Evaluation of Potentiating Effect of a Drop of Lignocaine on Tropicamide-Induced Mydriasis

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PURPOSE. To analyze whether preinstillation of lignocaine potentiates mydriasis by tropicamide in dark eyes and to determine possible mechanisms for this effect.

METHODS. This investigation was conducted in two phases, the first being a double-masked, placebo-controlled, randomized clinical trial, enrolling 60 healthy dark brown eyes in 30 subjects aged 7 to 58 years. The control eye received a drop of (nonlignocaine) placebo before tropicamide 1%, and the contralateral study eye received a 4% lignocaine drop 3-minutes before the 1 drop of tropicamide was administered. A ruled pupillometer recorded pupil diameters every 10 minutes for 50 minutes. In phase II, to elucidate pathomechanisms after lignocaine, corneal and tear parameters were compared with baseline records in a further 60 such eyes.

RESULTS. Pupillary diameters in the study eyes increased by 3.62 ± 0.75 mm, significantly more than in the placebo (control) group (P = 0.000). Ninety percent of study eyes attained the clinically significant 6-mm size with preinstillation of lignocaine—many more than the 67% of control eyes (P = 0.016). The median time to achieve this critical 6-mm size was significantly faster in the study group (P = 0.005). In phase II, the 1 drop 4% lignocaine did not show corneal changes with slit lamp or fluorescein staining and did not reduce media clarity or induce a significant change in tear pH. It markedly decreased Schirmer values (P = 0.000), reduced tear break-up time (P = 0.005), and increased corneal thickness measured by optical pachymetry (P = 0.010).

CONCLUSIONS. The phase II findings indicate corneal microepithelial damage and reduced tearing. Both may enhance intraocular penetration and hence potentiation of tropicamide. This remarkable phenomenon could find use with many other important topical medications. (Invest Ophthalmol Vis Sci. 2001; 42:1581-1585)

Dilatation of pupils is a desirable accompaniment to routine eye examinations, especially to facilitate the evaluation of ocular fundi, even for primary care practitioners. It is inescapable today in many intraocular surgeries, such as cataract, and in specialized outpatient procedures, such as laser treatments. Rapid yet adequate dilatation has always remained a problem, especially in dark-colored eyes. More than one theory has been put forward to account for this. These darker eyes may require much more mydriatic drops and time to achieve adequate dilatation, thus also increasing chances of local and systemic side effects.

India’s population consists almost solely of dark brown eyes equivalent to grade 4 and 5 of an iris color classification scheme,13 in which 5 is the darkest. A chance observation by two of the authors (SG, HK) that when a drop of mydriatic solution was put in an eye that had received topical 4% lignocaine (a local anesthetic of the amide group), earlier or soon after, the pupil dilated better and also faster, even in young children and infants. Use of proparacaine before instillation of mydriatics has been commented on earlier. Various topical anesthetics—0.5% proparacaine, 0.4% benoxinate (oxybuprocaine), and tetracaine 0.5% (all of the ester group)—when compared for their potentiating effects, were found to almost equally enhance the efficacy of phenylephrine. Another study on irides of all colors used different combinations of phenylephrine along with tropicamide or cyclopentolate. When a drop of 0.5% proparacaine was used 1 minute before these mydriatic combinations, dilatations were better. Using such combinations, however, makes it impossible to know whether proparacaine enhances the mydriatic effect of the sympathomimetic agent, the parasympatholytic agent, or both.

Tropicamide has enjoyed worldwide popularity as a powerful and rapid mydriatic drug for almost 40 years, mainly because of its suitable duration of action and minimal side effects. However, there have been only two studies in this context for potentiation of tropicamide alone, but with somewhat disparate conclusions. Mordi et al.17 stated that preinstilling 0.5% proparacaine 5 minutes before tropicamide, significantly hastens the speed of dilatation with 1% tropicamide in blue-green eyes, but not in hazel-brown eyes. This pretreatment also affects the extent of dilatation, but a complete statistical analysis for this was not made available.

