Comparison of Superficial Punctate Keratitis Induced by Fluorocaine and Flurate

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Abstract: This study was conducted to compare the corneal epithelial toxicity affects of two topical anesthetic-fluorescein combinations commonly used for Goldmann applanation tonometry, Fluorocaine (proparacaine hydrochloride 0.5% with sodium fluorescein 0.25%) and Flurate (benoxinate hydrochloride 0.4% with sodium fluorescein 0.25%). A double blind study was conducted in which the bottles of anesthetic-fluorescein were disguised with label A (Flurate) and label B (Fluorocaine) both of which were unknown to the examiner and to the patient. One drop of Flurate went to one eye and one drop of Fluorocaine went to the other eye prior to performing Goldmann tonometry. Both eyes then received one drop of 1% tropicamide and 2.5% phenylephrine. Later, both eyes were observed by a second clinician to determine the amount of SPK produced in each eye. The results were recorded as well as which drops went to which eye and tabulated to compare the effects of each combination anesthetic in 60 patients. This experiment showed that proparacaine 0.5% combined with 0.25% sodium fluorescein showed a slightly greater toxic epithelial effect than 0.4% benoxinate combined with 0.25% sodium fluorescein.

Goldmann applanation tonometry requires the use of an anesthetic and fluorescein. This may be achieved by using a combination drop that contains both anesthetic and fluorescein or by applying an anesthetic initially, then instilling fluorescein separately. In this double-blind study we monitored if there was a difference in the amount of superficial punctate keratitis (SPK) induced by a fluorescein-proparacaine hydrochloride (Fluorocaine) combination compared to a fluorescein-benoxinate hydrochloride (Flurate) combination.

Materials and Methods

The commercially produced Fluorocaine by Akron and Flurate by Bausch and Lomb were used as the test drops. Unopened, fresh bottles of the Flurate and Fluorocaine were labeled A and B respectively. The experimenters instilling the drops had no prior knowledge of the bottle size (this was necessary because the Fluorocaine bottle is slightly narrower than the Flurate). Fluorocaine is 0.5% proparacaine combined with 0.25%

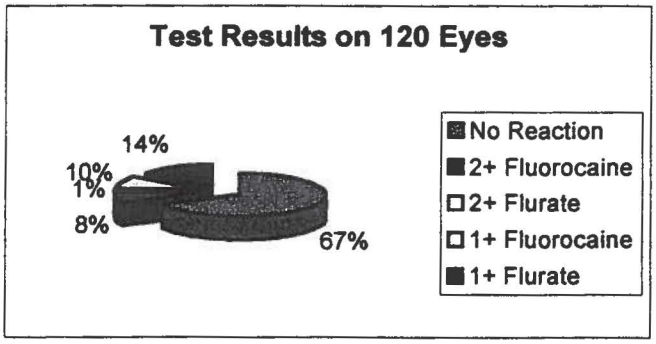
fluorescein and Flurate is 0.4% benoxinate with 0.25% fluorescein. Flurate is a generic version of Fluress. Slit-lamp biomicroscopy was used to evaluate the cornea for SPK.

Clinical Procedure

During the routine exam, the patient was instilled in one eye with Fluorocaine and the other eye with Flurate. The drops were alternated to different eyes for each trial. Goldmann applanation tonometry was performed and the patient was dilated using 1% tropicamide and 2.5% phenylephrine. Approximately fifteen minutes later when the patient was dilated, a second clinician assessed the cornea for SPK. SPK was graded from 0 (no cells lose) to 4+ (entire cornea). The clinician evaluating the cornea had no knowledge of what labeled drop was instilled into either of the eyes. At the end of the exam, the patient was asked if either eye felt irritated.

Data

A total of sixty patients were evaluated. Of these sixty, 39 (65%) patients were graded as having no SPK, 8 (13%) patients had a 2+ reaction to Fluorocaine in one eye and a 1+ to the Flurate. Nine (15%) patients had an equal 1+ reaction to both drops while 3 (5%) patients had a 1+ reaction to Fluorocaine and no reaction to Fluress. One (1.6%) patient showed a 2+ SPK to both Fluorocaine and Flurate. Twenty-seven complaints of eye pain were reported, only 6 patients reported that one eye hurt more than the other. Four patients reported that the eye that Fluorocaine was more uncomfortable.



