	0.15	0.20	0.20	147	95	95
11	R	22.66	16.8	17.66	0.14	0.27	0.30	165	63	70
	L	23.33	20.0	19.66	0.14	0.19	0.24	165	115	84
12	R	35.33	20.33	21.66	0.07	0.13	0.20	515	154	110
	L	30.66	20.33	20.5	0.10	0.15	0.13	300	134	154
13	R	22.0	21.0	17.33	0.25	0.20	0.19	88	105	95
	L	23.66	21.66	23.33	0.21	0.16	0.16	114	136	144
14	R	25.33	24.66	26.0	0.13	0.13	0.13	195	195	200
	L	23.0	19.33	19.0	0.21	0.15	0.19	110	134	100
15	R	19.0	16.0	18.0	0.23	0.26	0.25	83	61	64
	L	20.33	19.0	18.0	0.24	0.23	0.23	84	83	75
16	R	23.0	20.0	22.0	0.25	0.24	0.25	88	83	88
	L	23.0	22.0	19.33	0.30	0.25	0.29	73	88	65
17	R	33.0	19.0	30.66	0.11	0.17	0.06	290	112	500
	L	30.0	17.66	17.0	0.10	0.17	0.17	300	106	100

Po = pressure after placebo

Co = outflow after placebo

Po/Co = Po/C after placebo

P pilo = pressure after pilocarpine

C pilo = outflow after pilocarpine

Po/C pilo = Po/C after pilocarpine

P acec = pressure after aceclidine

C acec = outflow after aceclidine

Po/C acec = Po/C after aceclidine

browache, smarting, red eye, watering eye, running nostrils, watering mouth, blurring and/or darkening of vision, sneezing, gastrointestinal symptoms (cramps, diarrhoea).

(b) Observation of relative hyperaemia of two eyes.

(c) Estimation of pupil size either by using the graticule on Goldmann's perimeter, or by direct confrontation with the pupillometry wheel on the Hamblin/Morton ophthalmoscope

under uniform conditions of lighting and fixing distant object. With practice, accuracy of 0.25 mm. is possible (*e.g.* between the 2.5 and 3.0 mm. marks), considered adequate for the purposes of the test.

(*d*) Applanation tonometry: using Goldmann tonometer mounted on Haag-Streit 900 slit lamp, checked for accuracy before each session with calibration device for 20 and 60 mm. Hg. Three readings made on each eye, changing eyes between each reading, and mean pressure recorded.

(*e*) Tonography: using Schwarzer recording tonometer. P_0 taken as applanation reading. As far as possible 45 to 60 minutes allowed to elapse between recording of two eyes. Only good tracings accepted. Correction for scleral rigidity not included.

(*f*) Pilocarpine 2 per cent. and aceclidine 2 per cent. dispensed at Hospital Pharmacy in bottles marked Right and Left plus a code symbol corresponding to a number in a scientifically randomized series.

(3) *Third visit* (end of second week). Questionnaire, etc., as on second visit.

Two sets of drops issued; (*a*) Two bottles of placebo for third week; (*b*) Two bottles of pilocarpine/aceclidine in sealed envelope for use at beginning of week four (date specified on envelope).

(4) *Fourth visit* (14 days after third visit). Procedure as at third visit.

At the conclusion of the trial each patient resumed his previous therapy.

B. Non-placebo or "Short" Trial (20 eyes) (Table IIB)

Table IIB *Clinical particulars of 10 non-placebo cases (20 eyes)*

Case no.	Eye	<i>P</i> acec	<i>P</i> pilo	<i>C</i> acec	<i>C</i> pilo	<i>P</i> ₀ / <i>C</i> acec	<i>P</i> ₀ / <i>C</i> pilo
1	R	23	22.66	0.13	0.13	175	175
	L	24.1	25.0	0.09	0.10	265	250
2	R	20.33	19.88	0.13	0.30	154	67
	L	16.0	15.66	0.26	0.12	62	133
3	R	24.0	24.33	0.26	0.16	92	150
	L	24.0	23.16	0.13	0.21	185	110
4	R	21.66	14.0	0.12	0.11	183	128
	L	18.0	13.0	0.08	0.11	222	118
5	R	30.66	28.0	0.10	0.14	310	200
	L	28.0	27.33	0.10	0.18	280	150
6	R	37.0	30.0	0.18	0.15	205	200
	L	32.0	26.66	0.11	0.14	280	194
7	R	18.66	19.33	0.17	0.24	112	83
	L	21.33	17.66	0.19	0.17	113	106
8	R	23.33	21.66	0.31	0.20	77	110
	L	20.0	20.0	0.19	0.24	105	83
9	R	27.33	37.33	0.10	0.05	280	740
	L	24.0	16.66	0.09	0.12	255	142
10	R	28.33	22.66	0.16	0.21	179	110
	L	22.0	22.33	0.09	0.14	244	161

One eye placed on gutt. pilocarpine 2 per cent. and the other on gutt. aceclidine 2 per cent. (according to the randomized series) for a period of 2 weeks. After 2 weeks, cross-over carried out.

