THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

JANUARY, 1946

COMMUNICATIONS

A CLINICAL TRIAL OF A SYNTHETIC MYDRIATIC* (Dimethylaminoethyl Benzilate Ethochloride)

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THERE was a possibility at one period of the recent war that a serious shortage of the mydriatics usually employed in ophthalmology might develop. Under the direction of Sir Robert Robinson a series of relatively simple compounds were prepared which might be expected to show mydriatic properties. This was done by Dr. Ing and Dr. Ford-Moore at the Dyson Perrins Laboratory, Oxford. These workers made a large number of synthetic mydriatics which were of four main chemical classes; choline derivatives, dimethyl- and diethyl-aminoethanol derivatives, piperidine derivatives and morpholine derivatives. Quantitative estimations of the mydriatic activities of these synthetic substances were carried out on mice and cats by Dr. Edith Bülbring and Mrs. Isabella Wajda in the Department of Pharmacology, Oxford. The general conclusion reached from these investigations on experimental animals was that dimethylaminoethyl benzilate ethochloride was an efficient atropine substitute for the immediate war problem, provided that this view were confirmed by trials in

* Received for publication, October 11, 1945.

man. This substance was referred to as E.3 and this appellation will be used in the following account of certain clinical trials.

A 1 per cent. wt./vol. solution of E.3 in distilled water was made. Solutions of atropine sulphate 1 per cent. and of H. and C. (homatropine hydrobromide 1 per cent. and cocaine 2 per cent.) were also prepared. Three drop bottles with the dropper contained in the ground glass stopper were used for the trials. The size of drop delivered by the three stoppers was estimated by filling a 1.0 c.c. tuberculin syringe with drops delivered at the usual angle employed in putting drops into an eye and calculating the mean. The findings were:—

1. Bottle E.3 1 per cent.	delivered a drop	0.043 c.c.	average size
2. Atropine 1 per cent.		0.045 c.c.	„ „
3. H. and C.		0.051 c.c.	„ „

For clinical purposes the sizes were comparable, although greater accuracy of dosage might have been obtained by delivering the solutions into the conjunctival sac from a tuberculin or micro syringe.

Mydriatic effect

The size of the pupils was estimated by means of the pupillometer fitted to the driving wheel of a Morton ophthalmoscope before the drops were placed in the eyes. In five subjects two drops of E.3 were placed in the right eye and two drops of atropine in the left eye. Readings were taken of the size of the pupils at time intervals up to seven days. The mean distribution is shown in Table 1 A and B. The first line, A, shows the effect of E.3 upon the right eye and the second line, B, the effect of atropine. It will be observed that the effect of E.3 is neither so rapid nor so prolonged as that of atropine. By plotting the averages on a time scale of log. hours Diagram 1 was constructed. This confirmed the clinical impression that the effect of E.3 was less powerful than that of atropine.

Concurrently a similar series of comparisons was made between E.3 and H. and C. Ten subjects were investigated and the results are tabulated in Table 1 C and Table 1 D in a manner similar to the atropine group. Diagram 2 shows the results plotted in the same way as in the atropine series. It would appear that the action of E.3 is less rapid than H. and C. but of similar intensity. It is of course probable that the cocaine accelerates the mydriasis produced by homatropine, but the combined solution was used because it is the one frequently employed in routine work in ophthalmic clinics. When homatropine 1 per cent. was used alone the curves were very similar and are shown in Diagram 3. This is based upon the readings obtained from twelve patients.

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TABLE I
Average Pupil Size in Millimetres

GROUPS	HOURS												DAYS						
	0	1/4	1/2	1	2	4	5	6	8	10	15	20	24	2	3	4	5	6	7
Five Cases																			
A E.3 1 per cent. R.E. ...	4'2	5	5'9	8'2	7'7	7'5	8	7'5	7'7	—	—	—	5	4'7	3'8	4	3'7	3'8	4'3
B Atropine 1 per cent. L.E.	4'2	7	8'2	8'3	7'7	7	9	7	8'3	—	—	—	8	7'9	7'3	6'7	5'8	6	5'7
Ten Cases																			
C E.3 1 per cent. R.E. ...	3'4	5'5	6	8	8'1	7'4	—	7'3	6'3	5'8	4'2	4	4'8	3'8	4'3	4	—	—	—
D H. and C. L.E....	3'4	8	8	9'2	9	7'4	—	7'2	6'3	6'3	4'2	4'3	4'3	3'2	3'5	3'7	—	—	—
Fifty-one Cases																			
E E.3 1 per cent.	4'5	5'8	6'8	7'8	7'8	8	7'7	7'1	7'1	6'5	5'6	5	5'2	4'1	4'1	3'5	3'5	4	4

DIAGRAM 1.

