THE IMPORTANCE OF EYELID CLOSURE AND NASOLACRIMAL OCCLUSION FOLLOWING THE OCULAR INSTILLATION OF TOPICAL GLAUCOMA MEDICATIONS, AND THE NEED FOR THE UNIVERSAL INCLUSION OF ONE OF THESE TECHNIQUES IN ALL PATIENT TREATMENTS AND CLINICAL STUDIES

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ABSTRACT

Purpose: To review the effects of nasolacrimal occlusion (NLO) and eyelid closure (ELC) on the ocular and systemic absorption of topically applied glaucoma medications and emphasize the need for the universal application of these techniques during patient treatment and in clinical studies of topically applied glaucoma medications.

Methods: Following a review of data suggesting great clinical benefit from NLO and ELC, the absence of inclusion of these simple techniques in published studies of topical glaucoma medications is identified. The effect of this oversight on these studies is noted with reference to each of the 5 major groups of glaucoma medications.

Results: A review of the literature suggests that NLO and ELC improve intraocular penetration of topically applied glaucoma medications and discourage systemic absorption. The US Food and Drug Administration and the National Institutes of Health discourage the inclusion of these techniques in studies of the efficacy and toxicity of topically applied glaucoma medications. Consequently, all glaucoma studies reported in the literature lack the inclusion of these techniques for 5 minutes. This omission has major implications for patient informed consent, study protocol consistency, and the value of clinical studies, and directly affects the therapeutic index of glaucoma medications in unpredictable and undesirable ways. The undesirable influence on the therapeutic index of each drug influences the safety and efficacy and has implications for the cost of medical treatments, the reproducibility of clinical study results, and dosing regimens, including those of combination therapy, as reflected in the peer-reviewed literature.

Conclusions: Patients should use NLO or ELC for 5 minutes following eye drop treatment with topically applied glaucoma medications. Furthermore, it is essential that these techniques be included in all clinical studies of topically applied glaucoma medications to ensure the most favorable therapeutic index and its accurate determination. This will also help provide the most consistent, reliable, and reproducible study results.

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INTRODUCTION

The potential clinical benefits of nasolacrimal occlusion (NLO) and eyelid closure (ELC) have been recognized for many years.[1-9] However, the US Food and Drug Administration (FDA), National Institutes of Health (NIH), and National Eye Institute (NEI) omit these simple techniques from the study of glaucoma medications. Furthermore, these government agencies discourage the use of these valuable techniques by the pharmaceutical industry within the studies of the efficacy and safety of glaucoma medications that they sponsor.

Following a review of the effects of NLO and ELC for 5 minutes on the ocular and systemic absorption of topically applied glaucoma medications, the importance of employing these techniques during clinical studies is summarized. In addition, potential obstacles and objections to the inclusion of NLO and ELC for 5 minutes in clinical studies of glaucoma medication are summarized. Several methods to help overcome these difficulties as reflected within the literature are outlined. The importance of the universal application of NLO or ELC for 5 minutes following the administration of topical glaucoma medications during all clinical studies to ensure an accurate impression of the efficacy and safety of these medications is emphasized.

METHODS

Following a survey of the peer-reviewed literature focused on the clinical benefit from NLO and ELC for 5 minutes, the absence of these simple techniques in published studies of topical glaucoma medications was noted. The potentially undesirable effects of this oversight on the results of clinical studies of topically applied glaucoma medications are described here, with references to the peer-reviewed literature and specific mention of each of the 5 major groups of glaucoma medications. Reasons for the omission of these important techniques from these clinical studies of efficacy and safety as reflected within the literature are identified and discussed. In addition, the current literature is used to formulate the proposed solutions for the problems and obstacles associated with requiring the universal use of NLO and ELC for 5 minutes in all clinical studies of topical glaucoma medications. Specific references to clinical studies that provide recognized methods to maximize compliance with NLO and ELC for 5 minutes are summarized. Finally, methods of applying the suggestions for increasing compliance with glaucoma treatment regimens are identified.

RESULTS

Following the ocular instillation of drugs prepared in solutions, suspensions, and ointments, the pharmacologically active chemicals within these vehicles are pumped from the periocular area by the eyelids down the nasolacrimal outflow paths to the nasal mucosa.[10]

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The vascular nasal mucosa can readily absorb the drugs delivered in these vehicles, resulting in measurable systemic blood levels, which can be associated with significant systemic toxicity.11 In other words, blinking following eye drop or ointment instillation within the eye discourages the intraocular penetration of a drug by minimizing ocular contact time and maximizes the systemic absorption of a drug as it is quickly and efficiently pumped into the nasolacrimal system and ultimately exposed to the vascular nasal mucosa. This effectively minimizes therapeutic effect and maximizes systemic toxicity of topically applied medications.[1]

Well-designed clinical studies suggest that NLO and ELC for 5 minutes improve intraocular penetration of topically applied glaucoma medications and discourage systemic absorption. In one study,[1] after 5 minutes of NLO or ELC, the systemic absorption of timolol maleate 0.5% was reduced 67% and 65%, respectively, as determined by radioimmunoassay in normal volunteers. Furthermore, 5 minutes of NLO or ELC increased the peak fluorescence within the anterior chamber of the eyes of these subjects by 46% and 69%, respectively, following 1 μL of fluorescein 10% placed in the lower cul-de-sac of the eye as measured by fluorophotometry. In addition, the duration of stay of fluorescence in the anterior chamber increased 33% for NLO and 100% for ELC.[1] A subsequent study by these investigators confirmed that the systemic absorption of timolol maleate 0.5% is reduced similarly by employing NLO or ELC for 5 minutes following ocular instillation of the solution.[3]

A comprehensive study of ophthalmic vehicles[5] demonstrated that ELC, or "no blinking," increased the half-life of each vehicle labeled with radioactive technetium as follows: saline 40%, polyvinyl alcohol 30%, methylcellulose 300%, and ointment 350%. The same investigator[6] completed an exhaustive investigation of extraocular fluid dynamics, applying the radioactive technetium 99 techniques in 173 volunteers with the goal of determining how best to apply topical ocular medication. This study concluded, "Closure of the lids prevents loss of solutions by inhibiting flow into the lacrimal outflow system, enhances entrapment of fluid under the lid, and increases the volume of extraocular fluid. Pressure on the lacrimal sac, especially with lids closed, is a most effective method to increase ocular contact time."

