Eyedrop instillation for reluctant children

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Abstract

Pupillary responses to pilocarpine eyedrops applied by different techniques have been studied in healthy volunteer subjects. In particular a novel method was evaluated in which eyedrops were applied to the inner canthus with eyes tightly closed and the subject supine, followed immediately by opening of the eyes. The response to this technique indicates that drug penetration into the eye was 66% (confidence intervals 28 to 104%) of that obtained by conventional instillation, into the conjunctival sac, with or without 2 min pressure on the inner canthus. This method of instillation, which is free of aggravation, may be clinically useful for patients, especially children, unwilling or unable to tolerate conventional instillation.

It is everyone's experience that some children are resolute in their refusal to submit to instillation of eyedrops. Overcoming this resolve is traumatic for the patient, parents, nursing staff, and ophthalmologist alike. The author's personal experience as an affected parent led to the present experiments, designed to explore the efficacy of a less traumatic mode of instillation suitable for use in children.

The method involves placing eyedrops on the inner canthus with the subject lying supine and with eyes tightly closed. Once the eyedrops are in place the subject is instructed to open his or her eyes, allowing the eyedrops to enter the eye.

The investigation reported here was designed to measure the efficacy of this method by comparison with conventional modes of administration. Pilocarpine was used as marker and its miotic effect as a measure of its penetration into the eye. The observations were made on young healthy adults, because such experiments on children are considered unethical.

Subjects and methods

Ten healthy subjects (6M, 4F) aged 20 to 33 years took part in the study. Each attended on four occasions at least three days apart and received a single eyedrop (0.037 ml) of pilocarpine nitrate in one eye by each of the following methods in balanced order:

- pilocarpine 0.25% with pressure on the inner canthus;
- pilocarpine 0.5% with pressure on the inner canthus;
- pilocarpine 0.5% without pressure;
- pilocarpine 0.5% to inner canthus with eyes closed.

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Accepted for publication
3 January 1991

Miotic response (mean (SEM)) to pilocarpine following different methods and doses of administration. A: 0.25% with pressure on the inner canthus. B: 0.5% with similar pressure. C: 0.5% without pressure. D: 0.5% with eyes closed.

All eyedrops were made up by dilution of pilocarpine 2% Minims in phosphate buffer pH 7.0. With all but the last method the eyedrops were placed in the conjunctival sac. In the first two methods digital pressure on the inner canthus was maintained for 2 min.

Measurements of darkness pupil diameters of both eyes were made by infrared TV pupillography¹ before and at 15 and 30 min and 1, 2, 4, and 8 h after drug instillation. The miotic response was defined as the difference in pupil diameter between treated and untreated eyes, corrected for any diameter difference before treatment, and expressed both as peak values and as areas under the response curves. The relative efficacy of the different modes of administration was assessed by reference to the dose response relationship found with pressure on the inner canthus as previously reported.²

Each subject gave written consent to participation, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

Results

The time courses of miotic responses to the four treatments are shown in the figure, the peak and area under the response curves (AUC) in the Table. With digital pressure on the inner canthus significantly larger peak and AUC responses were obtained with 0.5% than with 0.25% pilocarpine ($p=0.029$ and 0.010 respectively from paired t tests). Without such pressure pilocarpine 0.5% responses did not differ significantly from those obtained with pressure, and the overall mean comparative bioavailability was 94.1% on peak response and 88.8% on AUC.

Instillation of the same dose to the inner canthus with eyes closed produced responses intermediate between those obtained with 0.25% and 0.5% with pressure on the inner canthus but not differing significantly from either. The overall mean bioavailability was 64% on peak response and 62.5% on AUC. The times to peak response (30 min to 1 h) were identical.

Peak responses and areas under the response curves (AUC) (mean (SEM)) to pilocarpine by different methods and dose of application. Pressure=2 min pressure applied to the inner canthus

Method	Concentration	Peak Response (mm)	AUC (mm h)
A With pressure	0.25%	2.32 (0.41)	6.46 (1.73)
B With pressure	0.5%	3.47 (0.53)	12.30 (2.01)
C Without pressure	0.5%	3.37 (0.48)	11.31 (1.30)
D Eyes closed	0.5%	2.73 (0.53)	8.70 (1.92)

Estimation of the confidence intervals for bioavailability was based on measurements in seven of the 10 subjects in whom clear dose response relationships could be established. These limits, based on peak responses, were 25–117% (conjunctival sac) and 28–104% (inner canthus).

Discussion

This study shows clearly that drug solution placed on the inner canthus with the eye closed subsequently penetrates the eye, albeit to a somewhat lesser extent than by the conventional mode of instillation into the conjunctival sac. The slight reduction was to be expected because the technique places the eyedrop close to the puncta, patency or occlusion of which is well-known to influence drug penetration.^{3,4} Nevertheless sufficient bioavailability exists to suggest that this method of giving eyedrops should be effective clinically. Casual observations by the author and two colleagues indicate that its use on patients unwilling or unable to submit to conventional instillation is devoid of aggravation.

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- 3 Fraunfelder FT. Extraocular fluid dynamics: how best to apply topical ocular medication. *Trans Am Ophthalmol Soc* 1976; 74: 457–87.
- 4 Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP. Improving the therapeutic index of topically applied ocular drugs. *Arch Ophthalmol* 1984; 102: 551–3.