J. Pharm. Pharmacol. 1992, 44: 682–684
Communicated December 10, 1991

Visual recovery using small dilating eye drops

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Abstract—It is well established that reduced size dilating eye drops of 1% tropicamide and 10% phenylephrine (micro drops) are effective for clinical purposes. Excellent pupil dilatation (mydriasis) is achieved and pupil constriction does not occur in response to light. In this study, the effect of micro drops of 1% tropicamide on distance and near visual recovery was compared with standard drops in a group of 20 healthy volunteers. For each person studied, one eye was selected at random to be tested first with the standard drop size, and then after a minimum of one week, the same eye was again tested using a drop of the same drug one fifth standard size. An iris photograph, Snellen visual acuity at 6 m, and reading visual acuity was obtained for each test procedure: before drop instillation and at 30 min, 1, 2 and 4 h after drug instillation. Use of the micro drops caused a small but statistically significant improvement in the rate of recovery of distance and near visual acuity. These findings, allied to the known beneficial effects of reduced systemic absorption using micro drops, lend further weight to the argument that mydriasis may be achieved more safely, with fewer side effects, and with earlier return of normal vision when reduced size drops are used. It is hoped that practical micro drop dispensers will be developed.

It is frequently necessary to use dilating eye drops during the course of a routine eye examination in order to see clearly the crystalline lens, vitreous and retina. Unfortunately, the use of these drops can cause the patient's vision to become blurred afterwards, although this risk is not as great as it is commonly held to be (Montgomery & MacEwan 1989). Furthermore, untoward systemic side effects of topically applied drugs are well recognized (McReynolds et al 1956; Fraunfelder & Scafidi 1978; Kumar et al 1985; Lai 1989; Reid & Fulton 1989). Sometimes, particularly in the setting of a general practitioner's surgery, it may be prudent not to use these drops at all because of the patient's need to drive home. The patient would then be required to attend again for completion of the eye examination.

Tropicamide is a short acting parasympatholytic agent, and in drop form is the most commonly used drug to dilate the pupil for diagnostic purposes. Dilatation reaches a maximum within 30 min, and its effect usually wears off completely within 6 h. It has been established that drops of this drug one-fifth the normal size are adequate for pupil dilatation (Gray 1991). This study was undertaken to determine whether the reduced amount of drug also resulted in earlier return of normal vision.

Materials and methods

Twenty healthy volunteers from the staff of the Oxford Eye Hospital were tested (average age 31 years, range 22–60). Exclusion criteria included previous intra ocular surgery, use of eye drops known to affect pupil function, and diabetes mellitus.

For each volunteer, one eye was selected at random. Corrected distance vision was tested using a Snellen chart, and near vision was tested (with reading glasses if required) using near vision charts. A polaroid iris photograph was also obtained for each test occasion. All measurements were repeated at 30, 60, 120 and 240 min after installation of the eyedrop being tested.

At the first test procedure, the eye received a standard (macro) minim drop of 1% tropicamide. (Minims are disposable single use units supplied in sterile packaging.) The average volume of this drop has been measured to be 26 μL (Gray 1991). After an interval of at least one week, the same eye was then tested in an identical manner using a small, or micro drop instead of the standard drop size. As previously described, this was achieved using a narrow bore cannula attached to the minim, and the volume of the drop administered in this way averaged 5 μL (Gray 1991).

For the purposes of analysis, Snellen vision was converted to a logmar score, and near vision measurements were assigned ordinal integral values. The polaroid photographs were used to measure horizontal pupil and corneal diameter, and the ratio of pupil to cornea diameter was calculated.

Results

Pupil size. Horizontal pupil to corneal diameter ratios were calculated for each test occasion (Fig. 1). For both drop concentrations, the ratio rose to a maximum at 30 min, and gradually reduced over the remaining 3·5 h. Statistical analysis confirmed there was no significant difference in pupil to cornea ratios before instillation of drops for the macro and micro conditions (paired *t*-test, $t = -1{\cdot}041$, df 19, $P = 0{\cdot}31$ two tailed). The recordings provided parametric data which was subjected to two-way repeated measures analysis of variance. The interaction between drop size and time approached but did not reach statistical significance.