Trial lasted 4 weeks as for standard trial, but included only three visits, 14 days apart, at which the procedure was the same as for the standard trial.

Results

The results were evaluated statistically, using Student's *t*-test. The *t* and *P* values are given in Table III.

Table III Statistical evaluation of results

(1) Comparison of pilocarpine and aceclidine with placebo (full trial cases only)

Drug	Mean intraocular pressure	C-value	P ₀ /C	Pupil diameter
Pilocarpine	Per cent. fall 25.54 <i>t</i> = 6.8 <i>P</i> < 0.001	Per cent. rise 34.37 <i>t</i> = 4.3 <i>P</i> < 0.001	Per cent. fall 54.13 <i>t</i> = 4.8 <i>P</i> < 0.001	Per cent. reduction 47.8 <i>t</i> = 14.2 <i>P</i> < 0.001
Aceclidine	Per cent. fall 19.10 <i>t</i> = 5.0 <i>P</i> < 0.001	Per cent. rise 31.25 <i>t</i> = 4.6 <i>P</i> < 0.001	Per cent. fall 41.16 <i>t</i> = 3.6 <i>P</i> < 0.001	Per cent. reduction 52.43 <i>t</i> = 12.7 <i>P</i> < 0.001

(2) Comparison of pilocarpine with aceclidine

Drug		Pilocarpine	Aceclidine	Difference	<i>t</i>	<i>P</i>
Mean I.O.P. (mm. Hg)	All cases	20.28	21.81	1.53	3.49	> 0.05
	Full trial	19.05	20.40	1.35	2.33	> 0.05
Mean C-value	All cases	0.20	0.19	0.01	1.09	> 0.15
	Full trial	0.215	0.21	0.005	0.78	> 0.15
Mean P ₀ /C	All cases	110.54	147.65	37.11	1.67	> 0.15
	Full trial	102.0	123.38	21.38	1.79	> 0.15
Pupil diameter (mm.)	Full trial	1.94	1.82	0.12	1.24	> 0.15

(1) INTRAOCULAR PRESSURE

The mean intraocular pressure in cases on placebo was 25.18 mm. Hg. That in all cases on pilocarpine was 20.28 mm. Hg (S.E. 0.58). That for the 34 eyes on the full trial was 19.05 mm. Hg, and for the 20 eyes on the non-placebo trial 22.37 mm. Hg. The mean pressure for all cases on aceclidine was 21.81 mm. Hg (S.E. 0.71), for all cases on the full trial 20.40 mm. Hg, and for those on the non-placebo trial 24.19 mm. Hg. The percentage fall in pressure from placebo to pilocarpine was 24.5 per cent. and from placebo to aceclidine 19.10 per cent. Both drugs produced a statistically significant fall as compared to the placebo. The difference between the two was not significant.

(2) AQUEOUS OUTFLOW

(a) *Outflow coefficient*

Mean coefficient value (C-value) on placebo 0.16 (S.E. 0.013).

Cases on pilocarpine 0.20 (S.E. 0.013) (full cases 0.215; non-placebo cases 0.16).

Cases on aceclidine 0.19 (S.E. 0.013) (full cases 0.21; non-placebo cases 0.15).

Percentage rise from placebo to pilocarpine 34.37 per cent., that from placebo to aceclidine 31.25 per cent. Both drugs produced a statistically significant increase in the coefficient-value as compared to the placebo. The difference between the two drugs was not significant.

(b) *Outflow fraction*

Mean P_o/C value for cases on placebo 209.83.

Cases on pilocarpine 110.54 (S.E. 7.56) (full cases 102.0; non-placebo cases 170.5).

Cases on aceclidine 147.65 (S.E. 11.22) (full cases 123.38; non-placebo cases 188.90).

Percentage change from placebo to pilocarpine 54.13 per cent., that from placebo to aceclidine 41.16 per cent. Both drugs produced a statistically significant fall in the outflow fraction compared to the placebo. The difference between the two drugs was probably not significant. There was a rather large scatter in the figures.

