Optometry 699
Special Studies

Intraocular Bioavailability:
A Preliminary Evaluation of an Eyedrop Instillation Technique

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Abstract

A method of instilling eyedrops, the contact pool (CP) technique, was developed in pursuit of a means for enhancing the intraocular bioavailability of topically-applied medications. The topic of this paper is a pilot study evaluating the mydriatic efficacy of the CP and two other common techniques following the instillation of tropicamide. The CP technique resulted in the greatest mean increase in pupil diameter. The validity of the differences between the means of all three techniques was confirmed by the F-test; however, a small sample size strongly limits its overall significance. An expanded study in the future may provide more definitive conclusions.

Key Words

Intraocular bioavailability, contact pool, systemic adverse effects, drop instillation technique

Introduction

Clinicians are responsible for not only determining correct diagnoses and appropriate treatment regimens, but also for educating their patients as to the proper means of administering medications. In all health care fields, a significant impact can be made upon clinical efficacy, patient safety, and cost containment through proper patient education of medication administration techniques and through patient compliance. Eye care is no exception. And there exists a need for the development of new techniques which are simple to perform and which further enhance the therapeutic index of prescribed topical ophthalmic pharmaceuticals.

The intraocular bioavailability of administered ophthalmic medications is relevant to the therapeutic management of certain conditions, such as glaucoma. It has been shown that a trans-corneal route is responsible for the majority of intraocular absorption of most topically-applied medications[1]. Emphasis has been placed upon increasing corneal contact time in order to increase absorption[2]. It would also seem apparent that providing a means for the full dose, i.e. the entire drop of solution, to

remain in apposition to the cornea would optimize the transfer of the medication to the intraocular tissues. There have been a number of reports which discuss the nearly immediate loss of the majority of medication upon eyedrop instillation when using conventional eyedroppers and techniques[3,4,5,6].

While in pursuit of greater intraocular bioavailability, the potential for systemic adverse effects through topical instillation must be considered. The nasopharyngeal mucosa is reported to be the major site of systemic absorption[7] and mechanical techniques to minimize this uptake have been recommended[8].

The instillation techniques currently in practice by patients who must administer topical medications is quite varied. The final or, at times, the evolving technique adopted by patients is a reflection of whether or not they received instillation education and/or training and their comprehension of such. Furthermore, physical limitations can influence one's capacity to adequately instill drops.

In pursuit of a relatively simple method of applying drops by which intraocular bioavailability could be increased and nasopharyngeal mucosal absorption could be decreased, an instillation technique was developed. A pilot study, the topic of this paper, was designed and run to gain an initial impression about the efficacy of this technique as compared to two other commonly utilized methods of instillation. Other objectives were to determine the practical feasibility of this technique and to provide the background for more comprehensive studies on the efficacy and safety of this technique.

Methods

The three instillation techniques which were employed in the study are described in the following paragraphs.

The blink-dab (BD) technique simulates what one of the author's (TIM) has noted as a common method employed by patients with a previous history of topical ophthalmic medication usage prior to seeking the author's care. This technique involves having the drop instilled directly onto the cornea followed by the subject rapidly blinking the eyelids 5 times and then dabbing the closed eye once

with a tissue. The same blinking and dabbing is immediately repeated twice and then normal blinking ensues.

The naso-lacrimal occlusion (NLO) technique is commonly recommended to increase intraocular absorption and decrease systemic uptake. Described in detail elsewhere[9], the technique employs drop instillation into the inferior cul-de-sac followed by 5 minutes of eyelid closure combined with digital pressure to the lacrimal sac.

Seeking a method of instillation which would be relatively simple to perform, provide adequate corneal contact time, and would minimize nasolacrimal absorption, one of the authors (TIM) developed the contact pool (CP) technique. The initial steps of this technique require the subject to slightly tilt his head back (approximately 30 degrees) and pull his inferior lid downward enough to create a small pouch. Next, the subject is instructed to direct fixation upward while one drop of solution is instilled into the pouch. While still holding the lid and maintaining the pouch, the subject rotates his eye downward bringing the cornea in contact with the small pool of tears and solution. Informed of an adequate infraversion by the drop administrator, the subject notes his present point of fixation. This point of fixation and head tilt are maintained for 5 minutes. Reflex blinking is permitted since it does not appear to disrupt the pool.