On the contrary, Siderov et al.18 reported that the speed of dilatation was not changed in either light or dark irides by prior use of proparacaine. In their study, instillation of 0.5% proparacaine followed by 0.5% tropicamide (at an unspecified time interval) produced a statistically significant increase in pupil size in light-colored irides, but not enough in the dark-colored ones.

The potentiation of tropicamide induced mydriasis by preinstillation of topical anesthetics would be obviously important, especially in dark irides, for both speed and extent of dilatation. Studies so far in darker eyes have expressed doubts about this potentiation; therefore, the present evaluation was undertaken with 1% tropicamide in our dark brown eyes, using 4% lignocaine as the topical anesthetic. As a topical instillation, lignocaine (lidocaine, Xylocaine; Astra IDL, Bangalore, India) is very effective with a proven track record and wider safety margin. In our part of the world, as in many other countries, lignocaine remains the most popular topical anesthetic, although its efficacy as a potentiator has, to the best of our knowledge, never been evaluated earlier, or the mechanism for this potentiation elucidated.

METHODS
This clinical investigation in healthy dark brown eyes followed the tenets of the Declaration of Helsinki, with due approval from our

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institutional ethics committee. After informed consent, each subject during enrollment underwent a workup including history, general physical examination, corrected visual acuity, slit lamp biomicroscopy for corneal and pupil examination and determining anterior chamber depth by the Van Herick method, direct ophthalmoscopy with undilated pupil, and digital tension.

Subjects with any abnormality of pupils or anterior chamber, glaucoma, uveitis, trauma, or previous ocular surgery; corneal changes, contact lens wear, dry eyes, epiphora, known allergy to any of the drugs used, concurrent medications within past 2 weeks; or systemic diseases such as diabetes mellitus, hypertension, arthritis, and thyroid disease were excluded.

A brief, placebo-controlled evaluation at the outset confirmed that 4% lignocaine drops alone did not dilate the pupils at all. The present investigation itself was divided into two phases to separate the clinical effect study group from the pathomechanism group. The former was to confirm whether topical lignocaine potentiates the mydriatic action of tropicamide in dark eyes, the latter to explore the possible reasons for this interesting and useful phenomenon.

**Phase I**

A total of 60 dark brown eyes of 30 healthy subjects between 5 and 60 years of age were enrolled in this double-masked, placebo-controlled, randomized clinical investigation. Two drug conditions were used: in the control subjects, 1 drop of placebo was followed 3 minutes later by 1 drop of 1% tropicamide, whereas in the study group, 1 drop of 4% lignocaine was followed by 1 drop of 1% tropicamide at the same time interval of 3 minutes. With an expected mean dilatation of 3.0 mm with 1% tropicamide in our control dark brown eyes and assuming the common SD under both control and study conditions to be 0.5 mm, it was worked out that a study of 25 eyes in each group would have 90% power to detect a difference of 0.5 mm between mean pupil dilatations in the control and study groups, with a 0.05 two-sided significance level. Thus, a sample size of 30 eyes was studied in each group.

None of the drops used contained the preservative benzalkonium chloride, which is known to affect corneal epithelial integrity.\(^{22-24}\) commercially available 1% tropicamide drops (Tropicacyl; Sunways India Pvt. Ltd., Mumbai, India, containing chlorobutanol 0.5% as a preservative) were used for both the control and study conditions. Lignocaine hydrochloride was obtained as 4% Xylocaine (Astra IDL; colorless eye drops containing 1 mg/ml methylparaben as preservative) and transferred into fresh, clean, sterile vials in the pharmacy of our eye center. For the (nonlignocaine) placebo, vehicle for Xylocaine (i.e., water for injection along with 1 mg/ml methylparaben) was freshly prepared in our pharmacy and poured into identical vials. The fresh sterile eyedroppers used were selected to deliver a standardized uniform drop size of 40 to 50 μl. Both the lignocaine- and placebo-filled vials were coded A or B for the double-masked phase I study.