Discussion

All topically applied anesthetics reduce corneal sensitivity by blocking sodium channels at the nerve cell membrane. By blocking the channels, the anesthetics prevent the conduction of pain signals via the afferent nerves.[1,3,4,6] Benoxinate and proparacaine have quick onsets of 20 and 15 seconds respectively, but the duration of proparacaine is 14 minutes compared to 10 minutes for benoxinate.[1] It has been demonstrated that lower than commercially available concentrations of benoxinate and proparacaine would provide sufficient anesthesia for applanation tonometry.[1] The amount of anesthesia produced by proparacaine and benoxinate are similar.[1]

The suggested method by which anesthetic causes an SPK is two fold: exposure and tear film instability.[6] Anesthetic use causes shorter tear break-up times, decreased blink rate and reflex tearing, thus increasing tear film evaporation and SPK. The keratitis will not manifest initially but after a short period of time it will become more apparent. Both proparacaine and benoxinate have been shown to cause allergic reactions but these are rare.[1,6] A separate study indicated that proparacaine can cause cell sloughing up to 6 hours after installation.[7] Proparacaine is less toxic than tetracaine to the cornea, however no studies could be found to compare benoxinate and proparacaine toxicity.[4] No cross sensitivities have been observed, hence if a patient is allergic to benoxinate, it is safe to try to use proparacaine.[1]

Flourocaine's active ingredients, as noted previously, are proparacaine hydrochloride 0.5% and fluorescein sodium 0.25%. This solution is preserved with thimerosol 0.01%. It also contains povidone, glycerin, boric acid, polysorbate 80, purified water, and sodium hydroxide and/or hydrochloric acid to control pH. Fluorocaine is

indicated for tonometry, gonioscopy, removal of corneal foreign bodies, and short term corneal and conjunctival procedures requiring anesthesia. The recommended dosage is 1-2 drops in each eye. For deeper anesthesia, 1 drop every 5-10 minutes for 5-7 doses is recommended. It is also recommended that Fluorocaine be stored at 2-6 degrees Celsius before and after opening and away from sunlight.

Flurate's active ingredients are benoxinate hydrochloride 0.4% and fluorescein sodium 0.25%. It also contains povidone, boric acid purified water, and hydrochloric acid. Flurate contains chlorobutanol 1% as preservative, which may offer to be advantageous in those patients with known sensitivity to thimerosol. The recommended dosage for Flurate is also 1-2 drops prior to performing the procedure. Flurate should also be stored at 2-6 degrees Celsius, but may be kept at room temperature for up to 1 month after opening unlike Fluorocaine. Although both Fluorocaine and Flurate are effective against microbial contamination, Flurate has been shown to have more rapid, self-sterilizing properties than Fluorocaine.[5]

Mydriacyl contains 1% tropicamide along with sodium chloride, edetate disodium, purified water, and hydrochloric acid and/or sodium hydroxide to control pH. Mydriacyl is preserved with benzalkonium chloride 0.01%. Phenylephrine hydrochloride 2.5% is also preserved with benzalkonium chloride. Other ingredients include dibasic and monobasic sodium phosphate and boric acid. Phosphoric acid or sodium hydroxide may be added to control pH. Mydriacyl has been shown to cause SPK, however this amount should be constant since both eye received equal amounts.[1]

Topical anesthetics have been shown to reduce epithelial healing times.[6,8,9] The suggested mechanism is dissociation of the vinculin-based epithelial cell motility

complexes responsible for cell migration.[6] Proparacaine has been shown to cause significant loss of surface microvilli and microplicae after a signal dose.[6]

Topical anesthetic abuse has been widely documented to cause severe toxic keratitis. Patients suffering corneal abrasions and various injuries can over use medications, thus increasing healing times.[1,2,6,8,9] Secondary fungal infections to corneal anesthetic abuse have been observed.[9]

Summary

The clinical trial demonstrated that Fluorocaine caused a greater number of SPK reactions then Flurate. Although it is likely that this difference is caused by the anesthetics (proparacaine vs. benoxinate), we cannot rule out that the difference may be induced by the preservatives (thimerosol vs. chlorobutanol). One subjective finding by the clinicians was that the mires observed with Goldmann tonometry were much thinner on average in the Fluorocaine trials versus the Flurate trials. The clinicians reported that this difference in mire thickness made it easier to measure the intraocular pressure in the Fluorocaine trials.

Potential experimental design flaws include the subjective nature of evaluating the amount of SPK. Photodocumentation would prove to be a more objective method of evaluating the degree of SPK. A second potential flaw is that the preservatives may have induced SPK. Using nonpreserved benoxinate and proparacaine solutions combined with fluorescein would eliminate this factor.

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