Influence of Topical Anesthesia on Tear Dynamics and Ocular Drug Bioavailability in Albino Rabbits

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Abstract □ The bioavailability of topically applied ocular drugs is very poor, due largely to drug loss through drainage and tear turnover. The use of high viscosity solutions or solid matrixes to delay or eliminate drainage is the usual approach for decreasing drug loss but the alternative approach of chemically reducing tear turnover and/or solution drainage has not been investigated. By means of a simple isotopic dilution technique, using radioactive technetium sulfur colloid, the quantitative influence of topical anesthetics on tear production and instilled solution drainage was determined. The reduction in the rate of tear turnover and solution drainage varies for different anesthetics and is dose dependent. The implication of these results for some long accepted clinical procedures is discussed, and questions are raised regarding the present understanding of the mechanisms of tear production. Quantitation of precorneal drug loss through instilled solution drainage and tear turnover permits the establishment of a baseline for ocular drug bioavailability. Aqueous humor drug concentration *versus* time profiles of radioactive pilocarpine nitrate were obtained, both in the presence and absence of topical anesthesia. The results verify the importance of tear turnover and instilled solution drainage as a major route of drug loss in the eye. Moreover, the success of the present study in improving ocular drug bioavailability by the chemical approach of repressing solution drainage and tear turnover suggests that this approach is viable for improving drug bioavailability.

Keyphrases □ Ophthalmic drug bioavailability—effect of topical anesthetics on solution drainage and tear turnover, rabbits □ Anesthetics, topical—effect on tear production and solution drainage, ophthalmic drug bioavailability evaluated, rabbits □ Tear dynamics and ophthalmic drug bioavailability—effect of topical anesthetics, rabbits □ Bioavailability, ophthalmic—effect of topical anesthetics on solution drainage and tear turnover, rabbits

Ophthalmic drug bioavailability is generally conceded to be very poor from topically applied solutions. For most drugs, less than 1% of an instilled dose crosses the cornea to the anterior chamber. Several routes of loss account for this poor drug availability, but the two major mechanisms appear to be drainage loss of an instilled solution and the continuous replenishment of tears, *i.e.*, tear turnover. A recent publication from this laboratory (1) considered the influence of solution drainage and tear turnover on drug bioavailability and reported rate constants for drainage and tear turnover, but a quantitative model of drug availability was not developed. Clearly, to maximize drug activity through improved availability in the eye, a complete mechanistic understanding of drug movement and loss is needed.

Any attempt to minimize drug loss by controlling instilled solution drainage and/or tear turnover should prove useful in improving ocular drug bioavailability. The principal approach has been to use viscous solutions (2–6) which delay instilled solution drainage but are presumed not to influence tear turnover. These attempts, however, have not been based on fundamental information related to tear production and movement or instilled fluid dynamics but rather on clinical observations to improve a particular biological response.

Since it is clear that tear dynamics are an important factor in ophthalmic drug bioavailability, an alternative approach to using formulation factors to increase corneal contact time would be to decrease the extent of instilled solution drainage and tear production through the use of drugs or to utilize the normal circadian rhythm, *i.e.*, apply a drug at bedtime since tears are not formed during sleep. Neither approach has been previously explored, but the use of drugs to decrease or inhibit selectively tear turnover and/or solution drainage to improve drug bioavailability seems particularly attractive. It has been shown (7) that rabbits under systemic anesthesia, whose tear production is inhibited (1, 8), achieve significantly higher aqueous humor levels of an instilled drug.

In the present work, the feasibility of controlling tear turnover and/or instilled solution drainage through chemical means is examined. In addition, the extent of improvement in ocular drug bioavailability, as a function of tear turnover and solution drainage, is discussed.

EXPERIMENTAL

Materials—Water was doubly distilled from alkaline permanganate in an all-glass distillation apparatus.

Technetium solutions were prepared using a package[1] of solutions and equipment used to prepare technetium, ^{99m}Tc, suspensions. The preparative procedure was described previously (1). Local anesthetics were obtained from commercial sources[2–4]. All other chemicals were either reagent or analytical grade.

