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Clinical study comparing ketorolac tromethamine with diclofenac sodium for the treatment of ocular surface inflammations

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Abstract

Thirty patients with various ocular surface inflammations were enrolled in a double-masked study comparing ketorolac tromethamine 0.5% (Acular) and diclofenac sodium 0.1% (Voltaren Ophthalmic). At the initial visit, baseline measurements of various inflammatory signs were taken. The patients were instructed to use Acular in one eye and Voltaren Ophthalmic in the other eye four times a day for a period of seven days. After this seven day treatment period, the patients completed a questionnaire and were evaluated for signs of inflammation. At this time, the drops were reversed for each eye. Once again the patients were instructed to use the drops four times daily for seven days. After this second week of treatment the patients were reevaluated for signs and symptoms of inflammation. Quantification of signs and symptoms occurred at the one week and two week evaluations. After two weeks the Acular-treated eyes showed significant decreases in conjunctival injection ($p = 0.0192$), tear debris ($p = 0.0052$), papillae ($p = 0.0092$), and follicles ($p = 0.0046$) compared to baseline. The Voltaren Ophthalmic-treated eyes showed significant decreases in chemosis ($p = 0{,}0113$), conjunctival injection ($p = 0.0268$), tear debris ($p = 0.0373$), papillae ($p = 0.0068$), and follicles ($p = 0.0039$). Subjectively patients found more overall satisfaction with Voltaren Ophthalmic than with Acular ($p = 0.0010$). Results of this study show that both Acular and Voltaren Ophthalmic are effective in reducing the signs of ocular surface inflammations.

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CLINICAL STUDY COMPARING KETOROLAC TROMETHAMINE WITH DICLOFENAC SODIUM FOR THE TREATMENT OF OCULAR SURFACE INFLAMMATIONS

By

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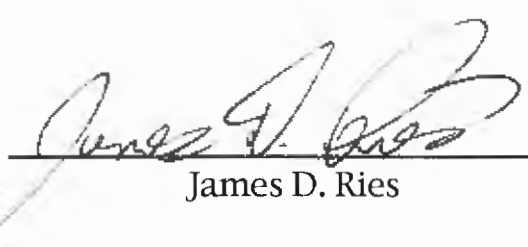

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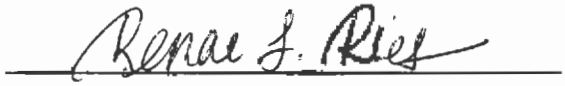

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Biographies

James D. Ries received a Bachelor of Science degree from the University of South Dakota in May of 1992. He is currently attending Pacific University College of Optometry with an expected graduation date of May 1996. His future plan is to practice full scope optometry and to become an associate member of an established practice with future intentions of purchasing a practice. He would like to work in the midwest with emphasis on South Dakota.

Renae L. Ries graduated from the University of South Dakota with a Bachelor of Science degree in May of 1992. She went on to attend Pacific University College of Optometry with an expected graduation date of May 1996. While at Pacific University, she has been a recipient of the Vincent Salierno scholarship and the Peg Gilbert award for excellence in visual science. She is also a member of Beta Sigma Kappa optometric honor society.

She plans to practice full scope optometry as an associate in a private practice with plans to become an eventual partner in the practice. She would like to locate somewhere in the midwest.

Abstract

Thirty patients with various ocular surface inflammations were enrolled in a double-masked study comparing ketorolac tromethamine 0.5% (Acular) and diclofenac sodium 0.1% (Voltaren Ophthalmic). At the initial visit, baseline measurements of various inflammatory signs were taken. The patients were instructed to use Acular in one eye and Voltaren Ophthalmic in the other eye four times a day for a period of seven days. After this seven day treatment period, the patients completed a questionnaire and were evaluated for signs of inflammation. At this time, the drops were reversed for each eye. Once again the patients were instructed to use the drops four times daily for seven days. After this second week of treatment the patients were reevaluated for signs and symptoms of inflammation. Quantification of signs and symptoms occurred at the one week and two week evaluations. After two weeks the Acular-treated eyes showed significant decreases in conjunctival injection ($p = 0.0192$), tear debris ($p = 0.0052$), papillae ($p = 0.0092$), and follicles ($p = 0.0046$) compared to baseline. The Voltaren Ophthalmic-treated eyes showed significant decreases in chemosis ($p = 0,0113$), conjunctival injection ($p = 0.0268$), tear debris ($p = 0.0373$), papillae ($p = 0.0068$), and follicles ($p = 0.0039$). Subjectively patients found more overall satisfaction with Voltaren Ophthalmic than with Acular ($p = 0.0010$). Results of this study show that both Acular and Voltaren Ophthalmic are effective in reducing the signs of ocular surface inflammations.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-pyretic, and anti-inflammatory activities. The major mechanism of action of NSAIDs is believed to be their ability to inhibit the cyclo-oxygenase pathway and therefore inhibit prostaglandin synthesis. Prostaglandins are mediators of inflammation which are believed to have the following ocular effects: elevation of intraocular pressure, dilation of ocular blood vessels, and pupillary miosis. Prostaglandins have been isolated from the ocular tissue and aqueous of inflamed eyes.[1]