After the baseline measurements of both pupils were recorded, one eye of each subject received a drop of coded 4% lignocaine (A or B), and the other eye acted as a control and received a drop of coded placebo (B or A). Whether the left or right eye received drop A or B was decided randomly; and the contralateral eye received the other. Three minutes later, a drop of 1% tropicamide was instilled in both of the eyes. Drops were instilled in a standardized manner\(^{25}\) into the inferior cul-de-sac of each eye. The subject was then asked to close the eyes gently and not to blink or squeeze the eyelids for 1 minute, if possible. Care was also taken to ensure that only a single bubble-free drop was instilled and the dropper tip did not touch the subject’s eye, to avoid contamination.

The horizontal pupil diameter was subsequently measured at 10-minute intervals for 50 minutes after instillation of tropicamide. Measuring in the dark (as with infrared) cannot simulate the clinical environs and illuminations of ophthalmoscopy, especially before and during the initial dilatation stages, when a relatively larger pupil size in darkness would give misleading conclusions. Therefore, to measure pupil size, a simple, convenient, ruled pupillometer\(^{14}\) was used in similar dimly lit surroundings, with standardized, reproducible, low, oblique illumination from a fully charged direct ophthalmoscope with its rheostat at half maximum, kept at a comfortable 0.5-m distance. This pupillometer is accurate up to 0.5 mm with a wide range of 1.5 to 8.0 mm, without requiring undue instrumentation or the patient’s cooperation. It was placed transversely at the midlevel of the pupil, as close to the eye as possible without touching it or the lashes. Pupil size was compared with the painted black semicircles of different sizes on the edge of the scale, while the subject fixated on a distant object.

For purposes of analysis (as detailed later), a pupil diameter of 6 mm was considered clinically adequate for most examinations, including indirect ophthalmoscopy.\(^{20-28}\) The number of eyes reaching 7-mm pupil diameter was also noted. The fundus was again examined at the end of the procedure with a direct, as well as indirect, ophthalmoscope, and a note made of any loss of media clarity after the study.

**Phase II**

The effects of topical lignocaine on various corneal and tear parameters were studied in a further 60 eyes of 30 subjects. Before lignocaine was instilled, the following six parameters were recorded: the first four in one eye and the last two requiring fluorescein in the other eye of the same subject, to avoid vitiating our observations and conclusions for the first four, especially when reassessing after lignocaine administration: (1) slit lamp biomicroscopic examination; (2) optical pachymetry of central cornea (using the Haag-Streit attachment I); (3) pH of tears (using a pH paper with least count of 0.5); (4) Schirmer test (without any local drop), with care not to touch the cornea; (5) tear break-up time, using a fluorescein strip in the lower fornix; and (6) fluorescein staining of corneal epithelium.

Topical anesthesia and touching the cornea were strictly avoided for any of these procedures. To study the effect of lignocaine on these parameters, the listed baseline (prelignocaine) values were compared with the same parameters reassessed after lignocaine, beginning 1 minute after the drop of lignocaine was administered. Any change in corrected visual acuity was also recorded.

**Statistical Analysis**

For both phases I and II, data were recorded on a predesigned form and the data transferred to a spreadsheet (Excel 97; Microsoft, Redmond, WA). Entries were double-checked for any possible keyboard errors. After confirming the approximate normal distribution for the quantitative variables, these were summarized by means and SDs for both groups separately.

Because for each study eye, there was a contralateral control eye from the same subject, a paired \(t\)-test was used to compare the difference in mean values of pupil dilatation in phase I. The percentage of eyes reaching 6- and 7-mm dilatation levels in the study and control groups were compared by McNemar’s test. A Kaplan-Meier survival analysis\(^{29}\) was used to study the median time taken to reach a 6-mm dilatation in both the groups. A log rank test for equality of survivor functions was used to compare the difference in these median times between the two groups. For phase II, because each parameter was recorded in the same eye before and after lignocaine, a paired \(t\)-test was used to compare the differences in mean values.