Standardized sterile Schirmer tear strips were obtained commercially[5].

Male, albino rabbits, 1.8–2.4 kg, were used throughout this study[6]. The rabbits were fed a regular diet with no restrictions on the amount of food or water consumed.

Tritiated pilocarpine was obtained commercially[7] and was purified immediately before use. The reasons for the purification and the methods used were reported earlier (9). The specific activity of the pilocarpine used throughout these studies was 18.8 Ci/mmole.

Methods—*Determination of Onset and Duration of Action of Local Anesthetics*—For each local anesthetic tested, three rabbits were positioned in restraining boxes so that they remained approximately in their normal posture. A drop of the appropriate

[1] Collokit, Abbott Radio-Pharmaceuticals, North Chicago, Ill.
[2] Tetracaine hydrochloride, 0.5%, Cooper Laboratories, Wayne, N.J.
[3] Proparacaine hydrochloride, 0.5% (Ophthetic), Allergan Pharmaceuticals, Irvine, Calif.
[4] Lidocaine hydrochloride, 1% (Seracaine), Rachelle Laboratories, Long Beach, Calif.
[5] Cooper Labs, Wayne, N.J.
[6] Klubertanz, Edgerton, Wis.
[7] New England Nuclear, Boston, Mass.

Table I—Determination of Onset and Duration of Action of Topically Applied Proparacaine Hydrochloride, 0.5%, by the Corneal Reflex Technique

Time after Instillation, min	Rabbit 1		Rabbit 2		Rabbit 3	
	Anesthetized	Control	Anesthetized	Control	Anesthetized	Control
5	−[a]	+[b]	+	+	−	++
10	=[c]	++[d]	−	+	=	+
15	=	+	−	+	=	++
20	=	++	+	+	+	++
25	+	++	+	++	+	++
30	+	+	+	+	++	++
35	+	+	+	+	++	++

[a] A (—) response indicates that there was no corneal reflex produced by a single touch of the probe in the center of the cornea. [b] A (+) response indicates that a single touch of the probe to the cornea evoked a corneal reflex response, but the response was somewhat delayed and not severe. [c] A (=) response indicates that further and more severe probing of the corneal still did not evoke a response. [d] A (++) response indcates that a single touch with the probe produced an immediate and severe response.

type and concentration of local anesthetic was instilled onto the cornea of one eye, using commercial plastic dropper bottles that deliver a drop of 50–65 μl when held completely inverted. A drop of normal saline was instilled into the second eye of each rabbit as a control.

At 5-min intervals, the effectiveness of the local anesthetic was measured by means of a corneal reflex test. A thin smooth glass rod was touched to the center of the cornea, and the blink response was observed. In this way, a qualitative measure of the onset and duration of action of the local anesthetics was obtained. This procedure was helpful in gaining an idea of which drugs and what dosing regimens might be useful in the isotope studies, and it provided a means of observing the general response of the eye under the influence of local anesthetics.

Determination of Lacrimal Turnover Rate and Instilled Solution Drainage Rate—The general procedure for the determination of drainage rate and lacrimal fluid turnover rate by the nonsampling method was reported previously (1). In experiments where a local anesthetic was used, 10 min was allowed to elapse following instillation of local anesthetic into the eye before technetium was instilled and counting commenced. The 10-min interval was selected to allow complete drainage of the anesthetic solution (10).

Schirmer Number 1 Test—Rabbits were positioned in restraining boxes in the normal manner. The test was administered in a dimly lit, indirectly illuminated room. Care was exercised so that the strips did not touch the cornea because of the pain and reflex lacrimation produced, which invalidates the test. The rounded bent end of the sterile strips were hooked over the eyelid border at the junction of the middle and nasal one-third of the lower eyelid margin. After 5 min, the strips were removed and the length of the moistened area of the strips was measured.