Other investigators have experimented with different durations of NLO and ELC. For example, NLO for 1 minute was observed to decrease systemic absorption of timolol maleate 0.5% by 50% in a study of 9 patients. [9] The investigators recommended NLO with ELC for at least 1 minute after eye drop administration in all patients. Other clinical researchers[7] described the variability of systemic absorption following intraocular administration of 20 μL of timolol 0.5% followed by 10 minutes of NLO with all subjects in the supine position. Their experience inspired them to study different beta blockers and several parasympatholytic drugs more extensively.[8] The investigators concluded, "Patient instruction using all eye drops should increase drug safety in ophthalmology."

Surprisingly, there are no studies of the efficacy and toxicity of glaucoma medications published in the peer-reviewed literature that include 5 minutes of either NLO or ELC. One group of clinical investigators has published several clinical studies that include 1 minute of NLO after eye drop instillation within their protocols.[12-17] However, even this group has been inconsistent in the application of ELC or NLO within their protocols and has never used a full 5 minutes.[18] A review of the literature suggests that the inclusion of these simple techniques may have influenced the results of efficacy and toxicity studies related to each of the 5 major groups of glaucoma medications as reviewed within the "Discussion." The omission of NLO or ELC for 5 minutes from clinical studies of topically applied glaucoma medications has significant implications for patient informed consent, study protocol consistency, the value and potential application of the results from clinical studies, and the effectiveness and safety of each drug. The effect of omitting these techniques on the therapeutic index of each drug influences the cost of medical treatments, the reproducibility of the studies, and the dosing regimens for individual drugs and combination preparations. In addition, this omission influences the integrity and value of all clinical studies of topically applied glaucoma medications and limits applicability of these studies to many clinical practices. Finally, the omission of these simple techniques influences the determination of an accurate therapeutic index for each of the glaucoma medications in unpredictable and undesirable ways.

DISCUSSION

Numerous studies from different investigators published in peer-reviewed journals support the use of NLO or ELC for 5 minutes to enhance intraocular absorption and discourage systemic absorption of topically applied glaucoma medications.[1-9] Although many investigators conclude that these simple techniques are important, there are no clinical studies of the efficacy and toxicity of the currently used glaucoma medications in our literature using these techniques for 5 minutes. In fact, the FDA, NIH, and NEI discourage the inclusion of these techniques in studies of the efficacy and toxicity of topically applied glaucoma medications. Consequently, all glaucoma studies sponsored by the pharmaceutical industry and approved by the FDA lack the inclusion of ELC or NLO for 5 minutes following eye drop instillation.

Although the specific reason for this attitude and influence reflected by several government agencies is unclear, it most likely reflects either concern about harming eyes during punctal occlusion or concern over the proven clinical value of these techniques, or it assumes patients will not comply with these techniques. Many ophthalmologists discourage patients from touching their eyes and periocular area because they fear inducing allergic symptoms or introducing infective organisms. Therefore, a preference for ELC rather than NLO for 5 minutes is understandable. It is reassuring that either technique can be used with adequate results because there is evidence that these procedures can be used interchangeably with insignificant difference in clinical effect.[3]

Although additional clinical studies to further establish the clinical value of these simple techniques may be interesting, the data that exist today in the literature are sufficient to enthusiastically recommend the universal inclusion of ELC or NLO for 5 minutes in all future clinical studies of glaucoma medications and within the clinical practice of glaucoma treatment, as investigators have previously suggested.[1-9] Therefore, the burden of additional proof concerning the question of whether or not these techniques should be instituted now in all clinical studies is on those who choose to ignore the published data and those who minimize the importance of

the basic principles of pharmacokinetics. After all, if a new drug demonstrated 70% increased ocular penetration and 70% decreased systemic absorption, even the FDA would approve these advertisements. In fact, such advertisements can frequently be found in our peer-reviewed journals.[19]

However, the most likely reason the FDA and NEI discourage the pharmaceutical industry from including these techniques in clinical studies is because of bias related to poor patient compliance issues. The usual argument against including ELC and NLO for 5 minutes in clinical studies recognizes published evidence that it is well proven that patients are poorly compliant with their application of glaucoma eye drops.[20,21] Therefore, requesting that 5 additional minutes be added to the usual treatment regimen is at best "wishful thinking" and at worst may further reduce compliance. In recognition of this proven poor compliance, it is only prudent to design clinical studies that simulate "actual practice." After all, it is only prudent to err on the side of caution when approving efficacy and safety of glaucoma medications.