Tropicamide was chosen as the agent to test the intraocular effectiveness of the three techniques. It is relatively innocuous and it's mydriatic effect can be readily and reliably measured. The authors served as the two subjects for this pilot study. Dose-response curves for tropicamide-induced mydriasis were obtained for each subject in order to determine the dose which would produce at least some, but not maximal, mydriasis. It was felt that such a dose would most accurately demonstrate the differences in pupillary responses from the three instillation techniques by mitigating the likelihood that each subjects' physiological limitations in the degree of response to the drug would be reached and would mask differences in technique effectivity. To determine these dose-response curves of the subjects, tropicamide concentrations of 0.50%, 0.25%, 0.13%, 0.06%, and 0.03% were instilled on successive days and pupillary mydriasis from a baseline was measured over time each day under the same lighting and fixation conditions. The technique of instillation employed for these dose-response curves was that of instilling the drop directly onto the cornea

immediately followed by gentle eyelid closure for 5 minutes. For both subjects, 0.06% was found to be the optimal concentration.

The subjects waited at least 24 hours between each individual instillation. One fourth-year optometry student independently determined the random order for three single-drop administrations utilizing each of the three techniques for a total of nine separate instillations for each subject, and also served to instill all applications of drops. The authors measured pupil size on one another and were masked as to which technique was utilized. A Ciba Vision ultra light ruler with solid semi-circles representing pupil diameter gradations was employed for measuring the degree of mydriasis to the nearest 0.50mm. The pupils were always measured in the same room under the same conditions: illumination, head posture, and fixation. The left eye was used throughout the study as a control for possible systemic effects from the tropicamide or other possible exogenous or endogenous factors which could influence the tonic pupillary state. The subjects' state of mydriasis was measured 20 minutes after instillation of the drops and then every 10 minutes up to 40 minutes after instillation. At that point or thereafter the trial was concluded when successive measurements were equal or a decrease was noted. The subjects' activities between measurements were typical for clinical duties such a examining patients, computer tasks, and reading.

Mean maximum findings were analyzed utilizing the F-test with post-HOC differentiation.

Results

The largest increase in pupillary diameter, accordingly adjusted for the few occasions where a slight fluctuation occurred in the control eye, was recorded for each of the 18 trials. The means of these maximums were 0.67mm (SD=0.61) for the NLO, 1.33mm (SD=0.61) for BD, and 2.33mm (SD=0.61) for CP (Graph #1 and Table #1). Statistical analysis demonstrates that each of these three means independently differ significantly from the other two ($p=0.05$).

Discussion

A significant difference between the means of all three techniques

is grossly evident since all differ from each other by an amount greater than the 0.50mm sensitivity of measurement. The validity of these differences was confirmed by the F-test, however, the small sample size still strongly limits its overall significance. Nevertheless, these results do point to the CP technique or a modification thereof being a potentially effective method which deserves further, and more conclusive study.

For the subjects, both involved in eye care delivery, performing the CP procedure was not difficult with the exception of maintaining fixation. This difficulty may be overcome by providing a more dynamic target, e.g. television. To the general patient population, many of whom have medical ailments with concomitant physical limitations, the CP task may prove more difficult. Whereas, the subjects had a third party to instill the drops, such an option, e.g. spouse, can be recommended to some patients. In any event, instillation should typically prove no more difficult than commonly-practiced methods. Many patients detect the successful instillation of a drop by sensing a change in temperature or a feeling of discomfort after administering the drop directly onto the cornea. The CP technique could be modified to permit this type of direct instillation onto the cornea without affecting the 'pool' aspect of the method.

In addition to obtaining a larger sample size, there are other aspects of this study which could be modified to provide a more comprehensive evaluation. If mydriasis is again to be evaluated, a more accurate measurement device such as an infrared pupillometer could be employed. Consideration could be given to studying intraocular bioavailability through the utilization of other agents. Florophotometry has been used to study the amount of fluorescein in the anterior chamber following topical administration[10,11,12].

Systemic spillover is a concern with respect to all methods of administering drops, especially in light of the common use of topical adrenergic beta-blockers. It is hypothesized that the CP technique, by maintaining a drug/tear 'pool' level below the inferior punctum, would allow for greater intraocular absorption and, hence, for less absorption through the nasolacrimal system. Contradictory to this, the CP technique may not lessen and may in fact increase the systemic absorption by possibly providing a mechanism for greater conjunctival absorption. Further study, such

as a radioimmunoassay of blood plasma following topical instillation of timolol as has previously been done[13], should be completed to determine the systemic implications of the CP technique.

The intraocular bioavailability of topical medications is pertinent to a number of ophthalmic treatment regimens. Often, as in most cases of glaucoma, the treatment is for an aged individual who also suffers from a variety of conditions such as cardiovascular and bronchial disease. Such an individual may have motor and cognitive dysfunction and have limited income which must often be dedicated to funding other medical treatment regimens. The need, therefore, continues for medically and cost-effective treatment modalities which are simple to perform and are relatively safe. The CP technique of instillation could possibly improve eyedrop utilization and warrants further study.