Basic Secretion Test—The test procedure is the same as for the Schirmer Number 1 test, except that 2 drops of 0.5% proparacaine hydrochloride were instilled into each eye and a cotton swab moistened with 4 drops of 4% cocaine hydrochloride was held on the lower lid for 15 sec prior to inserting the Schirmer strips. After 2 min, the lower cul-de-sac was dried with a cotton swab and the strips were inserted. A similar test was also performed after instilling 5 drops of 0.5% tetracaine hydrochloride at 1-min intervals. Ten minutes after the last drop of tetracaine hydrochloride was instilled, the strips were inserted and the test begun.

Aqueous Humor Concentration versus *Time Profiles for Pilocarpine Nitrate in Presence and Absence of Topical Anesthesia*—All test animals were held in wooden restraining boxes in the normal upright position during the experiments to minimize movement. The animals were acclimated to these test conditions by being placed in the restraining boxes for 2–3 hr on several successive days before the experiment (1).

In the case of animals in the absence of topical anesthesia, 25 μl of 1×10^{-2} *M* tritiated pilocarpine nitrate was instilled onto the cornea, collecting in the lower cul-de-sac. During instillation, the lower lid was pulled slightly away from the globe but was immediately returned to its normal position after instillation. Where topical anesthesia was employed, 1 drop of 0.5% tetracaine hydrochloride was instilled per minute for 5 min; 10 min was allowed to elapse, and then 25 μl of tritiated pilocarpine nitrate solution was instilled.

At 5, 10, 15, 20, 30, 60, and 90 min postinstillation, rabbits were sacrificed by rapid injection of an overdose of pentobarbital sodium into a marginal ear vein. Eyes were rinsed with distilled water and wiped dry with tissues, after which 100–150 μl of aqueous humor was withdrawn from the anterior chamber.

One hundred microliters of aqueous humor was transferred[8] to scintillation counting vials containing 20 ml of liquid scintillation solution[9]. The vials had been refrigerated for 24 hr prior to addition of the samples and were stored in the dark at room temperature for at least 48 hr before counting to minimize chemiluminescence. Two consecutive 1-min counts of each sample were made using a liquid scintillation spectrometer[10]. Quenching of radioactivity by the aqueous humor was found to be relatively constant from animal to animal; therefore, blank corrections were made on the basis of aqueous humor from a single animal in each experiment.

RESULTS

Determination of Onset of Action, Duration of Action, and Depth of Anesthesia of Various Topically Applied Local Anesthetics—The onset and duration of anesthesia from the various local anesthetics are functions of the intrinsic activity of the local anesthetic, the concentration of the agent used, and the dosing regimen.

Table I indicates the results obtained with 0.5% proparacaine hydrochloride. From the data, it was determined that the onset of action of 0.5% proparacaine hydrochloride was from 0 to 10 min, with a duration of action of 10–20 min. At the 10-min point, all three anesthetized eyes began to appear dry, in noticeable contrast to the control eyes. At the 25-min point, all anesthetized eyes appeared to be regaining their moisture; and by 35 min, the anesthetized eyes could not be distinguished from the control eyes on the basis of visual appearance of the tear film.

Table II reports the data obtained from identical experiments using 0.5% tetracaine hydrochloride. The table indicates an onset of action of 0–25 min and a duration of action of 30–55 min. As was the case with proparacaine hydrochloride, drying of the eye and return to normal appearance seemed to approximate closely the loss and resumption of the corneal reflex. In comparison with proparacaine hydrochloride, tetracaine hydrochloride apparently acted somewhat slower but had a much longer duration of action. In addition, the incidence of the deeper (=) anesthesia appeared to be sustained for longer periods with tetracaine. The implications of these observations will become clearer on examination of the results of the isotope studies to follow.

Similar experiments were performed using lidocaine hydrochloride. In the three rabbits tested, 1% lidocaine hydrochloride appeared to have little or no effect on the corneal reflex. In addition, there apparently was little, if any, inhibition of lacrimation; *i.e.*, the anesthetized eyes of all rabbits displayed no observable differences in appearance from the control eyes.