Distance visual acuity. The mean logmar visual scores over 4 h for macro and micro conditions are presented in Fig. 2. Because the distribution of distance visual acuities were highly positively skewed, the Wilcoxon test was used to compare vision before drops were instilled. There was no difference between groups ($T = 0$, $P = 1{\cdot}0$).

The differences between visual acuities in the two conditions for each subject were normally distributed. These differences were analysed by one-way repeated measures analysis of variance. There was a significant main effect of time ($F = 4.66$, df = 4,76, $P = 0{\cdot}002$). For this analysis, differences between

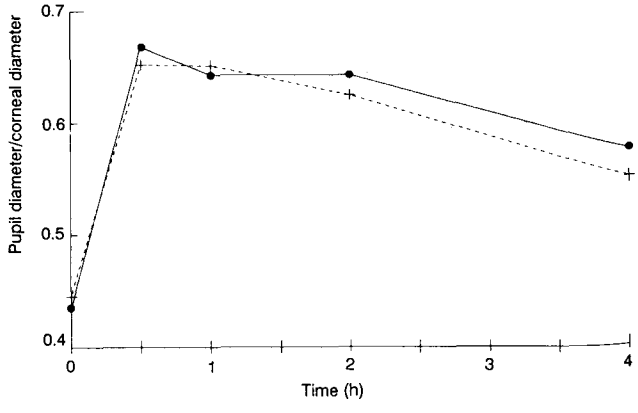

FIG. 1. Change in relative pupil size with time. ● = macro drop, + = micro drop.

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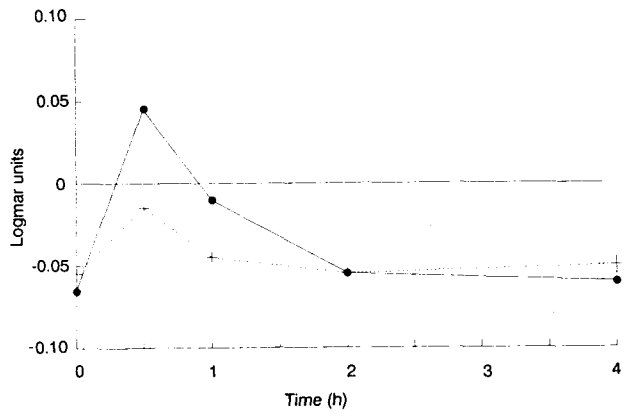

FIG. 2. Change in distance vision with time. ● = macro drop, + = micro drop.

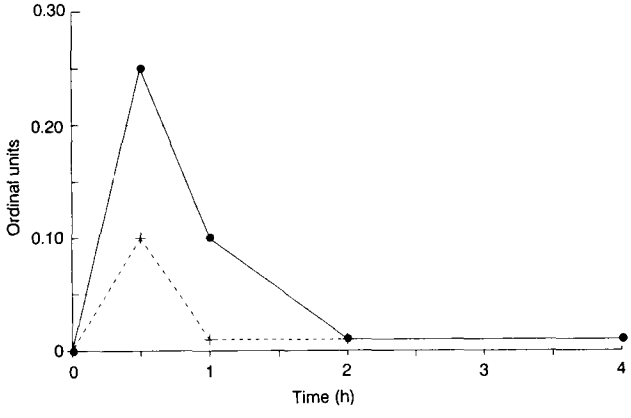

FIG. 3. Change in near vision with time. ● = macro drop, + = micro drop.

means were taken for each test interval, so the finding of significance is equivalent to the interaction of drop size and time in the preceding two-way analysis.

