The potential clinical benefits of nasolacrimal occlusion (NLO) and eyelid closure (ELC) for 5 minutes have been recognized for many years. Following the ocular instillation of drugs prepared in solutions, suspensions, and ointments, the pharmacologically active chemicals within these vehicles are pumped from the periorcular area by the eyelids down the nasolacrimal outflow paths to the nasal mucosa. This results in less intraocular drug absorption. In addition, 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. Therefore, the rapid passage of eye drops into the nasolacrimal outflow system effectively minimizes therapeutic effect and maximizes systemic toxicity of topically applied medications.

Well-designed clinical studies suggest that NLO and ELC, when performed for 5 minutes, improve intraocular penetration of topically applied glaucoma medications and decrease systemic absorption. After 5 minutes of NLO and 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 and 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. A subsequent study by these investigators confirmed that the systemic absorption of timolol maleate, 0.5%, is reduced similarly by using NLO or ELC for 5 minutes following ocular instillation of the solution.

A comprehensive study of ophthalmic vehicles demonstrated that ELC, or “no blinking,” increased the half-life of each vehicle labeled with radioactive technetium as follows: saline by 40%; polyvinyl alcohol by 30%; methylcellulose by 300%; and ointment by 350%. 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 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, but all have agreed, “Patient instruction using eye drops should increase drug safety in ophthalmology.”

Although 1 group of investigators has published studies that include 1 minute of NLO after eye drop application within their protocols, it has been inconsistent in using this criterion. Furthermore, the evidence for 1 minute of NLO being equivalent to 5 minutes is lacking. Therefore, there are no studies of the efficacy and toxicity of glaucoma medica-
...tions published in the peer-reviewed literature that include 5 minutes of either NLO or ELC.

Despite studies suggesting that ELC or NLO for 5 minutes enhances intraocular absorption and reduces systemic absorption, the Food and Drug Administration (FDA), the National Institutes of Health, and the National Eye Institute do not insist that the pharmaceutical industry use these techniques within its studies of glaucoma medications. This is puzzling, because these government agencies encourage study methodology that favors reproducibility and consistent, reliable data. Furthermore, because the FDA should help insure that patients are exposed to drugs that are minimally toxic and maximally effective, thereby helping to provide the most favorable therapeutic index for studied and approved medications, the inclusion of these techniques would further this important goal by providing more consistent and predictable absorption. A detailed description of how eye drops should be administered, including the number of doses daily and ELC for 5 minutes, should be required within the “Methods” section of each study to provide the possibility for consistent and reproducible absorption of topically applied glaucoma medications.

The explanation for this universal omission is unclear. However, it most likely reflects 1 of 3 concerns: (1) the possibility of harming eyes during digital punctal occlusion, (2) the lack of solid evidence of the proven clinical value of these techniques, or (3) the assumption that patients will not adhere to a longer regimen. Many ophthalmologists appropriately discourage patients from touching their eyes and periorcular area, because they fear that it will induce allergic symptoms or introduce infective organisms. This undesirable ocular digital contact may include NLO if the fingertips touch the lacrimal lake, caruncle, or conjunctiva during the procedure. Therefore, a preference for ELC rather than NLO for 5 minutes is understandable. It is reassuring that studies confirm that either technique can be used with equal results.5

Although additional clinical studies to further establish the clinical value of these simple techniques may be edifying, the data that exist within the literature are sufficient to enthusiastically recommend the universal inclusion of ELC or NLO for 5 minutes in all clinical studies of glaucoma medications and within the clinical practice of glaucoma treatment.1,8 If a new drug demonstrated 70% increased ocular penetration and 70% decreased systemic absorption, the FDA would approve these advertisements. In fact, such advertisements appear in our peer-reviewed journals, having been approved by the FDA, claiming enhanced ocular penetration of drugs as a significant clinical advantage.29

Another reason these techniques are not included in all clinical studies of glaucoma medications is the assumption that patients will not add 5 minutes of ELC to a regimen to which they are already poorly adherent.20-22 It may be better than most believe.23 In fact, an excellent adherence of 97% is described in at least 1 well-designed study using an eye drop monitor in a large population of patients; this study also reported 96% to 98% adherence in patients treated with 2 drugs.24 However, even if adherence is poor, is it reasonable to inadvertently penalize adherent patients for the potential poor adherence of others, ignoring the clinical importance of ELC for 5 minutes in clinical studies of glaucoma medications and patients’ treatments? This query begs the question of what the importance of ELC for 5 minutes following glaucoma eye drop instillation is. The inclusion of this simple procedure is important for all treatments of experimental subjects because it may (1) improve informed consent, (2) benefit study protocol consistency, (3) increase the value and usefulness of all clinical studies, and (4) improve the therapeutic index of all topically applied glaucoma medications.