These experiments were in no way intended to be definitive

[8] Biopette, Schwarz/Mann, Orangeburg, N.Y.
[9] Aquasol, New England Nuclear, Boston, Mass.
[10] Packard 2002, Packard Instrument Co., Downers Grove, Ill.

Table II—Determination of Onset and Duration of Action of Topically Applied Tetracaine Hydrochloride by the Corneal Reflex Technique

Time after Instillation, min	Rabbit 1		Rabbit 2		Rabbit 3	
	Anesthetized	Control	Anesthetized	Control	Anesthetized	Control
5	−[a]	++[d]	++	++	++	++
10	=[c]	+[b]	−	++	+	++
15	=	+	=	++	+	++
20	=	+	−	+	+	++
25	=	+	=	+	−	++
30	=	+	=	+	−	++
35	=	+	=	+	=	++
40	=	+	=	++	−	++
45	−	+	−	+	=	++
50	−	+	=	+	−	+
55	+	+	+	++	+	++
60	+	+	−	+	+	++
65	+	+	+	+	+	++
70	+	+	+	+	+	++
75	+	+	+	+	+	++

[a,b,c,d] See footnotes to Table I.

quantitative studies; in fact, with somewhat more sophisticated equipment, more quantitative methods for measuring corneal sensitivity are available (11). However, the experiments performed were reproducible when repeated on the same rabbits and do provide a basis for judging the effectiveness of various local anesthetics as well as a means of making some overall observations as to changes in general characteristics of the precorneal portion of the eye while under the influence of these drugs.

Determination of Lacrimal Fluid Turnover Rate and Instilled Volume Drainage Rate in Rabbits under Topical Local Anesthesia—Varying numbers of drops of 0.5% tetracaine hydrochloride were instilled into the eyes of rabbits at 1-min intervals. Following a lapse of 10 min after the last drop of local anesthetic, 25 μl of radioactive technetium suspension was instilled. By monitoring the decline in technetium in the tear film, it is possible to determine tear turnover and drainage rates as previously described (1, 12). Table III shows the data obtained for lacrimal turnover rates following various numbers of drops of 0.5% tetracaine hydrochloride as well as after 1 drop of 0.5% proparacaine hydrochloride.

Analysis of the data reveals that both tetracaine hydrochloride and proparacaine hydrochloride caused a significant decrease in the normal turnover rate of the lacrimal fluid, indicating decreased tear production. Moreover, the tetracaine data reveal a dose dependency in that the larger number of drops resulted in a greater decrease in tear production than the smaller number of drops. In addition, tetracaine hydrochloride had a more pronounced effect in reducing the turnover rate than proparacaine hydrochloride at a given dose level. This observation is consistent with the results of the previous section that the duration of action and the duration of deep anesthesia were greater with tetracaine hydrochloride than with proparacaine hydrochloride.

As stated in Table III, the turnover rates are calculated by multiplying the observed first-order rate constants by the lacrimal volume of 7.5 μl. Rabbits under general anesthesia were found to accommodate a larger lacrimal volume of about 12 μl (1). It is not unreasonable to assume that this may also be the case with rabbits under topical local anesthesia. If so, the drop in turnover rate in Table III would not be as large in magnitude as reported, but it would still be a significant decrease.

Table IV shows the data obtained for the drainage rate constants following a 25-μl instilled dose of technetium. As was the case with turnover rates, tetracaine hydrochloride was able to reduce substantially the drainage rate of an instilled solution. The trend is that the greater the number of drops, the more pronounced is the effect. Also, 1 drop of tetracaine hydrochloride had a significantly greater effect in decreasing drainage than did a similar dose of proparacaine hydrochloride. In fact, a single drop of proparacaine hydrochloride had no effect in decreasing drainage of a 25-μl instilled dose of technetium suspension when compared with the data for fully awake unanesthetized rabbits (1).