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Notification

In its current form, this document is being submitted only for the purpose of satisfying William R. Harmon's Optometry 699, Special Studies requirement. As agreed upon by both authors prior to the inception of this study, Timothy I. Messer, O.D., reserves the right to solely modify this document and submit for publication as he desires.

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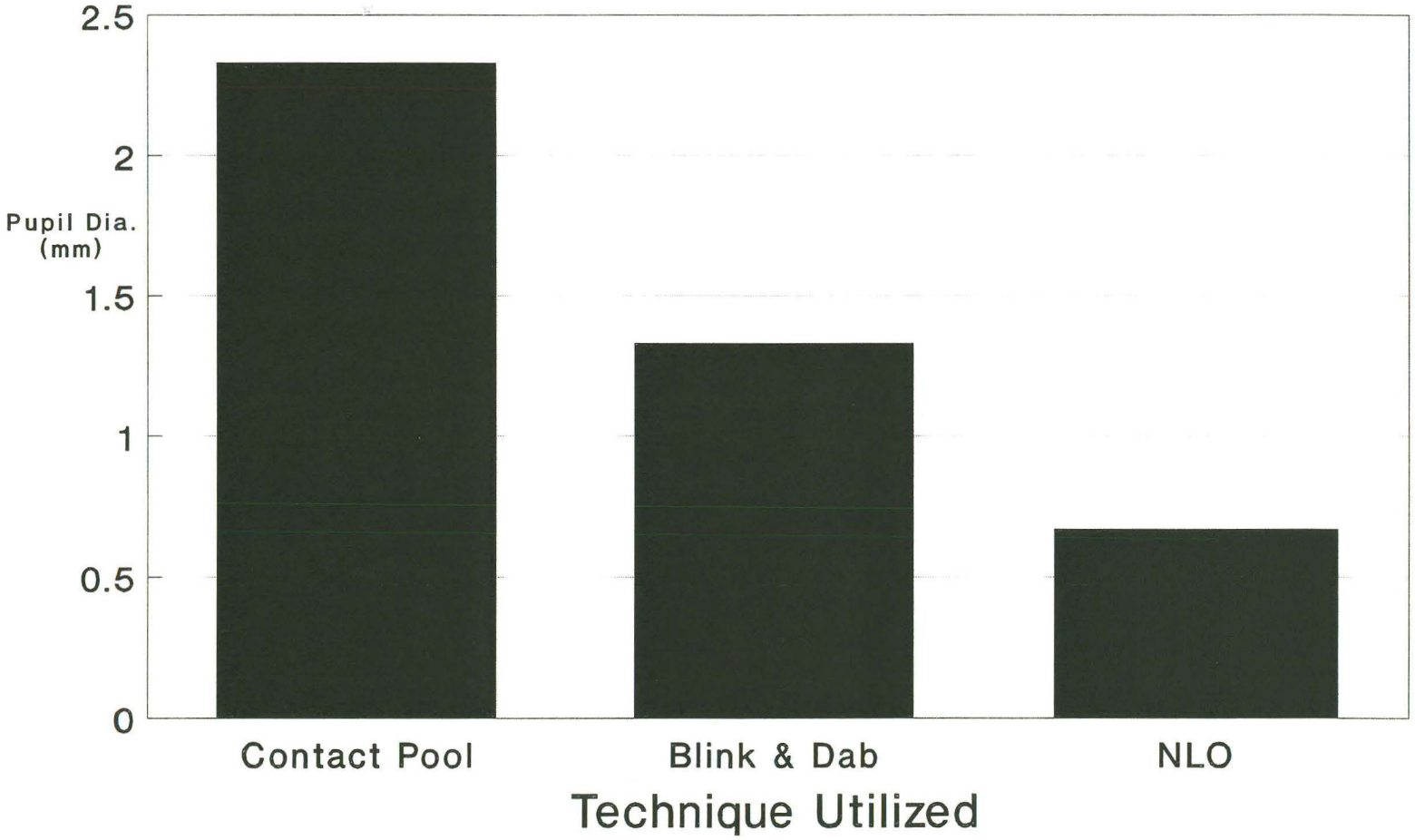
Maximum Mean Increase In Pupil Diameter

Technique	Mean	Standard Deviation
Contact Pool	2.33mm	(0.61)
Blink & Dab	1.33mm	(0.61)
NLO	0.67mm	(0.61)

Table #1

Maximum Mean Change In Pupil Diameter



Graph #1