There are at least 3 reasons to believe that patient compliance today is actually better than the current peer-reviewed literature suggests. First, patients are more informed and sophisticated today compared to the 1980s. For example, cartoons appearing in our daily newspapers often reflect our patients' interests and concerns about their medical care and frequently demonstrate an understanding of medicine and pharmacology not commonly present within the general population 30 years ago. Humorous comments and illustrations concerning vitamins in place of mints on pillows in hotels at bedtime, the use and misuse of placebos, and the influence of the pharmaceutical industry on the practice of medicine can be found in many current periodicals on a regular basis.[22-24] These clever and insightful artistic efforts suggest that the patient population and their fund of knowledge that we are treating today is quite different from that which we treated during the 1980s. Second, there is reason to believe that the classic studies of compliance completed in 1986 and 1987, the studies most frequently referred to as proof of patient poor compliance, were inadvertently designed to encourage poor compliance.[20,21] More specifically, within the study of pilocarpine compliance, "Patients were instructed to use the medication as usual," and within the study of timolol compliance, "Patients were instructed not to alter their normal use of the drug."[20,21] Therefore, both studies ignore the proven benefits of patient education on compliance within the methods of their protocol designs.[25-29] Proper patient education about diagnosis and treatment is now recognized as the most successful method used in improving compliance. Therefore, by failing to educate the subjects about the proper technique and importance of treatment, the investigators inadvertently encouraged poor patient compliance within both of these studies. Finally, and most impressive of all, there is direct evidence from a well-designed study utilizing an eye drop monitor in a large population that demonstrates an excellent 96% to 98% adherence to once-daily dosing, which was present even in 2-drug patients.[30] This study protocol included reminding patients they were being monitored, which could have influenced the results. Furthermore, the once-daily dosing lends itself to better compliance compared to 4 times daily or twice-daily dosing in the classic studies of compliance. Simpler dosing schedules can improve compliance as demonstrated by simply changing from 4 times daily to 3 times daily dosing.[31] However, it is also possible that the increased compliance reported in this study reflects the 3 decades of research, education, and clinical efforts on the part of physicians and patients, activity that was initially stimulated by the classic compliance studies of the 1980s.[20,21]

However, even if we choose to assume that compliance remains a problem, it is difficult to avoid the important question, Is today's evidence for poor compliance so compelling that we should continue to ignore the importance of ELC and NLO for 5 minutes? This query begs the related questions, What is the clinical importance of ELC and NLO for 5 minutes for clinical studies of glaucoma medications and patients' treatments? and What clinical impact might the application of these techniques have on patient care and the integrity of clinical studies? The inclusion of these simple procedures in all treatments of experimental subjects and patients is important because it will (1) improve informed consent, (2) benefit study protocol consistency, (3) increase the value and usefulness of each clinical study, and (4) improve the therapeutic index of each of the drugs in all 5 of the major glaucoma medication groups. In other words, these improvements are important not only for further understanding the science of glaucoma treatment, but also for the ethics of informed consent relating to both medical treatment and the experimental study of glaucoma medications.

During February 2008, *The Wall Street Journal* included an article on the importance of intelligible consent forms for patients.[32] The article's author emphasized the importance of a carefully crafted description of risks and benefits in simple terms for all patients and subjects treated with medications or surgical procedures. This description must include alternative treatments and a full disclosure of related risks and benefits, including how they might be increased and decreased. Therefore, the article implies that withholding an explanation of the value of NLO or ELC for 5 minutes from subjects recruited for studies of glaucoma medications does not fulfill the basic requirements of informed consent. Subjects and patients must not only be informed of the relative risks associated with treatments and procedures, but each subject must be given the opportunity to choose a less risky treatment that is likely more effective over one that is not, if there is evidence that one exists. Although every investigator and clinician may have a personal opinion as to the clinical importance of NLO and ELC for 5 minutes, it is reasonable that all investigators are obligated to share with their experimental subjects and patients a brief summary of the data that exist in the literature suggesting these techniques are of potential value. This permits the patient or subject to participate in the decision about treatment, providing an opportunity for an active role in adherence and not simply a passive role in compliance during their treatment regimen.

An excellent editorial published during 2000[33] describes potential "pitfalls" in studies on the efficacy and safety of glaucoma medications, pitfalls that might undermine the practice of evidence-based medicine, with the goal of improving future studies and educating readers to be critical during their review of clinical studies of glaucoma medications. Variable compliance is one of the potential problems noted that might adversely influence results in studies of medical treatments. The omission of a careful description of the technique of ELC or NLO for 5 minutes and an explanation of its value and importance during the study of glaucoma medications and during the practice of medicine guarantees variable and poor compliance. The method of eye drop administration

must be carefully described within each protocol to permit each subject or patient to comply with the same regimen as other subjects to ensure consistency within the study and between studies. It would be unreasonable to advocate a less than optimum regimen. Therefore, to omit this education and description is not only the antithesis of informed consent, but it minimizes consistency within and between clinical studies. This ultimately makes the application of the study results and comparisons within the same patient and between patients difficult.

The value of any clinical study, even a study performed with great rigor and ultimately resulting in a paragon of evidence-based medicine, is minimal if the results cannot be applied to patients within clinical practice. As investigators have emphasized, at the conclusion of a well-designed study one must always ask, "Does my patient and their treatment reflect this particular study population?" If patients' characteristics or treatments differ significantly from the clinical study, the conclusions from this study must be applied with caution or perhaps not at all to these patients.[34] Unfortunately, well-trained ophthalmologists who presently advocate NLO or ELC for 5 minutes following glaucoma medications within their practices will be unable to find studies within the current literature that simulate their practice. Clearly, this shortcoming limits the usefulness of all existing studies of glaucoma medications for determining the safety and efficacy of glaucoma medications as used in these practices.

Finally, improving the therapeutic index of any drug provides a more favorable balance of efficacy and safety. Therapeutic index is defined as the ratio of the toxic dose for 50% (TD 50) of a population to the effective dose for 50% (ED 50) of the population.[35] It is a statement of how selective the drug is in producing its desired effects vs it adverse effects. Because NLO or ELC for 5 minutes improves intraocular penetration of the applied drug, favoring efficacy, and minimizes systemic absorption, discouraging systemic toxicity, the omission of these simple techniques from studies of efficacy and toxicity makes the determination of an accurate and consistent therapeutic index for the medication studied difficult. Furthermore, the omission of NLO or ELC from a study protocol has major implications for both the subjects recruited for the study and the study results. To ignore the pharmacokinetic advantages of NLO or ELC for 5 minutes in studies of efficacy and safety of topically applied glaucoma medications guarantees minimal and variable intraocular absorption and maximal and variable systemic absorption, making the drug potentially less effective and more toxic for the subject or patient. In addition, the study will report an inaccurate and variable therapeutic index for the drug. This is less than optimum treatment with undesirable and potentially dangerous results.