DIAGRAM 2.

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DIAGRAM 3.

DIAGRAM 4.

Diagram 4 is founded upon repeated observations on fifty-one patients. It suggests that E.3 reaches its maximum mydriatic effect in about one hour and that the effect begins to wear off after five or six hours. Table 1 E shows the mean of all the readings made upon the eyes of these patients and the time intervals at which the observations were carried out. There are certain practical difficulties in obtaining repeated readings from healthy subjects. The patients were suffering from conditions unlikely to affect the iris, ciliary body or visual pathway, such as dacryocystitis, minor corneal abrasions and errors of refraction.

The vertical columns of Table 1 A and B, C and D, are comparable in that the averages calculated are based upon the same number of patients, the figure in section A being derived from the right eye and that in section B from the left eye and so on. Each pair of eyes was thus treated as if they were uniovular twins. It must be realised that, although the individual vertical columns are derived from strictly comparable material, this does not apply equally to all the pairs of time columns. Some patients contributed more readings than others. Thus, although the pooled data are presented in a diagrammatic graph form, they are not graphs in the strict sense.

The data were divided into four age groups, those under fifteen, between sixteen and forty, forty-one and sixty and over sixty. No significant difference was found, although the older patients did not dilate so widely as the younger ones. There was no sex difference found.

Cycloplegic effect

In routine clinical refraction work E.3 proved to be a satisfactory substitute for homatropine. In a woman aged 31 years, the refraction was estimated by retinoscopy on twelve occasions during the trial, and the cycloplegia with E.3 was less efficient than with atropine. A woman aged 27 years was estimated nine times, and there was no significant difference between E.3 and atropine. Atropine was better in a boy aged 5 years, whose refraction was done ten times. No difference was found in a boy aged 11 years with four estimations.

In the homatropine and cocaine group four patients had the refraction estimated three times, two four times and one on five occasions without any significant difference being observed between the two eyes.

The cycloplegic effect of E.3 was thus found to be equivalent to homatropine and cocaine, but less powerful than atropine for routine clinical work. No opinion was formed as to the time taken for the cycloplegic effect to wear off.

Atropine irritation

Fifteen patients, who were known to have atropine irritation, tolerated the E.3 solution without ill effect. In one the mydriatic action produced was less well maintained than that produced by hyoscine discs. This patient had one broad synechia in one eye and a clover-leaved pupil in the other. By estimating the arcs of the unattached portions it was possible to take four readings from this patient—one in the right eye and three in the left eye on successive occasions. In each case the curves were 0.5 to 1.0 mm. smaller when she was using E.3.

Effect on corneal epithelium

In over fifty patients under my care who have used E.3 no changes in the corneal epithelium were observed. They were all examined with a loupe and a few studied in detail with the slit-lamp. In two or three cases the usual mild H. and C. changes were seen in the left eye.

Summary

A clinical trial of the mydriatic and cycloplegic effect of dimethylaminoethyl benzilate ethochloride (E.3) on human subjects is described. Two drops of a 1 per cent. solution were placed in the right conjunctival sac of fifteen patients; atropine 1 per cent. was put into the left eye of five of those patients and homatropine 1 per cent. with cocaine 2 per cent. was used in the other ten. The size of the pupils was recorded in each case before the drops were instilled. Readings of the pupil sizes were taken in both eyes at various time intervals. The mean pupil size of fifty-one patients is given; no significant sex or age difference was observed. The data are presented in tabular form, and summarised in diagrammatic graph form. The ordinate records the pupil diameter and the abscissa the time interval in the logarithm of the hours. By this device the table is compressed.

Conclusion

The impression gained is that E.3 is probably an efficient substitute for homatropine both as a mydriatic and a cycloplegic.

The action of E.3 in 1 per cent. solution is neither so rapid nor so prolonged as that of atropine. It reaches a maximum in an hour, and the effect commences to fall off in five or six hours.

No skin irritation was found in subjects known to suffer from atropine sensitivity. No changes were observed in the corneal epithelium.

This clinical investigation was originally carried out on behalf of the Ministry of Supply.