(3) PUPIL DIAMETER

Mean diameter for cases on placebo 3.84 mm.

Cases on pilocarpine: overall mean 1.87 mm. (S.E. 0.09) (full cases 1.94 mm.; non-placebo cases 1.71 mm.).

Cases on aceclidine: overall mean 1.71 mm. (S.E. 0.09) (full cases 1.82 mm.; non-placebo cases 1.58 mm.).

Percentage reduction in pupil diameter from placebo to pilocarpine 47.84 per cent.; that from placebo to aceclidine 52.43 per cent. Both drugs produced significant miosis but the difference between the two was not significant.

(4) HYPERAEMIA

This was observed in 34 cases. It was more frequent with aceclidine than with pilocarpine.

Discussion

(1) INTRAOCULAR PRESSURE

In the present study, aceclidine was found to have a definite effect in lowering the intraocular pressure of eyes with open-angle glaucoma. This is in agreement with all the published work. The overall mean pressure in cases on aceclidine was 1.53 mm. Hg higher than that in cases on pilocarpine 2 per cent., a difference that is not statistically significant. The difference between the mean pressure produced by the two drugs was higher in the non-placebo cases (1.72 mm.) than in the full trial cases (1.36 mm.), suggesting that in patients with a high initial intraocular pressure (or a shallow anterior chamber) a stronger concentration of aceclidine might be necessary.

These results are similar to the results of the chronic experiments of Demailly (1968), in which the pressure in cases on pilocarpine was 19.1 mm. Hg, and that in cases on aceclidine

was 20.2 mm. Hg. However, in his acute experiments, pilocarpine produced a percentage fall in pressure of 27 (± 12) compared to 30.6 (± 13.8) for aceclidine. Leopold (1968) found, in acute experiments in cases of chronic simple glaucoma, that 2 per cent. aceclidine salicylate had a greater action in lowering the intraocular pressure than pilocarpine 2 per cent. Étienne, Barut, and Gonzalès-Bouchon (1967), in twenty cases of chronic simple glaucoma, found a mean lowering of the intraocular pressure with aceclidine of 7.65 mm. Hg. Agugini and Stecchi (1968) reported no difference in the hypotensive action of the two drugs when the three daily readings over 3 days were averaged, although the figure for aceclidine (20.95 mm. Hg) was slightly lower than that for pilocarpine (22.29 mm. Hg). Brancato and Boschi (1968), comparing the action of the two drugs in ten subjects, found that aceclidine was "incomparably better", but gave no statistical evaluation.

(2) AQUEOUS OUTFLOW

It was this aspect of the effect of direct-acting parasympathomimetic miotics that appeared to be the most intriguing. In the present study, aceclidine was found to have a definite effect in improving the facility of outflow in eyes with open-angle glaucoma. The difference in the mean C-value of cases on pilocarpine and aceclidine was 0.01 (full trial cases difference = 0; non-placebo cases difference = 0.01). Lieberman and Leopold stated categorically that, so far as their work was concerned, aceclidine had no effect whatsoever on outflow facility (except in their chronic simple glaucoma suspects and secondary glaucoma cases), a unique property in a miotic. They observed a definite pressure-lowering effect, which led them to a most interesting theoretical discussion of how the drug produced this effect (see below). Demailly (1968), in his chronic and acute experiments, found that aceclidine produced a significant improvement in outflow but was no significant difference between the effects of pilocarpine 2 per cent. and aceclidine HCl 2 per cent. on the C-value or on P_o/C . However, the effect of aceclidine was consistently less powerful. A study, in the acute experiments, of the logarithm of the C-values, usually of a Gaussian distribution in normal subjects, revealed a significantly greater improvement with pilocarpine than with aceclidine. Among the other studies, Étienne and others (1967) found a highly significant improvement of outflow with aceclidine in cases of glaucoma simplex; the mean improvement in the C-value was 0.048. Riegel and Leydhecker (1967) observed an improvement in the C-value with aceclidine from a base line of 0.17 to 0.20, rather less than the 0.22 obtained with 2 per cent. pilocarpine. Gil del Rio (1968) found a mean increase of 0.051. Lepri and Tota (1967) observed an improvement in C-value of the order of 0.03. Brancato and Boschi (1968) observed an "identical" improvement in the C-value on both drugs. Magouritsas and Coliopoulos (in press) and Mazzilli and Mazza (1967) also observed a definite improvement in outflow.