It is interesting to anticipate what the impact of NLO or ELC for 5 minutes may have on patient care and the results of clinical studies of glaucoma medications by reflecting on past clinical studies lacking these techniques. This consideration may reduce the cost of the medical therapy of glaucoma, may help provide us with more reproducible clinical studies, and may help to clarify appropriate dosing regimens for each group of glaucoma medications.

Encouraging consistent results during clinical studies and improving the therapeutic index of a drug from any of the 5 groups (parasympathomimetics, sympathomimetics, beta blockers, topical carbonic anhydrase inhibitors, prostaglandin analogs) of glaucoma medications is always desirable. It is of additional interest to identify studies relating to each of these groups of medications in an attempt to predict the potential impact of 5 minutes NLO or ELC on each of these experimental situations. For example, the usefulness of pilocarpine is limited by 3 or 4 times daily dosing. However, there is published evidence that pilocarpine gel can be used at each bedtime with good therapeutic effect in many patients, which permits a more convenient once-daily dosing.[36] The inclusion of ELC or NLO for 5 minutes within this study would have improved the effects and increased the likelihood of more patients responding with a good effect. This suspicion is consistent with the demonstration that an ointment vehicle combined with ELC increased ocular contact time 350% in normal volunteers.[5] In addition, ELC or NLO for 5 minutes would make twice-daily dosing with more viscous preparations of pilocarpine more likely to be effective in patients, as suggested by the 300% increased ocular contact times for methylcellulose vehicle systems when used without blinking reported in the literature.[5] The indirect-acting parasympathomimetics, which can be used once or twice daily, are less popular today because their potential systemic toxicity is greater than that of many of the newer glaucoma medications. Obviously, NLO or ELC for 5 minutes after their instillation would make them safer to use. Presently, the parasympathomimetics are infrequently used.[37] If the therapeutic index of these drugs were improved and their dosing regimen simplified by proper eye drop administration, the increased use of these agents would provide another useful group for the treatment of glaucoma with a savings in cost of therapy.

The sympathomimetics include epinephrine, its related prodrug dipivalyl epinephrine, and the relatively specific α_2 agonists apraclonidine and brimonidine. The use of each of these agents has been associated with clinically significant systemic side effects.[38-41] Five minutes NLO or ELC decreases systemic absorption of these drugs and makes systemic toxicity from their use less likely. Furthermore, the associated increased ocular penetration would make adequate therapeutic effects more likely with lower concentrations of epinephrine. The relatively specific α_2 agonists apraclonidine and brimonidine are most effective given 3 times daily, but with twice-daily dosing, they achieve 80% of their maximal pressure-lowering effect.[42] The increased ocular penetrance associated with NLO and ELC for 5 minutes would allow more patients to have an adequate therapeutic effect with only twice-daily dosing. In addition, the increased ocular absorption would make a missed dose within any of these sympathomimetic regimens less important for the patient.

Oral carbonic anhydrase inhibitors, which are sulfonamide derivatives, are the most toxic group of glaucoma medications commercially available.[43] They are capable of inducing any of the sulfonamide-related systemic toxicities, which include life-threatening side effects. Therefore, topically applied carbonic anhydrase inhibitors, if systemically absorbed to an excessive extent, may be capable of demonstrating some these same toxicities. Obviously, NLO and ELC for 5 minutes would help avoid this increased absorption and the associated increased blood levels. Furthermore, the European Glaucoma Study showed that topically applied dorzolamide was no different from placebo in its ability to lower intraocular pressure.[44] Although a thoughtful editorial suggests the

results may relate to the lack of choosing a target pressure, a substantial regression to the mean, and/or to patient dropout, NLO or ELC for 5 minutes might have influenced the results of this study.[45] Dorzolamide is not absorbed particularly well by the eye compared to many drugs, and it is likely that the additional intraocular absorption following ELC or NLO for 5 minutes would have influenced the study results.

Topically applied beta blockers can be associated with significant systemic toxicity.[46] For many years, many investigators have suggested that the systemic blood levels of these drugs can be minimized with ELC and NLO for 5 minutes.[2,5,8,46] However, these simple techniques are never used in clinical studies of efficacy and toxicity of these sympatholytic drugs. This not only exposes experimental subjects to unnecessary risks but also provides variable data, resulting in confusion over appropriate daily dosing. For example, new formulations of beta blockers are claiming effectiveness with once-daily dosing for the first time with this group of drugs.[47] However, the literature has much evidence that once-daily dosing with the existing commercially available beta blockers is frequently sufficient for a therapeutic effect in many patients, even without the use of NLO and ELC for 5 minutes.[48-53] Obviously, the use of these simple techniques would make once-daily dosing effective for more patients more often and help avoid excessive systemic toxicity. Furthermore, the use of the older beta blockers, once daily with ELC or NLO, in place of newer agents will be associated with decreased cost of therapy.

In recent years, many studies have been published attempting to prove that one prostaglandin analog among the several commercially available preparations has greater efficacy or less toxicity than another does. An editorial referred to these publications as the "prostaglandin wars," marveled over the small differences of 1 to 2 mm Hg between studies, and admitted that some of the results appear to be conflicting without a clear explanation.[54] It is possible that the inconsistent approach to eye drop application from one study to another or even within the same study and the unavoidable variability associated with this lack of consistency could explain some of these puzzling variations and inconsistencies. One study not mentioned within this editorial included NLO for 1 minute.[17] Even these investigators wondered, within their article's discussion, why their results differed from others in the literature, without considering that the other studies' unspecified, and therefore inconsistent, techniques of eye drop instillation might possibly be responsible. Furthermore, it is possible that properly administered eye drops including 5 minutes NLO or ELC in all of the published studies of prostaglandin analogs would have made greater differences in intraocular pressure more apparent in these studies.