Table III—Turnover Rate of Lacrimal Fluid in Rabbits following Various Doses of Local Anesthetics

Number of Drops of Local Anesthetic Instilled	Turnover Rate[a], μl/min	Standard Error of Mean	Number of Determinations
Tetracaine hydrochloride, 0.5%			
0[b]	0.66	0.03	—
1	0.20[c]	0.02	7
2	0.19[c]	0.04	11
3	0.13[c]	0.04	5
4	0.11[c,d]	0.02	4
5	0.10[c,d]	0.02	7
Proparacaine hydrochloride, 0.5%			
1	0.27[c]	0.04	4

[a] Obtained by multiplying the observed first-order rate constant times the lacrimal volume, found to be 7.5 μl in fully awake unanesthetized rabbits (1). [b] Refers to data obtained in fully awake, unanesthetized animals (1). [c] Statistical analysis of these values using the Student *t* distribution (95% level) shows them to be significantly different from the value for unanesthetized animals. [d] Statistically different (95% level) from the values for 1 and 2 drops.

Table IV—First-Order Drainage Rate Constants for a 25-μl Instilled Volume of Technetium Suspension following Various Doses of Local Anesthetics Using the Nonsampling Technique

Number of Drops of Local Anesthetic Instilled	First-Order Drainage Rate Constant, min^{-1}	Standard Error of Mean	Number of Determinations
Tetracaine hydrochloride, 0.5%			
0[a]	0.54	—[b]	3
1	0.39[c]	0.04	7
2	0.35[c]	0.06	9
3	0.42[c]	0.12	4
4	0.12[d,e]	0.05	3
5	0.06[d,e]	0.02	4
Proparacaine hydrochloride, 0.5%			
1	0.73[c]	0.10	3

[a] Refers to data obtained in fully awake, unanesthetized animals (1). [b] Reported to be within ±5% of the mean (1). [c] Statistical analysis of these values using the Student *t* distribution (95% level) shows no significant difference from the value for unanesthetized animals; however, on the 90% level, the value for 1 and 2 drops of 0.5% tetracaine is significantly different from the value for unanesthetized animals. [d] Statistical analysis of these values using the Student *t* distribution (99% level) shows them to be significantly different from the value for unanesthetized animals. [e] Statistically different (90% level) from the values for 1, 2, and 3 drops.

Table V—Schirmer Test in Rabbits

	Wetting in 5 min, mm	Standard Error of Mean	Number of Eyes Tested
Schirmer Number 1 test	14	1.10	14
Basic secretion test	5.6[a]	0.89	13
5 Drops of 0.5% tetracaine hydrochloride	3.9[a]	0.75	12

[a] No significant difference between these values (Student t distribution, 95% level).

The standard errors for some values in Table IV appear to be quite large; however, this is not unexpected due to the nature of the experiments; *e.g.*, time taken to position the probe (1) is critical, and there is a large potential for individual variations in the drainage apparatus among different rabbits.

Schirmer Number 1 and Basic Secretion Tests—The Schirmer Number 1 test and the basic secretion test were performed in rabbits as described in the *Experimental* section. In addition, the Schirmer test was performed following 5 drops of 0.5% tetracaine hydrochloride, the strips being inserted 10 min after the last drop of tetracaine (Table V).

In humans, a measurement of 15 mm of moistened area in 5 min in the Schirmer Number 1 test is regarded as a standard for normal tear production. The value of 14 mm in rabbits reported here is quite comparable to humans. Both the basic secretion test and the test performed following 5 drops of 0.5% tetracaine hydrochloride showed significant dropoffs in the tear production from the Schirmer Number 1 test; however, neither test showed as large a percentage decrease in tear production as was obtained in the technetium studies.

Effect of Topical Anesthesia on Aqueous Humor Levels of Pilocarpine Nitrate—Table VI shows data obtained when 25 μl of a 10^{-2} M solution of tritiated pilocarpine nitrate was instilled into the eyes of rabbits, both in the presence and absence of 0.5% tetracaine hydrochloride. Significantly greater aqueous humor levels of pilocarpine nitrate were obtained in the presence of topical anesthesia. In fact, computer analysis of these aqueous humor concentration–time profiles reveals the area under the curve for the experiments in the presence of tetracaine hydrochloride to be 2.5 times greater than in the absence of tetracaine hydrochloride, indicating that topically applied local anesthetics can indeed affect the bioavailability of an instilled drug solution. The pharmacokinetic analysis further revealed that the peak aqueous humor concentration in both cases occurred at 25 min and that the absorption and elimination rate constants were essentially unchanged by the use of the local anesthetic.