Of all the published studies, therefore, only that of Lieberman and Leopold (1967) reports no improvement in outflow with aceclidine.

Mechanism of the effect of the two drugs

(a) It could conceivably be produced by a reduction of aqueous formation. Pilocarpine itself has been demonstrated to have an inhibitory effect on the ciliary process *in vitro* (Berggren, 1965). This effect has not been studied for aceclidine.

(b) Demailly, comparing the effect of the two drugs, explained the greater tension-lowering effect of aceclidine by the smaller amount of reactive hypersecretion which occurs

after the use of both drugs. That this effect was indeed greater with pilocarpine was suggested by flow-studies, using both the results of tonography, with Goldmann's $F = (P_o - P_v)$ formula, and suction cup studies.

(c) Bárány (1962), experimenting on the monkey *Cercopithecus ethiops*, demonstrated that the increase in outflow facility produced by pilocarpine could be reversed by atropine in two stages, a fast and a slow. The fast stage lasted approximately as long as the accommodative spasm produced by pilocarpine, and could correspond to a facilitation of outflow produced by a pull of the ciliary muscle on the trabecular meshwork (and possibly on the endothelial cells of Schlemm's canal). The slow phase could correspond to the abolition of a histamine-like action of pilocarpine directly on the endothelial cells or a widening of the transendothelial channels (this latter phenomenon could not be confirmed in later experiments). In some individuals an increase in facility may be mainly due to the ciliary muscle pull, whereas in others it may predominantly correspond to the effect on the endothelium. It is possible that aceclidine lacks the latter effect (it produces intense miosis, so it is probably unlikely to be without effect on the ciliary muscle).

(d) Another explanation could be related to the recent concept of the uveo-scleral flow of aqueous along the interfascicular spaces of the ciliary body directly to the venous circulation (Bill and Bárány, 1966). Pilocarpine, possibly by causing ciliary spasm, is thought to close up this alternative pathway for aqueous outflow. The effect of aceclidine has not been studied and it could be weaker than that of pilocarpine.

(3) MIOSIS

In the present study, aceclidine was found to produce slightly more powerful miosis than pilocarpine.

Demaillly (1968) obtained the impression that the miosis produced after one hour was greater with aceclidine than with pilocarpine, though the pupillary diameters were not measured. Gil del Rio (1968), using an electronic flash photographic method, noted early miosis with aceclidine, starting 4 minutes after instillation and reaching its maximum between 20 and 80 minutes. Étienne and others (1967) also noted "intense miosis". Rouher (1966) observed miosis after 30 minutes, maximal after 90 minutes, the pupil then being 47 per cent. of its original diameter. Riegel and Leydhecker (1967) noted a mean pupillary diameter on pilocarpine of 1.6 mm. and on aceclidine of 1.7 mm. This would appear to be the only study in which the miotic effect of pilocarpine was noted to be stronger than that of aceclidine.

(4) HYPERAEMIA

This was more frequent with aceclidine in the present study (Table IV, opposite). Demailly (1968) observed that it produced the same degree of congestion as pilocarpine. Riegel and Leydhecker (1967) observed only three cases of hyperaemia in 51 eyes, lasting only for 1 or 2 days.

(5) BROWACHE OR HEADACHE

This was noted in 23 cases (Table IV), and was more frequent with aceclidine. Itin and Ricci (1967) reported slight headache in four out of fifteen patients.

(6) SMARTING

This occurred in thirty cases, being approximately equal with the two drugs. It also occurred in four eyes on placebo drops (Table IV).

Table IV

<i>Symptoms</i>	<i>Absent</i>	<i>A > P</i>	<i>P > A</i>	<i>Equal</i>	<i>More with placebo</i>
Pain, browache	20* > 31 11**	7 > 12 5	4 > 6 2	3 > 5 2	—
Smarting	19 > 24 5	10 > 12 2	2 > 11 9	1 > 7 6	4 > 4 0
Hyperaemia	13 > 20 7	10 > 18 8	2 > 2 0	9 > 14 5	2 > 2 0
Watering	24 > 33 9	3 > 7 4	2 > 4 2	5 > 10 5	—
Rhinorrhoea	15 > 12 8	8 > 12 4	3 > 4 1	8 > 15 7	—
Sialorrhoea	30 > 49 19	0 > 0 0	1 > 1 0	3 > 4 1	+1

* refers to cases in the full trial

** refers to cases in the non-placebo trial

(7) BLURRING AND DARKENING OF VISION

These occurred in 38 and 28 cases respectively, being more frequently noted with aceclidine. In Demailly's experience accommodative myopia is the same as with pilocarpine. The only other reference in the published work to this symptom is that of Itin and Ricci (1967), who noted transient visual disturbances in four out of fifteen patients.