Recently, topically applied combination preparations have been reintroduced with the hopes of simplifying patients' therapeutic regimens.[55,56] These preparations each include 2 different drugs from 2 different classifications of glaucoma medications—more specifically, a beta blocker combined with either a topical carbonic anhydrase inhibitor or a relatively specific α_2 blocker provided in each combination preparation to be given 1 drop twice daily.[54,55] These combination preparations are puzzling from the viewpoint of pharmacokinetics. For example, brimonidine tartrate 0.2%, usually administered 3 times daily for optimum effect, is combined with timolol maleate 0.5%, which can be effective given once daily, and provided in a single drop to be administered twice daily, resulting in an effect on intraocular pressure less than the 2 drugs given separately.[56] Five minutes NLO or ELC added to future clinical studies of combination preparations can only help clarify this confusing pharmacokinetic mismatch and the apparent effects on efficacy and safety reported within the results. In addition, proper eye drop instillation should help to ensure less toxicity and a greater clinical effect with these regimens, making the combination preparations safer to use for both patients and experimental subjects.

In view of the importance of ELC and NLO for 5 minutes and the potential impact of these techniques for clinical studies and for patients during their treatment of glaucoma, it seems clear that these simple additions should be routinely described and encouraged in all clinical studies of glaucoma medications and during the treatment of glaucoma patients. This includes all private and all academic medical practices. Furthermore, all clinical studies of the efficacy and toxicity of glaucoma medications, without regard to their source of funding, should include instruction about the techniques and their potential importance in achieving an optimum therapeutic index. The fundamental ethics of informed consent requires that all patients treated and all subjects included in clinical studies should be informed of the potential value of these simple techniques and that they should be encouraged to use them as part of the informed consent process. It seems apparent that patients are demanding to be fully informed about risks and benefits of all drugs administered to them.[32] They should have the opportunity to choose less risky and more effective treatments if they are available.

In addition to these educational activities, appropriate additions to and changes in the existing therapeutic routines and experimental treatment descriptions should be adopted to help ensure that NLO or ELC for 5 minutes is used. These modifications of "usual" therapeutic routines are best guided by the experimental and clinical experience reflected within the existing literature. For example, investigators have suggested that written instructions be given to patients because this will enhance their compliance.[57] These written instructions might be best be included within the prescription itself so these important instructions ultimately appear on the eye drop bottle that is dispensed by the pharmacist. For example, the resulting direction for treatment would read, "Instill one drop in each eye every morning followed by 5 minutes eyelid closure."

Also, the instructions about ELC or NLO for 5 minutes should appear on the eye drop bottle dispensed to the patient as an obvious, additional, individual colored label to emphasize the importance of the added effort. No pharmacist would dispense an ophthalmic suspension within an eye drop container without a conspicuous "Shake well" label placed securely on the bottle. This important addition ensures that the proper amounts of drug are present in each eye drop dispensed from the bottle. Therefore, it is only reasonable that the same eye drop container should have a label reading "ELC or NLO for 5 minutes" to ensure that an optimum amount of drug enters the eye from the instilled eye drop and that the drug is not excessively absorbed systemically via the nasolacrimal outflow system.

Finally, the importance of the sociologic aspects of ophthalmology has been recognized for many decades.[58] Throughout subsequent years, investigators mentioned the advantages of integrating daily treatment regimens into a patient's daily routine.[26] Some

advocated linking the therapeutic activity with a specific daily event.[27,28] With these suggestions in mind, it is useful to anticipate every patient's reluctance to "wasting 5 minutes" once, twice, or even 3 times daily during eye drop instillation. After recognizing and sympathizing with how tedious this activity can be, physicians can underscore the importance of the technique for an optimum therapeutic effect and avoidance of excessive toxicity. Then proceed to identify specific daily activities the patient performs and emphasize how neatly the 5 minutes of ELC will fit within the given activity. For example, a busy mother can take 5 minutes just after a child is put down for a daily nap so she can preserve her good vision to enjoy her child for years to come. A couch potato, just prior to watching a video, can take 5 minutes for ELC to ensure a continued good visual acuity, permitting the enjoyment of seeing videos for years to come. For anyone who meditates or enjoys yoga, an additional 5 minutes before or after seems like a small additional sacrifice to maintain his or her sight. Everyone should exercise daily in some manner to maintain a healthy cardiovascular system. It is only a natural extension of preventative medicine to agree to an additional 5 minutes of ELC to help ensure healthy eyes. Finally, most patients watch some television, which provides a perfect setting to include 5 minutes of ELC at the end of one program and the beginning of the next. This time interval is approximately 5 minutes, resulting from the 2 successive commercial breaks. Using this interval for ELC will help the patient to enjoy seeing television for years to come. In summary, taking 5 minutes for ELC or NLO from, or adding to, any of these routine, daily tasks is usually less ominous for the patient. In addition, it will have the added advantage of more fully informing the clinician about the patient's capabilities and interests, improving the physician-patient relationship. Appropriate charting of a few notes relating to these activities and suggestions will permit the particular activity to be discussed during subsequent appointments, serving to confirm that the patient is incorporating this technique into his or her daily life successfully. If a physician administers the patient's diagnostic dilating drops, this instillation period provides the perfect time to review with the patient the appropriate techniques of ELC or NLO for 5 minutes and their importance and to confirm that the patient is adhering to the regimen.