Newman-Keuls post hoc tests showed that the difference in visual acuities between macro and micro conditions was significantly greater after 30 min (vision worse with macro drop) than at the start or after 2 or 4 h ($P < 0.05$).

Near visual acuity. Near visual acuities were assigned ordinal values and medians were calculated and displayed graphically (Fig. 3). Wilcoxon analysis showed no significant starting difference for near visual acuities between the two conditions (median = 0, T = 1, $P = 1$).

Nonparametric Friedmann analysis of variance on the differences in near vision between conditions showed a significant main effect over time, indicating that near vision was better maintained in the micro drop test condition ($\chi^2 = 20.03$, df = 4, $P < 0.001$).

Discussion

The mydriatic response to macro and micro drops in the twenty volunteers was equal. This had been expected, and the result underlines the results of other studies showing that drug quantities of 1% tropicamide well below those currently employed are sufficient for clinical purposes (Brown & Hanna 1978; Brown et al 1987; Lynch et al 1987; Bacon et al 1989).

The rate at which pupil size returned to normal over the 4 h test period was also very similar. This suggests that the receptor sites in the sphincter pupillae are fully blocked in both cases, and excess drug at the time of administration does not appear to cause these sites to be occupied for longer.

The significant difference in recovery of distance vision with micro drops must be explained on the basis of the action of tropicamide on the ciliary muscle. The distance vision of most volunteers did not change, indicating that they did not require any ciliary muscle activity to see clearly, but for three volunteers there was a significant change, indicating that they needed ciliary muscle activity when looking in the distance (i.e. they were hypermetropic). These three volunteers were also below 30 years of age, and were able to mask their hypermetropia by ciliary muscle activity until the tropicamide was instilled. This is not possible for older people, whose hypermetropia requires spectacle correction because of a decline in ciliary muscle power.

It is known that ciliary muscle paralysis with tropicamide is partial, and recovery is quicker than for pupil dilatation (Gettes 1961). It is likely that even with a macro drop of 1% tropicamide the ciliary muscle parasympathetic receptor sites are not fully occupied, and when smaller quantities of drug are used, proportionately fewer sites are occupied. This would account for the better preservation of distance vision when micro drops are used.

Near vision also deteriorated less with micro drops, and recovered more quickly. Near vision is well known to suffer more than distance vision when the ciliary muscle is paralysed, because of the increased activity of this muscle during close up vision. The results again reflect the reduced cycloplegia with smaller drop size.

Reduced focusing capability is not the only cause of visual difficulty when dilating eye drops are used. The dilated pupil can cause dazzling (or glare) in some patients, and this tends to be worse in bright sunlight and may incapacitate the patient even though the vision is not blurred. Glare is notoriously difficult to measure, and it was not analysed in this study. However, the efficacy of small drops of 1% tropicamide with regard to pupil size suggests that glare would be the same whether or not small drops were used.

Pupil dilatation is an important part of a thorough eye examination, but is sometimes neglected because of concern about the patient's ability to see well enough afterwards to drive home or return to work. Micro drops shorten the duration of blurred vision in our group of healthy volunteers, and development of a practical micro drop dispensing system would be likely to benefit many patients.

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J. Pharm. Pharmacol. 1992, 44: 684–686
Communicated December 5th 1991

Comparison of salivary fluoride concentrations after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet

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Abstract—The in-vitro and in-vivo fluoride release of bioadhesive, slow-release tablets prepared from a mixture of polyethylene glycol polymers, containing 0·1 mg of fluoride as NaF was studied, and their ability to sustain fluoride levels in saliva were compared with conventional fluoride tablets with the same fluoride content. In-vitro release experiments showed that the bioadhesive tablets needed 8 h to release all their fluoride compared with < 1 h for the conventional fluoride tablets. In-vivo, the bioadhesive tablets had a retention period of 6 h and could sustain a salivary fluoride level of more than 10 μM above the baseline for 7 h. The conventional fluoride tablets achieved a peak concentration of 0·5 mM directly after dissolution in the mouth, but the fluoride level could not be sustained for longer than 1 h. A good agreement was found between the in-vitro swelling behaviour of the bioadhesive tablets and their in-vitro and in-vivo release characteristics and their in-vivo retention time.

