A method to evaluate the safety of an OTC ophthalmic solution in normal human volunteers

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Synopsis
The RABBIT model for ocular irritation and safety testing is much used and well documented, but HUMAN ocular irritation studies are not as available. A DOUBLE-BLIND, accelerated, one-day, human ocular irritation study was conducted prior to medical release of a reformulated proprietary ophthalmic preparation. Clinical SIGNS and SYMPTOMS were rated using a numerical severity scale.

INTRODUCTION
Methods of evaluating eye preparations from a human safety standpoint have remained somewhat obscure. Toxicology and predictive irritancy studies in animal models can be readily retrieved from the literature (1–4), but methods for human testing are not as available.

The rabbit is the species of choice for the preliminary evaluation of potential ocular irritation from toiletries, cosmetics and household products, as well as for proprietary and ethical ophthalmic preparations because the rabbit eye is more sensitive to irritation than the human eye (5). In addition, the standardization which exists for rabbit ocular irritation studies is well documented (6). Although the data generated in the rabbit model can prove most interesting and is extremely useful for predicting the potential for human ocular irritation, every eye product should be subjected to subsequent human safety testing prior to release to the marketplace.

The reformulation of an over-the-counter ophthalmic solution (Ocusol® Norwich-Eaton Pharmaceuticals) created the need for the evaluation of its ocular irritation potential.
Methods for evaluating human ocular irritation have been described for detergents (7) and cosmetic (8) preparations, but a lack of published methods exists for over-the-counter ophthalmic preparations; we therefore devised a one-day acute ocular irritation study. Sixty subjects were selected as being a large enough statistical sample. The evaluations by the investigators and the symptoms of the participants were all given numbers relative to the degree of severity.

EXPERIMENTAL PROCEDURE

We selected 61 normal men and women volunteers between the ages of 18 and 29 for the study. Each subject signed an informed consent after which a medical history was obtained. Then each subject underwent an ear, nose and throat examination as well as a slit lamp ophthalmological examination. Vital signs were also taken. All study subjects were found to be free from overt symptoms or clinical findings of ocular disease. The subjects were not allowed to smoke, wear contact lenses or eye make-up the day of the test. Any subject exhibiting signs or symptoms of an active upper respiratory infection, suffering from allergic rhinitis, or having taken antihistamines within seven days was excluded.

The study was conducted in a double-blind fashion. Each subject received the active solution (containing .05% tetrahydrozoline) in one eye and the placebo (the same vehicle but without the tetrahydrozoline) in the other eye. Neither the investigator nor the subject knew which eye had which solution.

Prior to dosing, each subject’s eyes were examined by the investigator and a baseline rating was obtained. The following clinical findings were rated on a scale from 0-5 (0 = none, 1 = mild, 2 = mild-moderate, 3 = moderate, 4 = moderate-severe, 5 = severe), for lacrimation, palpebral and bulbar conjunctival hyperemia, and lid edema. Each subject also gave his or her subjective opinion as to whether there was any burning, stinging or itching. The same numerical rating system was used by the subjects.

Each subject was randomly assigned two bottles of solution, both numbered by the subject number and labeled either A or B in such a manner that they could be readily distinguished, but the bottles and solutions appeared exactly alike. The investigator or a trained technician placed two drops of solution A in the right eye and two drops of solution B in the left eye of each subject. After administration the investigator waited 5 min and rated the clinical findings. The investigator also solicited the subjective evaluation of the subject as to the degree of discomfort, if any, he or she was experiencing. This was done after he had rated each eye.

This procedure was repeated every 3 hr for a total of four doses. The last dose was 9 hr from the first (i.e., 0, 3 hr, 6 hr, 9 hr). Thus each eye was rated by the investigator and the subject a total of four times.

RESULTS

For each clinical parameter, a scale of 0 to 5 was used to evaluate a reaction, with 5 being the most severe. Four such parameters were evaluated by the investigator at each of the four dosing periods; a cumulative maximum grade of 80 was possible per
Figure 1. These cumulative irritancy scores combine both the investigator's scores for signs of ocular irritation and the subject's scores for symptoms. The following scale was used: 0 = none, 1 = mild, 2 = mild-moderate, 3 = moderate, 4 = moderate-severe, 5 = severe.

Figure 2. Distribution of scores, includes those subjects who had no irritation, those with a single occurrence of rated irritation and those with multiple occurrences. The four signs and three symptoms were rated a total of four times after each of the four dosing periods.
subject. The three subjective parameters were also rated by every subject at each dosing period yielding a cumulative maximum score of 60 per subject.

As shown in Figure 1, nine of the subjects' eyes had a combined cumulative (combines both the investigators' clinical scores and the subjects' scores, with 140 the maximum) ocular irritation score of greater than 5, but only three subjects among this group showed clinically mild ocular irritation. One of these volunteers scored 6 for both the active and the placebo solution, the second subject showed 3 for the active and 7 for the placebo, the third scored an 8 for the placebo, 5 for the active. These same participants were also the only ones to have a 2 or 3 rating on any clinical parameter (Figure 2).

Several subjects had scores of 1 on their pre-dose readings and a few showed 2. These scores were generally limited to palpebral and bulbar conjunctival hyperemia. During the testing period it was observed that the overwhelming majority of clinical scores were for mild palpebral and bulbar conjunctival hyperemia. As would be expected, due to the vasoconstrictive properties of tetrahydrozoline, fewer of the eyes which received the active solution containing tetrahydrozoline exhibited conjunctival hyperemia than those eyes which received the placebo.

Those subjects who had either positive clinical scores or who experienced some subjective symptoms from either the active or the placebo, were fairly evenly distributed throughout the four evaluation periods; thus it appears that no cumulative dose-response effect versus time took place.

**DISCUSSION**

Safety and efficacy are extremely critical for eye preparations. Whereas a patient or consumer might tolerate slight irritation from a skin lubricating lotion, such stinging in the eye would spell the death knell of the ophthalmologic. A vesiculobullous eruption on the back might be uncomfortable but this would be insignificant compared to permanent corneal damage from a new product.

Although exaggerated usage studies in the rabbit are helpful and offer good predictions for human testing, nothing can replace trial in a human population. Some changes might be so subtle that most users would never be aware of the incurred damage from a product. As a result, a carefully monitored safety study becomes a must. Our method provides a single-day accelerated dosing schedule relative to the recommended dosage of the product. With the repeated instillation of eye drops, the subject is given far more chance to react than in a routine clinical trial which employs the normal dosing schedule.

The test product proved to be nonirritating; however, if more than a few reactions had been observed, then a five-day irritancy protocol (9) would have been initiated.

By conducting the study under double-blind controlled circumstances, several pitfalls are avoided. Subjects are told one eye will receive the active solution and the other eye a harmless eye wash. This tends to minimize their biases and helps to allay some of their prestudy anxiety. Similarly, prohibiting interference from outside sources, such as smoking, the wearing of eye cosmetics and contact lenses, allows a true testing of the preparation.
REFERENCES