A potential obstacle for introducing NLO or ELC for 5 minutes at this particular time reflects a significant financial bias. At present, many pharmaceutical companies have major, costly programs in progress to help remedy the perceived poor compliance. These programs usually include new ophthalmic formulations, such as combination preparations, and can be associated with innovative delivery devices. The addition of ELC for 5 minutes may be viewed as an obstacle to "improved compliance in glaucoma" and therefore potentially detrimental to the compliance programs. Therefore, efforts to encourage ELC or NLO for 5 minutes might be perceived as antagonistic to the commercial efforts and ultimate success. I hope that the laudable goal of "improved compliance" currently encouraged by the pharmaceutical industry can be viewed as synergistic with the universal introduction of NLO or ELC for 5 minutes. Ideally, the selling of "improved compliance" could be emphasized as part of pursuing a greater goal of "optimum compliance," with an "optimum regimen," for an "optimum therapeutic index," with hopes of achieving the ultimate goal of an "optimum therapeutic effect." Obviously, the industry's "thought leaders" and their cooperation with this effort will be essential for the overall success of optimum patient treatment.

In summary, the ethical and clinical importance of encouraging ELC or NLO for 5 minutes during all glaucoma treatments and within all clinical studies of efficacy and toxicity is obvious. There may be those who continue to argue that subjects and patients are not compliant with their topical treatments, and these pessimists may insist that including NLO or ELC for 5 minutes will exacerbate this compliance problem. However, it is unfair and unethical to continue to penalize all of the compliant subjects and every compliant patient because of the potential of poor compliance by others. To continue to deprive patients and subjects from this basic informed consent will simply ensure that even the compliant individuals will continue to be denied the potential advantages of these simple techniques. In addition, investigators and clinicians will continue to suffer the confusing consequences of less than optimally designed clinical studies of glaucoma medications that are inadvertently designed to provide inconsistent and inaccurate conclusions about the therapeutic index for each of the glaucoma drugs studied. Finally, it is important that patients and physicians who adhere to the appropriate methods of using eye drops have access to studies that incorporate these techniques and provide results and conclusions that can be more reasonable extrapolated to themselves.

CONCLUSION

Patients should use NLO or ELC for 5 minutes following eye drop treatment with topically applied glaucoma medications to maximize efficacy and minimize systemic toxicity. Furthermore, it is essential that a description of these simple techniques be included in all clinical studies of topically applied glaucoma medications to ensure the most favorable therapeutic index and its accurate determination and to comply with experimental subject informed consent. The consistent inclusion of these techniques combined with education, written instructions, and appropriate labeling should enhance compliance with appropriate therapy in all patients and experimental subjects and provide the most consistent, reliable, and reproducible study results. It is not acceptable to continue to penalize compliant patients for the potential poor compliance of others. Furthermore, it is only reasonable and prudent to encourage optimum compliance, with an optimum regimen, to achieve an optimum therapeutic index, which will result in an optimum therapeutic effect. This effort ultimately benefits our patients, our research, and medical ethics.

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PEER DISCUSSION

DR. HENRY DAVID JAMPEL: I would like to congratulate Dr. Flach for raising the important issue of maximizing the benefits and minimizing the risks of topical therapy for glaucoma by emphasizing safe eye drop instillation, specifically eye lid closure (ELC) and nasolacrimal occlusion (NLO). There is no doubt that ELC and NLO are safe, and there is a substantial literature, cited by Dr. Flach, that these maneuvers can decrease the blood levels of some intraocular pressure-lowering medications after topical instillation.

Dr. Flach emphasizes in his paper that it is imperative for the clinician investigator to include either ELC or NLO in the design and implementation of all clinical trials, and for all clinicians to instruct their patients to employ these techniques when using eye drops. All mandates come with a price, however, and Dr. Flach anticipates the argument that the price of insisting upon such techniques might be decreased adherence. Dr. Flach counters the argument of decreased adherence by citing a recent publication by Alan Robin, M.D. demonstrating up to 97% adherence with prostaglandin therapy[1]. If adherence is that good, then compromising adherence slightly with insistence on ELC or NLO might not be important. However, our group has accumulated data from electronic monitoring with the Travatan Dosing Aid and found a mean adherence of 72%, quite consistent with the older literature[2,3]. I would argue that adherence is currently not good, and one would not want to do anything that might further decrease it. Therefore, although I agree with Dr. Flach that all patients should be told about the advantages of ELC and NLO, I believe that they should be presented to the patient as an adjunct (desirable, but not mandatory) to the administration of eye drops.

More work is needed before the universal advocacy of ELC and NLO. Dr. Flach mentions 5 minutes as the appropriate duration for ELC and NLO, but I know of no evidence for choosing that particular length of time. If a patient is using two, or perhaps even three eye drops the period of ELC or NLO becomes 20 or even 30 minutes, which is highly impractical. Time course studies are needed to determine the optimal duration of ELC and NLO. Maybe one minute would be sufficient, in which case patient acceptance would likely be higher than for the longer duration.

Even if not ready for prime time in the clinic, I agree with Dr. Flach that all participants in clinical trials involving intraocular pressure lowering medications should be instructed in ELC and NLO. Unfortunately, without a mechanism for monitoring adherence

with these techniques, it will be difficult to show that they are having an effect.

We should thank Dr. Flach for raising our awareness of the importance of the act of eye drop instillation. ELC and NLO are an important piece of the puzzle. We all must strive to do a better job in instructing patients in all aspects of eye drop administration so that they may obtain the greatest benefit.

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DR. MALCOLM R. ING: I have no financial conflicts. Allan, I always enjoy your presentations. They are really lively, and I especially enjoyed the pictures. While you were showing the thought occurred of determining when would be the optimum time to emphasize the lid closure techniques, namely after yoga. Would we be helping our patients if we actually asked them to instill drops at night? If they use a daily dose drop at night, then everyone would use their drops at night. This is a natural time before sleep and we all experience eyelid closure. I know there is some evidence of a diurnal effect with some of the drops, which explains why they have different effectiveness when instilled at different times of the day. If we are going to emphasize compliance, then instructing our patients to simply instill their daily drops at nighttime would be the least intrusive time.

