The Influence of Drop Size on Pupil Dilatation

R. H. GRAY

Oxford

Summary

The clinical efficacy of reduced size dilating drops (micro drops), was assessed in 60 patients. For each patient, one eye received the standard 'minim' drop size (26 microlitres) while the fellow eye received a micro drop of five microlitres.

In 20 patients tropicamide 1% was followed after two minutes by phenylephrine 10%, another 20 patients were given tropicamide 1% alone, and for the last 20 patients, 0.5% tropicamide was used.

Satisfactory mydriasis was achieved for all pupils except those receiving micro drops of tropicamide 0.5% (25 micrograms tropicamide). Tropicamide 1% in micro drop formulation (50 micrograms tropicamide) gave almost identical mydriasis to that from standard drops (containing 250 micrograms tropicamide). Tropicamide 1% in combination with phenylephrine 10% was superior to tropicamide 1% alone, after standard or micro drop administration.

The micro drops used in this study were effective, easy to administer, and caused less patient discomfort.

Systemic effects of topically applied medications have become well recognised phenomena.¹⁻⁶ Adverse reactions may be minimised by occluding the lid punctae, reducing the concentration of administered drug, or reducing the drop volume. It is the latter manoeuvre that was investigated in this study, using the degree of pupil dilatation as the measure of clinical efficacy of the drugs examined.

Materials and Methods

Sixty patients requiring diagnostic pupil dilatation were selected and tested in the setting of outpatient clinics between June and December 1989. Those already on eye drops were excluded, as were those with obvious anterior segment pathology or history of intraocular surgery. Patients with diabetes mellitus or chronic glaucoma were also excluded because of the autonomic dysfunction that may affect the pupil in these conditions.^{7,8}

The average 'minim' drop volume of Phenylephrine 10%, Tropicamide 1%, and Tropicamide 0.5% was measured and found to be 26 microlitres. When the same drugs were administered via a 30 gauge Rycroft cannula, the average volume was 5 microlitres. (See Figure 1)

For all patients studied, vertical pupil diameter was measured using the focussed slit beam on a series 900 Haag-Streit slit lamp, immediately before instillation of drops, and at 20 minutes. For all eyes, a single drop of the drug studied was instilled into the lower conjunctival fornix.

For the first 20 patients (group 1), both 10% phenylephrine and tropicamide 1% were used. One eye was chosen at random to receive these drugs in micro-drop formulation, while the other eye received the standard drop size; two minutes elapsed before the second drop was given.

For the next 20 patients (group 2), 1% Tropicamide was used alone, again with the

Fig. 1 A 30 gauge Rycroft cannula, secured to minim dropper, was used to administer the micro drops.

standard drop in one eye, and micro-drop in the other.

For the final 20 patients (group 3), 0.5% Tropicamide was used alone in the same way.

Results

In Group 1 (tropicamide 1% and phenylephrine 10%), pupil diameter increased by an average of 4.62 millimetres (mm) for the standard drop size at 20 minutes, and by 4.28 mm

when the micro-drop formulation was used in fellow eyes. (See Table I)

In group 2 (1% tropicamide alone), average pupil diameter rose by 3.87 mm when standard drops were used, and by 3.7 mm for those pupils dilated with the micro-drop formulation in fellow eyes.

In group 3 (0.5% tropicamide alone), pupil diameter rose by an average of 3.7 mm at 20 minutes for the standard drop size, and by 3.14 mm for the micro-drop formulation in fellow eyes.

With a light stimulus provided by indirect ophthalmoscopy, it was noted that some pupil constriction occurred in eyes that had been dilated with a micro drop of 0.5% tropicamide. In all other eyes the pupils did not constrict 20 minutes after administration. It was also noted that patients experienced much less ocular discomfort with the reduced drop size.

A two way repeated measure Analysis of Variance (ANOVA) was carried out on the data. (For the purposes of this analysis it was assumed that the two eyes of any patient behave so similarly that they can be regarded as a single eye tested on two occasions⁶). The results of the analyses, (see Table II) show

Fig. 2 Effect of drop size on pupil dilatation. Filled bars represent large drops, striped bars represent small drops. 1 = Tropicamide 1% and phenylephrine 10%, 2 = Tropicamide 1% alone, 3 = 0.5% Tropicamide alone. (I = standard error of the mean).

Table 1 Mean pupil diameter (mm) at 0 and 20 minutes

	Standard drop	Micro drop
Tropicamide 1% + Phenylephrine 10%	2.53–7.15. (4.62)	2.49–6.77. (4.28)
Tropicamide 1%	2.23–6.10. (3.87)	2.22–5.92. (3.70)
Tropicamide 0.5%	2.52–6.22. (3.70)	2.50–5.64. (3.14)

(Change in pupil diameter in parentheses)

that there were main effects of choice of drug (s), ($f = 11.12$, $df = 2,57$, $p < 0.0001$) and drop size. ($f = 3.50$, $df = 1$, $p < 0.0001$). Also, a significant interaction was found between choice of drug(s) and drop size. ($f = 3.90$, $df = 2,57$, $p < 0.02$) This latter interaction was analysed further by testing the significance of the difference between the six means using Newman-Keuls *a posteriori* tests.¹⁰ These tests confirmed that the combination of tropicamide 1% and phenylephrine 10% gave significantly better dilatation than Tropicamide 1% alone, ($p < 0.01$) this being true for the macro or micro drop regimen. Also confirmed was the equal efficacy afforded by Tropicamide 0.5% when compared with Tropicamide 1%, although in this case it was only true when the macro drop of 0.5% tropicamide was used ($p < 0.01$).