Analyses of both phase I and II were performed on computer (STATA ver. 6.0, intercooled version; STATA Corp., Houston, Texas). In this study, \(P < 0.05\) was considered to be statistically significant.

**Results**

**Phase I**

Of 60 subjects within the 5 to 60 years age limits thus evaluated in total, the 30 subjects (M:F 16:14) in phase I had a mean age of 30.0 ± 16.1 years (range, 7–58). The pupil diameters recorded over time under the two drug conditions (study and control) are depicted in Figure 1. The baseline values under

\(6\)
both conditions (Fig. 1) were naturally identical (3.13 ± 0.59 mm). The mean maximum diameter reached in the study eyes (6.75 ± 0.80 mm) was much larger than that in control eyes (6.08 ± 0.97 mm). The actual mydriatic effect of tropicamide (i.e., the final or maximal pupil diameter minus the baseline) was 3.62 ± 0.75 mm under the study conditions, compared with 2.95 ± 0.76 mm in control eyes—a highly significant increase in mydriasis of 22.7% (P = 0.000).

Of all the 60 dark brown eyes tested in phase 1, 90% of the 30 eyes under study conditions reached the clinically important dilatation level of 6 mm or more (Fig. 2), compared with only 67% of the control eyes (P = 0.016). When times taken to achieve this critical pupil size of 6 mm (Fig. 2) were compared, it took a median time of 23.3 minutes under study conditions, compared with 30.0 minutes in control subjects. This clinically invaluable saving of almost 7 minutes, and also in dark brown eyes, was again highly significant (P = 0.005). In the study group, 60% of the eyes also touched the even better dilatation level of 7 mm or more, compared with 20% only in the control group (P = 0.0005). Because this 20% was less than 50%, comparison of median times was not statistically possible.

The faster and greater dilatation finally achieved in the study eyes was clinically resistant to the bright light of an indirect ophthalmoscope and permitted a good view of the fundus, both with direct and indirect ophthalmoscopy. There was no diminution in media clarity. None of the subjects studied evidenced any local or systemic side effect due to either drug.

**Figure 1.** Time or temporal sequence of the mean pupil size (diameter) with 1 drop of 1% tropicamide after a drop of placebo (control eyes) or 4% lignocaine (study eyes) at a predetermined fixed time interval of 3 minutes. The baseline pupil diameters just before the instillation of tropicamide (time 0) under both the conditions are identical; any pupillary abnormalities including detectable anisocoria were excluded by study protocol. The pupil dilated to a greater degree in the study eyes (probabilities were not significant at 10 minutes but were highly significant thereafter at 20, 30, 40, and 50 minutes). Maximal diameter in both the groups was attained at 40 minutes, and the same size was maintained until the end of study time at 50 minutes. The slope or speed of dilatation for both the groups was maximum at 10 to 20 minutes. The difference between the two slopes was also greatest during this same period. The time taken to reach the clinically significant pupil size of 6 mm was much faster (P = 0.005) in the study group. This aspect is analyzed separately in Figure 2.

**Phase II**

The 30 subjects (male-to-female ratio, 17:13) in this phase showed a mean age of 30.7 ± 13.2 years (range, 14–58). After 1 drop of lignocaine 4%, none of the 30 eyes tested showed any positive fluorescein staining. The 30 contralateral eyes also did not show any decrease in visual acuity or ophthahalmoscopically visible diminution in media clarity, nor did they exhibit any corneal changes detectable by slit lamp biomicroscopy even with retroillumination and epithelial specular examination.

Besides these, the effect of 1 drop of 4% lignocaine on the four other parameters studied is summarized in Table 1. The mean corneal thickness increased significantly by 13 μm or 2.1% (P = 0.010). The tear pH hardly changed (P = 0.085). The mean Schirmer value decreased by 6.1 mm or 34% (P = 0.000). The mean tear break-up-time also significantly decreased by 1.7 seconds or 10.6% (P = 0.003).