DR. ROBERT RITCH: No commercial interest. I cannot overemphasize the importance of what Dr. Flach said. Nasolacrimal occlusion is the first thing I teach to my new fellows, and I ask all new patients and old patients if they are doing it, and if they are doing it properly. I first started this about 25 years ago, when I heard about it from Thom Zimmerman. He showed that pilocarpine could be reduced from a QID to a BID dose and that doing this would double the duration of action. As Dr. Flach said, you get 70% more penetration into the eye, up to 100% longer duration of action, less systemic absorption, less systemic side effects, and less fluctuation in intraocular pressure throughout the day. We made a video of proper nasolacrimal occlusion and spacing between the drops, which is also important. Many patients instill multiple medications one right after the other. I tell them it is like getting three people into a bathtub that is ¾ full. It will overflow. The video is available at http://www.glaucoma.net, and if anyone wants a DVD to show to their patients, please e-mail me, and I will send you one. One thing that I do not ask patients to do is five minutes of lid closure after drop instillation. I have patients perform one minute of nasolacrimal occlusion. Back in the 1980s, we did an informal study and found up to 30% to 40% reductions in intraocular pressure when patients began using nasolacrimal occlusion. I agree that all studies should use nasolacrimal occlusion, because otherwise the results are inconsistent, unreliable, and suboptimal. This is a very important point. Corporate CEOs and investment bankers in New York will not tolerate five minutes of eyelid closure, but they will be compliant with one minute of nasolacrimal occlusion.

DR. DOUGLAS R. ANDERSON: No financial interest in this topic. Maybe no interest in this topic at all. I agree with this presenter that the evidence is certainly in the literature that eyelid closure, nasolacrimal duct occlusion, and such maneuvers enhance the absorption into the eye and reduce the absorption into the body. It is true that there has not been a dose response curve comparing one minute to five minutes to ten minutes to fifteen minutes of such activities, but on the other hand, the principle is there. When you run out of scientific knowledge, you have to use our intuition and common sense, and so, you say the longer you have the eyes closed, the more effect you have, of course with diminishing returns. Therefore, you compromise on something practical, and if that compromise for a particular patient is five minutes, then that is fine, and if that compromise is ten minutes that is also acceptable.

I cannot give a citation off hand, but I am reasonably sure it has been shown that the real problem is that when you blink, the pumping mechanism of the lacrimal system takes the tear film and the drugs into the nasolacrimal system. It is this action that removes the drug from contact with the cornea and reduces penetration into the eye. If direct nasolacrimal duct occlusion does not add much, then I think simple gentle closure of the eyes without blinking is probably something that is more practical and almost as effective. The point is, when you do nasolacrimal duct occlusion you are not going to blink, and likely it is the lack of blinking that is the most important.

The second point that I wanted to mention is that, and it has already been mentioned, a person who is using two drops needs to wait five minutes or more to let one absorb before you dilute it with a second eye drop. We need to also do that in our office when we use tropicamide and phenylephrine to dilate the pupils. If you put one drop in and immediately instill the other, you are not going to get the full effect from the first drop. We could also ask our patients to stay in the waiting room after the first drop, call in the next patient, and about the time you walk out you could put in the second drop, asking them to keep their eyes closed during that interval and then also after instillation of the second drop. This reaffirms to them that you feel it necessary to wait between instilling two eye drops, and it shows them what they need to do at home when they are using two different eye drops. A convenient strategy is for the patient to put one drop in before some activity, such as when undressing and getting ready to go to bed and to instill the second drop after he finishes that activity.

DR. EDWARD L. RAAB: No conflict. Those of us who examine premature infants for ROP are dealing with babies who, after installation of the drops, have prolonged periods of eyelid closure. I am not aware that drops given in this situation dilate the pupils more effectively or quickly. This is my first observation. The second is, even if you are correct and you preach the necessity for compliance, you are still left with the necessity of having some way to monitor it. I am reminded of having been shown an experimental eye patch for amblyopia therapy that was to be applied to the skin. Compliance with technique would be measured by either some chemical or some thermal reaction that could be measured. One hundred per cent compliance with that device could have been established if the parents had put it on the child's buttocks instead of over their eye.

DR. VERINDER S. NIRANKARI: I have no financial conflict. I think this is a very important paper. I want to expand on what Dr. Flach has just said and what we have been actually doing in patients who, for example, not only have glaucoma, but have infectious keratitis or uveitis or have had graft rejection and need frequent drops. You know how difficult it is for them to use them. If they seem noncompliant, we have inserted punctal plugs in the inferior canaliculus and seen a dramatic improvement. I do not know whether this occurred because the drug stays longer in the eye or if the patients are initially noncompliant. I urge everyone to look at their own patients and determine if they are using drops very frequently. Eyelid closure or putting the finger up in the corner may not be practical, but if you insert the plugs during the time that you need to treat an acute disease, then they can produce very positive effects.

DR. ROBERT L. STAMPER: I have received honorarium from various pharmaceutical companies for speaking. Allan, that was terrific. I believe that we all need to be reminded about this practice. It is something I use routinely in my practice and I do believe that it makes a difference. I would like to challenge you, or at least ask you a question about, mandating eyelid closure or punctal occlusion or both for FDA studies. I see a couple of difficulties with that recommendation. Since all of the proceeding studies have been done without that practice, comparison of future studies with previous studies would be rather difficult because you are not comparing the same circumstances. I believe that if you mandate this practice your studies will give a best case scenario. One of the problems that we already have with our studies is that they give us a better case scenario than exists in real life. I wonder how you might respond to that concern. Thank you.