Discussion

It is well known that topically applied drugs gain access to the nasolacrimal drainage system, decreasing topical efficacy and increasing the potential for systemic absorption. It is also clear that loss of drug from the eye will increase as drop size increases. Yet high concentrations of instilled drug in the pre-corneal tear film are required to achieve satisfactory ocular penetration: not only is the drug immediately diluted on contact with lacrimal fluid, but also the lacrimal fluid is itself being turned over at a rate estimated to be 16% per minute in humans.¹¹ The importance of high drug concentration was elegantly

demonstrated by Chrai *et al.*¹² on rabbit eyes using pilocarpine. He showed quite clearly that for a given amount of drug, maximum efficacy was obtained when drop size was decreased from 30 to 5 microlitres.

Human lacrimal fluid volume is about 7 microlitres, and the maximum quantity of fluid that can be accommodated without spillage is probably no more than 30 microlitres.¹³ Blinking considerably increases the rate at which this fluid is drained through the nasolacrimal apparatus. In this study the patients were allowed to blink, squeeze and wipe their eyes as they desired, because it was felt that this approach would more closely simulate the unsupervised administration of eye drops. One unexpected benefit to the patient of reduced drop size was greater comfort, to the extent that patients often questioned whether the drops had indeed gone into both eyes. The lack of squeezing, blinking, and wiping of the eyes probably aided the action of the micro drops.

One micro drop of tropicamide 0.5% gave inadequate pupil dilatation, indicating that the quantity of drug it contains (25 micrograms), falls below that required to achieve satisfactory mydriasis. Moreover, the absence of any significant difference in clinical efficacy between a micro drop of 1% Tropicamide (containing 50 micrograms) and a macro drop of 0.5% Tropicamide (containing 125 micrograms), indicates that no more than 50 micrograms of drug need be delivered to the eye to achieve maximum effect, provided it is delivered in a micro drop formulation.

Table 2 Analysis of variance. (ANOVA)

Source	Sum of SQ	DF	Mean SQ	F ratio	Tail prob
Condition (C)	22.3	2	11.12	7.77	0.00
Error (BG)	81.59	57	1.43		
Dropsizes (D)	3.50	1	3.50	21.65	0.00
D C	1.26	2	0.63	3.90	0.02
Error (WG)	9.22	57	0.16		

A statistically significant difference was demonstrated for the pupil dilatation achieved with a combination of 1% tropicamide and 10% phenylephrine when the macro drop was compared with the micro drop. However, the level of significance was only at the 0.05 level. This difference in effect is surprising, since Chrai *et al.*¹⁴ have shown in an animal model that the deleterious effect on the precorneal tear film concentration of a topically applied drug caused by subsequent administration of a second drug can be minimised if both drugs are given in as small a volume as practicable. Since the efficacy of topical 1% alone is as good in micro drop formulation, this difference must be attributed to the phenylephrine. It is possible that the micro drop of phenylephrine 10% contained too little drug for the desired clinical response.

Systemic absorption was not measured in this study. However, it has been shown by Lynch *et al.*¹⁵ that for 2.5% phenylephrine, drops of eight microlitres dilate the pupil as well as those of 30 microlitres, while systemic absorption was reduced by 50%. In a separate study,¹⁶ the same investigators showed that for a given quantity of phenylephrine, better dilatation was achieved when the drop size was reduced from 32 microlitres to eight microlitres.

Because of the undesirable drainage of topically applied drugs from their site of action, it might seem that their clinical efficacy would continue to rise as a given quantity of drug is supplied in ever smaller volumes. But this is not the case because at very small drop volumes, the turnover rate of lacrimal fluid will have a greater influence on the residual drug concentrations. These considerations led Chrai *et al.*¹² to conclude that the ideal drop volumes for topically applied drugs in humans should be 5–10 microlitres.

This and other studies make it clear that drug quantities well below those currently employed can be used to dilate the pupil with equal clinical efficacy, and with consequent reduction in systemic absorption. However, the technical difficulties of producing a commercial preparation of these drugs capable of delivering small drop sizes are great, and this has prevented their widespread use. A new

ophthalmic drug delivery system capable of low dose administration is currently being developed to circumvent this problem, and initial trial results have been promising.¹⁷

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Keywords: Dilate; Dilatation; Drop Size; Mydriasis; Pupil.

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