Topical NSAIDs available for ophthalmic use include ketorolac tromethamine 0.5% (Acular) and diclofenac sodium 0.1% (Voltaren Ophthalmic). The Food and Drug Administration (FDA) has approved the use of Acular for the treatment of itching associated with seasonal allergic conjunctivitis. Acular is a member of the pyrrolo-pyrolle group of NSAIDs. The typical dosage regimen for Acular is one drop four times a day. Acular's efficacy has not been established beyond one week of treatment. The FDA has approved the use of Voltaren Ophthalmic for the treatment of postoperative inflammation following cataract extraction. Voltaren Ophthalmic is one of a series of phenylacetic acids. The typical dosage regimen for Voltaren Ophthalmic is one drop four times a day beginning 24 hours after cataract surgery and continuing for two weeks after the surgery.

Other applications for both Acular and Voltaren Ophthalmic have been suggested. Studies have shown Acular to be an effective treatment in decreasing the signs and symptoms of seasonal allergic

contact lenses. This study was approved by the Institutional Review Board and all patients were required to sign an informed consent document prior to participation in the study.

A file was developed for each study patient which contained the informed consent document, patient instructions for use of the drops, intern instructions of the study protocol, two subjective questionnaires (one week and two week follow-up), three objective recording forms (baseline, one week and two week follow-up), grading scales for inflammatory signs, and the masked bottles of NSAIDs. Both NSAID bottles were covered with white labels and marked with either "R" for right eye or "L" for left eye.

Baseline measurements of lid edema, chemosis, conjunctival injection, tear debris, papillae, follicles, fluorescein staining, rose bengal staining, cells, and flare were taken on all patients using slit-lamp biomicroscopy prior to entrance into the study. Noted signs of inflammation were rated as follows: 0 = none, 1 = trace, 2 = mild, 3 = moderate, and 4 = marked. Intraocular pressure (IOP) was measured on all patients using Goldmann applanation tonometry.

Patients selected for the study were then randomly assigned the use of Acular on one eye and Voltaren Ophthalmic on the other eye. Patients were asked to administer one drop of the assigned agents to each eye four times daily for a period of seven days. After the completion of seven days of therapy, all objective measurements were retaken, qualified, quantified, and documented for the purpose of comparing initial findings to those observed after one week of treatment. At this time patients were also asked to fill out a subjective questionnaire which included the following items for each

of the treated eyes: itching of eyes immediately before using drops, itching of eyes one minute after using drops, pain immediately before using drops, pain one minute after using drops, stinging caused by drops, burning caused by drops, excessive tearing, photophobia, unusual discharge from eyes, halos in vision, excessive blinking, variable vision, and overall satisfaction with the eyedrops. A rating scale of 0 to 4 was used to quantify the subjective impressions with 0 = none, 1 = rarely occurs, 2 = intermittently occurs, 3 = almost always occurs, and 4 = always occurs. At the conclusion of the first reexamination, the patients were instructed to reverse the two eyedrops. The drop that had previously been used to treat the right eye was switched to be used on the left eye, and vice versa. The patients were again told to use each of the drops four times daily for a period of seven days. At the conclusion of this seven day treatment period, slit-lamp biomicroscopy was repeated with findings rated using the standard rating scale previously mentioned. Once again patients were asked to complete a subjective questionnaire comparing symptoms experienced for each of the treated eyes. Items included were identical to those of the first questionnaire administered.

Data gathered from the objective and subjective rating scales were analyzed separately using the Wilcoxon signed-rank test with a significance level of $p < 0.05$. The one week findings in the Acular-treated eye were compared to the initial findings of that same eye; the one week findings in the Voltaren Ophthalmic-treated eye were compared to the initial findings of that same eye. Also compared after one week were subjective impressions of Acular versus

Voltaren Ophthalmic. After the second week of treatment, findings from the eye that was being treated with Acular were compared to the initial findings from that same eye; findings from the eye that was being treated with Voltaren Ophthalmic were compared to the initial findings from that same eye. Also compared after the second week were subjective impressions of Acular versus Voltaren Ophthalmic.