DR. ROBERT C. DREWS: No conflicts. In observing my patients perform this eyelid and punctal occlusion exercise, I am concerned because some patients blink several times before they close their eyes or occlude their punctum and effectively wash out much of the drop. I am afraid this requires special monitoring. I am reminded anecdotally of an ophthalmologist we had in St. Louis 60 years ago, who did not allow his patients to put in their own eye drops. The patients were required to return to his office six days a week where the office technician would instill the eye drops with appropriate maintenance of lid closure. The lines out of his waiting room and around the rest of the building were enormous, but it was certainly effective treatment in that respect.

DR. ALLAN J. FLACH: I have used an entire tablet taking down notes, so I will try to be brief. First, of course, I would like to thank Dr. Jampel for the time he put into this. On my slide I am telling you why I feel so privileged. This is the one society that probably permits someone who is not in the glaucoma society speaking about glaucoma. Dr. Jampel, this is not a compliance issue. This is primarily an informed consent issue and any patient receiving an eye drop, in my opinion, must be informed that the existing literature shows that five minute eyelid closure will do exactly what I have said. If patients choose not to be compliant, so be it. You can lead a horse to the water, but you cannot make him drink. I can cite hundreds of examples of poor compliance. Life is filled with poor compliance and we do not aim at the lowest level of compliance. That would be a huge mistake. I am anxious to see your electronic monitoring system paper, but I would also like to ask how you know that five minutes eyelid will decrease compliance. There are studies in the literature showing that if you do not trivialize a task, such as using an eye drop once daily at bedtime and if you really make it an effort like they do to exercise regularly and discuss all the other things I mentioned, that they may be more compliant. This may be especially true if you tell them that closing their eye not only will save their vision, but in the case of beta blockers, for example, even save their life. The evidence for five minute eyelid closure, in my opinion, exists and is sufficient. If you want to study that topic further and establish dose response curves, then that is fine. I believe patients must be informed about the value of the five minute eyelid closure. Your resistance to what I am saying reminds me a little bit of this gentleman who was simply trying to get doctors to wash their hands 150 years ago. The risk of hand washing appeared minimal to him, and in fact he proved the value of this practice in some studies that others did not accept because there were about 100 ideas of how to perform better studies. This reluctance prolonged the introduction of hand washing for 30 years. During the interim, this doctor, Ignatz Semmelweis, was not only thrown out of Vienna because he suggested something nobody wanted to do until it was better studied, but he was driven out of his mind and eventually was killed, either by his own hand or his treatment in the insane asylum. The risk of eyelid closure seems minimal compared to the benefit of lack of death with a beta blocker. I am anxious to discuss this a bit longer.

Dr. Ing, yes, bedtime is wonderful, and now I would like to bring out another misconception. When Crowell Beard received his Howe medal, Dick Brubaker was at our table and in public I asked him, "Dick, are you against beta blockers at bedtime?" He responded, "Absolutely not, the half life is so long you can give them in the morning or at night, regardless of when one is sleeping." So, you can give any drug at bedtime, even beta blockers. Who cares if our patients fall asleep, the drug concentration within the eye remains therapeutic and the half life is long enough.

Dr. Ritch, thank you for your support. I have seen intraocular pressure reductions in patients scheduled for trabeculectomy that occurred after recommending eyelid closure. I agree with what you said.

Dr. Anderson, thank you for your support. You are 100% correct to wonder about nasolacrimal occlusion versus eyelid closure. Dr. Zimmerman presented a wonderful poster at ARVO in 1976 in which he demonstrated that nasolacrimal occlusion and eyelid

closure achieved exactly the same effect. Furthermore, for you to worry about the mechanics of the eyelid again reflects your usual brilliance. The work done by Dr. Fraunfelder for his AOS thesis showed that if you forcibly squeeze your eyes closed, you squirt the drop out of your eye, and that even if you close them gently with a the quivering motion that 5% to 10% of patients can actually also have this problem. You must train your patients not only to just gently close their eyes, but you must teach them to overcome the quivering motion of their eyes. The time interval between the applications of eye drops is ideally 10 to 15 minutes which can be cumbersome; however, this practice is worthwhile to improve the likelihood of preserving the patient's vision. Patients are out there running for half-hour. They are running marathons and patients are willing to do many things, if they really believe it will help save their vision.

Dr. Raab, children eyelid closure, you must prevent a systemic sympathomimetic and a parasympatholytic response. These children can go into hyperpyretic crisis and die. I know you are aware of that complication. On the other hand, monitoring compliance is not a big issue. Who cares about compliance? If they do it, then they do it. If they do not listen to you, it is their problem. If somebody skies down a double diamond slope and they are a beginner, and they have been warned, it is their choice. If patients do not want to comply with what we say, then that is OK. How much more do we need to study compliance? Are not all of you sick of these studies? It is somewhat like smoking and its relationship to lung cancer. What more do we have to prove?

Dr. Nirankari, I agree this recommendation can extend to improving the treatment of ocular infection. Punctal plugs are an interesting topic unto themselves.

Dr. Stamper, thank you. Although regarding a mandate I disagree with you, we need to have a mandate. If the past studies were done improperly, then why should we perpetuate improper studies? Let us start our database fresh. If the best studies were not accurate, do you want to believe forever that carbonic anhydrase inhibitors given topically do not have an effect? I mean to say that our past studies may have been flawed, and we are not perfect, but why should we perpetuate flawed studies? The example that comes to mind is one of Dr. Jampel's studies. I love the study that Dr. Jampel and Quigley did relating the effect of lovastatin and beta blockers on cholesterol levels, but that study should have been done on eyelid closure, if you are looking for a systemic effect.

Dr. Drews, thank you for your kind comment. Regarding blinking after instilling an eye drop, I agree you must prevent that from occurring. I really want to thank the Society and everybody for permitting me to go over my time limit. I apologize for that.