(8) SIALORRHOEA

This occurred in seven cases and was rather more frequent with pilocarpine than with aceclidine (Table IV). This is in contrast with the observations of Étienne and others (1967), who found that aceclidine produced no sialorrhoea in man as it did in animals.

(9) RHINORRHOEA

This occurred in 31 cases, more often with aceclidine than with pilocarpine (Table IV).

(10) SNEEZING

This occurred in eight cases: in four with aceclidine, one with pilocarpine, and three equally with both drugs. It also occurred in one case on placebo drops. The literature here is conflicting: Demailly (1968) reported no instance of sneezing following the instillation of aceclidine, whereas Étienne and others (1967) reported it in *all* patients.

(11) GASTROINTESTINAL DISTURBANCES

None was observed, and this finding is similar to that of other workers. Such disturbances are, in fact, seldom observed with pilocarpine but are frequent with carbachol, together with other manifestations of systemic intoxication.

Long-term tolerance of aceclidine

The following brief histories of patients outside the double-blind series are included as examples of good acceptance of aceclidine when pilocarpine was not tolerated.

(1) *Mrs. E. W.*

Irritation on pilocarpine with intolerable discomfort. Given aceclidine for 6 months. Quite comfortable on this therapy. Seen at 3-weekly intervals: ocular tension between 12 and 20 mm. Hg.

(2) *Mrs. W. P.*

Much irritation on pilocarpine. Given aceclidine for 19 months. Much less irritation, though more "darkening". Pressure during entire period between 20 and 22 mm. Hg (had been 32 mm. previously). On resuming pilocarpine the pressures were around 24 mm. Hg in each eye. Complained of pain around eyes and discharge. Eppy and eventually hydrocortisone drops necessary.

(3) *Mrs. D. B.*

Irritation on pilocarpine. Given aceclidine for 3 months. Initial comfort but slight discomfort for one month which passed off. Tension 23 to 27 mm. Hg on pilocarpine 2 per cent., and 21 to 24 mm. Hg on aceclidine. Resumed pilocarpine 3 per cent. and eserine 0.5 per cent. Gradually developed intense hyperaemia and discomfort. Local steroids attempted. Tosmilen eventually tried.

(4) *Mrs. T. P.*

Allergic to pilocarpine. Was receiving gutt. Betnesol. Given aceclidine for 12 months with excellent tolerance, much less discomfort, and much less congestion. With Eppy 1 per cent. in addition control was satisfactory. (Tensions 21 to 22 mm. Hg at all times.) When pilocarpine 2 per cent. was resumed the tensions were around 24 to 26 mm. Hg and she again complained of discomfort.

(5) *Mr. T. S.*

Sensitive to pilocarpine and eserine, and was given phospholine iodide with Eppy. The tensions were 24 to 26 mm. Hg. Given aceclidine with Eppy and seen monthly for a year. Much more comfortable. Pressures around 17 to 24 mm. Hg. When pilocarpine 3 per cent. was resumed absolute intolerance was complained of. Again given aceclidine and discomfort disappeared. When supplies of aceclidine were exhausted prostigmine (neostigmine) 3 per cent. was tried but caused a considerable burning sensation which was soothed to some extent by adrenaline.

Summary

The results of a double-blind cross-over comparison of aceclidine hydrochloride 2 per cent. and pilocarpine 2 per cent. in 54 glaucomatous eyes are presented. Both eye drops produced a significant lowering of intraocular pressure and improvement in outflow and in the degree of miosis, but the differences between the two were small and not significant. Hyperaemia and a variety of subjective symptoms were also compared: neither drug produced serious side-effects or discomfort. Aceclidine would appear to deserve a place

beside pilocarpine as a stable direct parasympathomimetic drug in the treatment of open-angle glaucoma, especially if pilocarpine is not tolerated, or if it is ineffective, or becomes so after a period of use.

My thanks are due to Messrs. Chibret, France, for generous supplies of aceclidine and assistance with the Continental literature, to Mr. Redmond J. H. Smith for his advice and encouragement, and to Mr. Baker, Chief Pharmacist, Moorfields Eye Hospital, for organizing the dispensing of random series of eye drops.

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