Table VI—Aqueous Humor Concentration of Pilocarpine Nitrate at Various Times Postinstillation from 25 μl of a 1×10^{-2} M Topically Applied Solution in the Presence and Absence of Topical Anesthesia

Minutes	Pilocarpine Nitrate in Aqueous Humor, μg/ml	Instilled Pilocarpine Nitrate Present, %	Number of Eyes
No Topical Anesthetic			
5	0.36 ± 0.03[a]	0.11	10
10	0.85 ± 0.13	0.25	8
15	0.68 ± 0.06	0.20	9
20	1.20 ± 0.10	0.36	12
30	0.66 ± 0.06	0.20	12
60	0.67 ± 0.05	0.20	7
90	0.24 ± 0.02	0.07	7
5 Drops of 0.5% Tetracaine Hydrochloride			
5	0.52 ± 0.03	0.16	8
10	1.89 ± 0.08	0.56	6
15	2.29 ± 0.22	0.69	9
20	2.64 ± 0.20	0.78	10
30	2.73 ± 0.15	0.81	10
60	1.44 ± 0.11	0.43	6
90	0.62 ± 0.10	0.18	8

[a] Refers to standard error of the mean.

DISCUSSION

Physiological and Clinical Implications of Influence of Local Anesthesia on Tear Dynamics—Boberg-Ans (11) examined the influence of retrobulbar injection of local anesthetics in humans on corneal sensitivity and tear production. His findings appear to substantiate the results reported here with regard to the dose dependency of the effects of local anesthetics on tear production. While the results cannot be compared quantitatively due to the differences in experimental procedure, the qualitative similarity of the effect lends validity to the use of rabbits in such studies. Boberg-Ans made no attempt to correlate the effects of local anesthesia on tear production with any possible influence on topical drug bioavailability in the eye.

Topical anesthetics used chronically may inhibit regeneration of the corneal epithelium (13, 14). In severe cases, such use can even lead to permanent reduction in visual acuity (15). Moreover, it seems that clinically the most effective topical anesthetics are those that are also the most toxic systemically (16). Computer analysis of the pilocarpine aqueous humor concentration *versus* time profiles reported here indicate that peak aqueous humor concentrations occur at about 25 min postinstillation both in the presence and absence of topical anesthesia. In addition, both the absorption and elimination rate constants are essentially the same in both the unanesthetized and anesthetized cases. The constancy of both the peak times and the absorption rate constants suggests that corneal damage is not responsible for the increased aqueous humor levels of drug, supporting the proposed mechanism that the increased drug levels are due to decreased tear production and/or instilled solution drainage.

When treating various eye disorders with some topically applied drugs, particularly antibiotics, many ophthalmologists commence therapy with a very large loading dose followed by smaller doses at regular intervals (17). The use of topical anesthetics prior to the initial dose would enable this initial dose to be reduced significantly with no resultant loss of drug at the active site. In this way, the benefit of a high drug titer at the target area can be achieved while minimizing the possibility of toxic side effects due to drug loss to the drainage apparatus.

The basic secretion test is used clinically to differentiate the function of the "basic secretors" from the "reflex secretors." The results reported here with regard to the Schirmer Number 1 test and the basic secretion test in rabbits seem to parallel the results in humans. This finding tends to support the use of rabbits as a model in studies to determine the effects of tears on drug movement in the eye.