**Discussion**

Various methods have been tried to achieve faster dilatation, especially in dark eyes, such as use of topical anesthetics before instilling mydriatic drops and even touching the cornea before instilling a mydriatic. Whereas actually touching the cornea is obviously a more invasive method with greater chances of complications, preinstillation of topical anesthetic seems an attractive and yet a more subtle approach, but exactly how this works is not yet established.

The second phase of the present study was therefore designed so that the possible etiopathogenetic factors could be better analyzed to confirm the proposed mechanisms of action. It must be emphasized that the corneal and tear parameters were evaluated without either touching the cornea or even instilling any anesthetic for the procedures—for example, optical pachymetry rather than ultrasonic measurements that would have naturally involved topical anaesthesia per se as well as touching the cornea. Our conventional optical pachymetry
may not be as sophisticated as the more recently described video pachymetry, but it has the advantages of being equally precise, readily available, and hence comparable.

Absence of any overt changes in visual acuity or clarity of media, supported by negative staining studies, together with our various corneal biomicroscopic observations, did not suggest any visible corneal epithelial damage in any eye after the 1 drop of 4% lignocaine. After all, 1 drop or even more of 4% lignocaine is widely used uneventfully in ophthalmology for so many procedures in everyday practice, at least in our part of the world. And yet the fact remains that just 1 drop is somehow capable of enhancing the mydriatic effect of tropicamide.

The small but significant lowering of the tear break-up-time after lignocaine, together with the slight but again significant increase of corneal thickness (Table 1), both point to subclinical microepithelial changes, and this minimal damage to the corneal epithelial barrier should allow increased transcorneal permeability of a drug, such as the tropicamide used in our study. This increase in pachymetric value has also been observed in another clinical context with proparacaine, but its significance in relation to drug penetration has not been commented on. No plasma membrane damage could be detected by electron microscopy in rabbit corneas with preservative-free tetracaine and proparacaine. Several later reports on rabbit and rat corneal epithelia, using lignocaine, proparacaine, tetracaine, and oxybuprocaine, demonstrated altered electrical resistance, as well as surface microdamage and other cytoskeletal changes, leading to loosening of tight junctions with disruption of intercellular spaces. These findings support our current clinical observations in humans. However, rabbit eyes may be more sensitive to chemical irritation than eyes of higher primates or humans.

Significant lowering of our postlignocaine Schirmer values also lends credence to the concept that topical anesthetic could diminish the amount of tearing, thus decreasing the dilution and outflow of the mydriatic instilled subsequently. Whether this decreased washout or the microepithelial damage are working together equally to increase the amount of mydriatic available at its site of action within the eye, or whether either one of these factors is contributing more, is difficult to determine conclusively at present.

Whatever it may be, with either one or both of these factors operating in tandem, this useful potentiation with a drop of lignocaine definitely works and consistently so ($P = 0.000$), even in the dark brown eyes in our population. Two prior reports on the potentiation effect of topical anesthetic on tropicamide stated that this works with the lighter colored eyes, but not with the darker ones. If this potentiation works by increasing the availability of mydriatic agent at the intraocular site of action, then this should be operative for both light- and dark-colored eyes, although perhaps to an unequal extent. The apparent disparity between our results and theirs could be ascribed to the use of different topical anesthetics, different concentrations of tropicamide, or even the ethnic variation of iris color (although our dark brown eyes were of similar grade), or, perhaps most important, because of the different time intervals between the two instillations.

The proper time interval between the topical anesthetic and the mydriatic could be very crucial. Instilling the mydriatic too soon after the anesthetic may not be desirable, because it would lead to dilution of the mydriatic by the anesthetic drop itself, which may still be present in the conjunctival sac. Moreover, it may also not allow enough time for the anesthetic to produce whatever effect is required for this potentiation. In fact, keeping too long a time interval might lead to the waning of this effect of the anesthetic and thus to a relative decrease in the potentiation. Keeping these factors in mind, an in-between time interval of 3 minutes was decided on for our present study, in contrast to an earlier study with a 5-minute time interval and another with an unspecified time interval.