First, the Wall Street Journal published an article that stressed the importance of intelligible consent forms and informed consent for patients.25 This article states clearly that a description of risks and benefits, in simple terms, for patients and experimental subjects treated with medications or surgical procedures is a mandatory and essential part of informed consent. Withholding an explanation of how ELC for 5 minutes decreases systemic absorption by 65% and increases intraocular absorption by 65% prevents patients from considering these techniques as a less risky treatment that is more likely to be effective over simple eye drop instillation. Although every investigator and clinician may have a personal opinion as to the clinical importance of ELC for 5 minutes and its potential effect on patient adherence, it seems reasonable that all investigators share with their experimental subjects and patients a brief summary of the data that exist in the literature and suggest that these techniques are of great potential clinical value so that patients can make their own decisions.

Second, protocol consistency is essential for the integrity and comparability of clinical studies. It helps to provide reliable and reproducible data for clinicians to evaluate and use in their practice of evidence-based medicine. This consistency helps to minimize the variability of results. If a detailed description of eye drop administration is not included within the “Methods” section of a glaucoma protocol, the investigators and readers do not know how the subjects actually used their medication during the study. Some subjects may have performed 5 minutes of ELC, while others may not have used the technique at all. This inherent inconsistency in eye drop technique can be associated with up to 70% differences in ocular and systemic absorption of the study drug as discussed in the introduction of this article.1-9 An excellent editorial published in 2000 describes potential pitfalls in designing studies on efficacy and safety of glaucoma medications.26 Variable adherence to prescribed eye drop regimens adversely influence results in studies of medical treatments.

Third, the value of any properly designed clinical study is minimal if the results cannot be applied to pa...
tients within clinical practice. If a patient's characteristics or treatment differs significantly from that of the clinical study population, the study's conclusions should be applied with caution or perhaps not at all to this particular patient.27 Unfortunately, ophthalmologists who presently advocate NLO or ELC for 5 minutes following glaucoma medications within their practices will be unable to find studies that simulate their patients' treatment regimens.23 Clearly, this shortcoming limits the usefulness of all presently published studies of glaucoma medications for determining their safety and efficacy as used by these patients within these practices.

Fourth and most important, the greatest advantage of ELC for 5 minutes is an improved therapeutic index for the administered drug. Therapeutic index is defined as the ratio of the toxic dose for 50% of a population to the effective dose for 50% of the population.28 It is a reflection of how selective the drug is in producing its desired effects vs its adverse effects. The efficacy and toxicity are directly related to drug concentration. Therefore, ignoring the pharmacokinetic advantages of ELC for 5 minutes, which will result in minimal and variable intraocular absorption and maximal and variable systemic absorption, will potentially make the drug less effective and more toxic for the subject or patient. Furthermore, the studies ignoring the value of ELC are likely to report inaccurate and variable therapeutic indices for the drug.

Complex drug regimens are always inconvenient for the patient. A patient using maximal medical treatment (parasympathomimetic 4 times daily, sympathomimetic twice daily, carbonic anhydrase inhibitor 3 times daily, and prostaglandin analog and β-blocker once daily) must make a significant time commitment because the drops must be administered 5 or 10 minutes apart to prevent 1 drop from washing out the previous one. This regimen is obviously inconvenient with or without ELC for 5 minutes. These patients can spend an hour each day just waiting to instill the second or third eye drop. However, many patients devote an hour or more daily to physical exercise, meditation, or yoga to promote better cardiovascular, pulmonary, and mental health. Therefore, it is clear that some patients are willing to make serious time commitments for their general health and enhanced longevity. It follows that it should be the individual patient's decision if it is worth additional time to preserve his or her vision. Furthermore, this additional ocular time can often be incorporated into their existing systemic health regimens.

In an effort to improve adherence to an optimum ocular regimen, in addition to appropriate patient education about the importance of 5 minutes of ELC with eye drop administration, detailed instructions and appropriate labels should appear on prescription bottles given to patients and experimental subjects. For example, “Instill 1 drop in each eye every evening followed by 5 minutes of eyelid closure,” should be included on each prescription. This would ultimately appear within the directions placed on the bottle of prostaglandin analog dispensed by the pharmacist. After all, the patient may reason that if the instruction is not important enough to be placed on the bottle, it cannot be that important. In addition, a label reading, “Eyelid Closure for 5 Minutes,” should be affixed to the dispensed bottle. This is comparable with a “Shake Well” label. Pharmacists always dispense suspensions with a “Shake Well” label to insure that the proper amount of drug is present in each liquid dose. It is reasonable that a dispensed eye drop bottle should have an appropriate label to insure that the optimum amount of drug enters the eye and the minimum amount is systemically absorbed. In addition, adherence may be further enhanced by individualizing eye drop treatments and integrating these treatment regimens into the patient’s daily routine, even linking it with a specific activity.29-31 The details of these approaches have been previously discussed.23

In conclusion, it is only prudent that patients and experimental subjects be given complete instructions for eye drop use, including the importance of ELC for 5 minutes and its effects on absorption. Furthermore, written directions placed on the prescription container including an appropriate label emphasizing ELC for 5 minutes should reinforce this instruction. The goal of this additional activity is to achieve an optimum adherence, with an optimum regimen, associated with an optimum therapeutic index and resulting in an optimum therapeutic effect.

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