However, the findings raise some serious problems with regard to the validity of these tests. First is the obvious need to standardize the concentration, type, and dosage of local anesthetic used since the degree of inhibition of tear production is a function of these variables. Second is the question of the mechanism of tear production itself. The major premise of the basic secretion test is that the local anesthetic will inhibit only the reflex secretors, thereby permitting a measurement of the function of the basic secretors. The basic secretors are thought to contribute approximately 50% to the normal tear output (18). Within the quantitative limits of this test, the basic secretion test in rabbits roughly supports this assumption since a 60% reduction was obtained. However, in rabbits, with 5 drops of tetracaine hydrochloride, using the more quantitative technetium dilution technique, an 85% reduction in tear production was obtained. There are several possible explanations for this finding:

1. The Schirmer method, being rather qualitative in nature, is not precise enough to enable one to make definitive statements about the degree of tear production.
2. The basic secretion test does not employ a high enough level of anesthesia to inhibit all reflex secretors completely. Therefore, the test does not give a true measure of basic secretion.
3. Local anesthetics do not selectively decrease only the reflex secretors but decrease all tear-producing glands to a very low level.
4. Local anesthetics shut off reflex secretors at a low level due to their effect on the efferent, parasympathetic nerve supply; then at higher levels they affect the basic secretors by exerting a local ef-

fect on the various glands. The reason for not being able to shut off the secretions completely is the difficulty of reaching all of the glands involved in basic secretion. This could explain the rapid dropoff in tear turnover seen with low levels of topical anesthetic, *i.e.*, inhibition of the reflex secretors, followed by a very slow decline with higher anesthetic levels due to a local effect on the basic secretors.

All of these points raise questions with regard to the understanding of the mechanism of tear production.

Finally, an important point should be made concerning the use of topical anesthetics as a tool to increase ocular drug bioavailability. The finding is that it is possible to improve drug bioavailability in the eye by chemically reducing tear turnover and instilled solution drainage. Thus, while local anesthetics are probably not the optimum agents to use, they do support the concept.

Effects of Tear Turnover and Instilled Solution Drainage on Amount of Drug Available for Absorption from an Instilled Solution—To illustrate the enormous effect that tear turnover and drainage can have on the amount of an instilled drug solution available for absorption, some simple calculations were made using some modest approximations. For the first 5 min after instillation of a drug solution, drainage is the primary factor responsible for drug loss from the precorneal pocket (1). In rabbits, at approximately 5 min postinstillation, the total precorneal volume has returned to the normal lacrimal volume; at this point, tear turnover accounts for loss of drug from the lacrimal fluid. The lacrimal fluid turnover rate of 0.66 μl/min divided by the normal lacrimal fluid volume of 7.5 μl gives the first-order turnover rate constant of 0.088 min^{-1}.

After 5 drops of 0.5% tetracaine hydrochloride, the corresponding apparent turnover rate constant is reduced to 0.013 min^{-1}. This is referred to as an apparent rate constant since if under topical anesthesia the eye can hold a larger than normal volume, as is the case in general anesthesia (1), the rate constant would be even smaller than reported here. The drainage rate constants in the absence and presence of tetracaine hydrochloride are 0.54 and 0.06 min^{-1}, respectively.

Using these rate constants, the amount of drug remaining in the lacrimal fluid at any time can be calculated. For example, suppose 25 μl of a 1×10^{-2} *M* pilocarpine nitrate solution was instilled into the eyes and, for purposes of simplicity, it is assumed that no drug absorption occurs. This corresponds to instilling 67.82 μg of pilocarpine nitrate. After 5 min in the absence of topical anesthesia, 4.56 μg of drug remains; after 5 drops of tetracaine hydrochloride, 50.24 μg remains. Similarly, after 20 min, 1.22 and 41.13 μg remain, respectively. From such calculations, it is obvious that the use of topical anesthesia results in a tremendously greater amount of drug potentially available for absorption into the aqueous humor.

The aqueous humor concentration *versus* time profiles for tritiated pilocarpine nitrate in the presence and absence of topical anesthesia confirm the influence of tear turnover and instilled solution drainage on aqueous humor levels of instilled drug solutions. The increase is not as large as might be expected from the differences of drug remaining in the tear film, but this can possibly be explained due to nonproductive scleral absorption and possible adsorption of drug on the lids and other eye tissues. This aspect of drug loss from the eye is currently being investigated.

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