Besides this predetermined time interval, the present investigation included strict selection criteria, was conducted in eyes with the almost uniform iris color of dark brown so frequently present in our population, and encompassed a wide age range. The extremes of age (<5 and >60 years) were not included in the study because of known variations in both pupil size and dilatability in such eyes. The fellow eyes of the subjects were used as the control, thus eliminating any other confounding factors such as age, sex, systemic diseases, and individual variation as far as possible. Double masking and also randomizing the eye obviated all possible bias for clinical observations and statistical analyses.

With this carefully designed protocol, a significantly greater number of eyes reached the 6- and 7-mm dilatation levels with potentiation and did so much faster ($P = 0.005$). Several studies have taken 6 mm as the clinically effective diameter for routine ophthalmic examination, including indirect ophthalmoscopy. Earlier workers seem to have overlooked the tremendous clinical potential of more rapidly achieving this 6 mm. Rapidity of dilatation is of the greatest value in saving valuable ophthalmic examination time for both patient and physician in a busy clinical schedule.

The mydriatic response in clinically difficult eyes with, for example, uveitis, synchiae, or pupillary abnormality, is likely to be different from healthy eyes as in our study, and many may require additional drops of tropicamide or a sympathomimetic such as phenylephrine. Enhancement by preinstillation of lignocaine should work and may be even more vital in these difficult eyes for reducing the amount of mydriatic required.

Because lignocaine appears to increase the intraocular penetration and hence the bioavailability of topically applied drugs, it seems logical that it should also potentiate the action of other topical drugs of different pharmacologic classes and actions, such as antimicrobials, anti-inflammatory agents, antiglaucoma drugs, and other cycloplegic agents. However, as-

### Table 1. Effect of a Drop of 4% Lignocaine on Various Tear and Corneal Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Values before 4% Lignocaine</th>
<th>Values after 4% Lignocaine</th>
<th>Change in Values</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal thickness ($\mu m$; $n = 30$)</td>
<td>622 ± 53</td>
<td>645 ± 52</td>
<td>+13</td>
<td>0.010</td>
</tr>
<tr>
<td>pH of tears ($n = 30$)</td>
<td>7.55 ± 0.20</td>
<td>7.50 ± 0.23</td>
<td>−0.05</td>
<td>0.083(NS)</td>
</tr>
<tr>
<td>Schirmer (mm; $n = 30$)</td>
<td>18.0 ± 5.96</td>
<td>11.9 ± 4.56</td>
<td>−6.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Tear break-up time (sec; $n = 30$)</td>
<td>16.1 ± 6.83</td>
<td>14.4 ± 6.65</td>
<td>−1.7</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. NS, not statistically significant.

$n = 60$ eyes. The first three procedures were performed in the same eye of 30 subjects ($n = 30$ eyes), whereas the tear break-up time was recorded in the contralateral eye of the same 30 subjects ($n = 30$ eyes).
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sessing even cycloplegia37 over different age groups, as well as the degree of potentiation in human eyes of the other drugs just mentioned, would always and by any means remain more difficult than evaluation of simple dilatation as in our study.

To conclude, whatever be the exact mechanism or mechanisms of this potentiation by lignocaine, it is undoubtedly true that being able to enhance the action of a mydriatic drug by the simple expedient of a drop of the ubiquitous lignocaine should be of tremendous advantage. To better use this potentiation clinically, further investigations are required to arrive at an optimum instillation schedule, choosing between the potentiating effects of 2% and 4% lignocaine and any additional benefit of a second drop of tropicamide, or for that matter a second drop of lignocaine.

References

1. Phillips CI. Dilate the pupil and see the fundus. BMJ. 1984;288:1779–1780.