Small concentrations of fluoride, if present in the oral fluids for sufficiently long periods of time, are effective in the prevention of dental caries (Margolis et al 1986). However, topical administration of fluoride in toothpastes, mouthrinses and gels, fails to sustain sufficient fluoride levels over long periods, despite the administration of high doses (Bruun et al 1982).

Recently, we reported sustained fluoride levels in saliva following oral administration of bioadhesive fluoride-containing slow-release tablets (Bottenberg et al 1991). These tablets were able to sustain fluoride levels in saliva for about 6 h with a dose of only 0·1 mg of fluoride.

In this study, another bioadhesive tablet formulation, prepared with a composition of two different mol. wt polyethylene glycol (PEG) polymers, was compared in-vitro and in-vivo with a conventional fluoride tablet. This tablet was either dissolved in the mouth (mixed topical/systemic administration) or swallowed (systemic administration).

Materials and methods

The slow-release tablet (PEG750C) was prepared from a mixture of two different mol. wts of polyethylene glycols (PEG, Polyox, Amerchol, Vilvoorde, Belgium): 95% Polyox WSR-N-750 (mol. wt 300 000 Da) and 5% Polyox Coagulant (mol. wt 5 000 000 Da). The conventional fluoride tablet was prepared using Avicel PH102 (FMC, Philadelphia, PA, USA). Both types of tablets contained 0·1 mg of fluoride as NaF (Merck, Darmstadt, Germany). Before compression the powder was mixed for 5 min (Turbula TA2 mixer, Bachofen AG, Switzerland) and compressed on an eccentric tablet press equipped with flat punches (diam. 7 mm, EKO, Korsch, Frankfurt/Main, Germany). The fluoride content of the tablets was analysed before the dissolution experiments with 6 tablets of each type. The swelling rate of the bioadhesive tablets in water was measured by immersing 6 tablets, each in a preweighed stainless steel basket, in 4 mL of deionized water. The weight of the tablets was determined every hour until no further weight change was observed. The relative weight gain (swollen weight/initial weight) was calculated.

In-vitro fluoride release. The kinetics of fluoride release were determined using a dissolution apparatus as described previously (Bottenberg et al 1991). With bioadhesive tablets, samples of 200 μL were taken every 30 min for 4 h and then every hour until 8 h. The fluoride release from the conventional fluoride tablets was determined using the same technique but as a faster release was expected, samples were taken every 5 min for 30 min and then after 1 h. Fluoride activity was determined with an ion-selective electrode (Orion 96-04, Orion Research, Boston, MA, USA).

In-vivo fluoride release. The experiment was performed essentially as described in our previous paper (Bottenberg et al 1991). Fourteen healthy volunteers, 7 male, 7 female, ranging from 20 to 22 years, participated in this study. Informed consent from the volunteers and permission from the Medical Ethics Committee of the Medical Faculty, Free University of Brussels were obtained. The experimental design included the determination of salivary flow rate before the release experiment, and a low fluoride intake the day before the trial. Every volunteer received one bioadhesive slow-release tablet and one conventional fluoride tablet in separate experiments, performed with an interval of 4 weeks. The conventional fluoride tablet was given to two groups of seven volunteers each. In one group, a purely systemic administration was obtained by swallowing the tablet with 20 mL of deionized water. The other group of volunteers was asked to suck the tablet until complete dissolution in the mouth in order to obtain a mixed topical and systemic administration. The bioadhesive slow-release tablet was applied to the attached gingiva in the region of the upper canine and held there for about 30 s with a slight pressure. Then the tablet and the upper lip were moistened with saliva to prevent sticking of the tablet to the lip. The volunteers were asked to note the retention time of the tablet and remark about the degree of irritation or discomfort.

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