Results

There were 30 patients with ocular surface inflammation enrolled in this study. After one week of treatment, 29 patients were allowed to continue in the study (one patient was discontinued due to an allergic reaction). After the second week, 26 patients were evaluated (three patients failed to return for their second week evaluations). An additional eight subjects with no signs or symptoms of ocular surface inflammation were used as a control group.

After one week of treatment, Acular-treated eyes had a significant decrease in the amount of rose bengal staining observed ($p = 0.0423$). The Voltaren Ophthalmic-treated eyes had a significant decrease in tear debris ($p = 0.0052$) and follicles ($p = 0.0330$). No significant decrease or increase was noted in the other objective measurements (table 1). One patient was discontinued from the study at this point due to an allergic reaction to the Voltaren Ophthalmic. This patient experienced an increase in chemosis, conjunctival injection, papillae, fluorescein staining, and rose bengal staining.

Subjective impressions after one week of treatment showed more stinging ($p = 0.0192$) and excessive tearing ($p = 0.0277$) with the use of Acular than with Voltaren Ophthalmic. No statistical significance was noted in any of the other subjectively rated items (table 2).

After the second week of treatment, the Acular-treated eyes showed a significant decrease in conjunctival injection ($p = 0.0192$), tear debris ($p = 0.0052$), papillae ($p = 0.0092$), and follicles ($p = 0.0046$) compared to the initial findings of the same eye. The Voltaren Ophthalmic-treated eyes showed a significant decrease in chemosis ($p = 0.0113$), conjunctival injection ($p = 0.0268$), tear debris ($p = 0.0373$), papillae ($p = 0.0068$), and follicles ($p = 0.0039$) compared to the initial findings of the same eye. No statistical significance was noted in any of the other objective measurements (table 1).

Subjective impressions after the second week showed more itch immediately before using the drops in the Acular-treated eye as compared to the Voltaren Ophthalmic-treated eye ($p = 0.0277$). Also noted was more burning ($p = 0.0121$) and excessive tearing ($p = 0.0431$) in the eyes treated with Acular as compared to those treated with Voltaren Ophthalmic. Subjectively more overall satisfaction was found with Voltaren Ophthalmic than with Acular ($p = 0.0010$) at the conclusion of the second week (table 2).

No statistical significance was noted in any of the objective measurements or subjective impressions for the control group.

Discussion

This study suggests that both Acular and Voltaren Ophthalmic are effective in reducing ocular surface inflammation and that both signs and symptoms are reduced, irrespective of the inflammatory "trigger". Several sterile inflammations were treated, and many were relieved by NSAID treatment.

After one week of treatment with Acular the only significant finding was a decrease in rose bengal staining. After the second week of treatment, the Acular-treated eyes showed significant decreases in conjunctival injection, tear debris, papillae, and follicles compared to baseline. There was also a decrease in chemosis that approached significance ($p = 0.0630$). All of these signs are consistent with those found in seasonal allergic conjunctivitis for which Acular is indicated.

Following one week of treatment with Voltaren Ophthalmic, significant decreases were noted in tear debris and follicles. At the conclusion of the second week, the Voltaren Ophthalmic-treated eyes showed significant decreases in chemosis, conjunctival injection, tear debris, papillae, and follicles.

Subjectively after one week of treatment, significantly more stinging and tearing were noted with Acular than with Voltaren Ophthalmic. At the conclusion of the first week of treatment, there was no statistical significance noted in the level of overall satisfaction between the two treatments. After the second week of treatment, patients noted significantly more itching in the Acular-treated eye than in the Voltaren Ophthalmic-treated eye immediately before

using the drops. Once again with the use of Acular there was significantly more burning and tearing noted than with Voltaren Ophthalmic. At this point, subjectively, there was also significantly more overall satisfaction with Voltaren Ophthalmic than with Acular.

Our findings suggest that both Acular and Voltaren Ophthalmic were effective in reducing the signs and symptoms of ocular surface inflammation although Voltaren Ophthalmic was significantly preferred by the patients.

Other studies have found decreases in ocular itching, conjunctival inflammation and injection, discharge/tearing, and foreign body sensation after one week of treatment with Acular.[2,3] Voltaren Ophthalmic has previously been shown to significantly reduce conjunctival injection, ciliary flush, and overall inflammatory response.[5]

Previous studies have found burning and stinging upon instillation to be the most common adverse effect noted with the use of Acular.[2,3] A transient burning sensation upon instillation has also been noted previously with the use of Voltaren Ophthalmic.[8]

Our findings may differ from those of other studies due to the fact that we were treating various ocular surface inflammations rather than strictly seasonal allergic conjunctivitis or postoperative inflammation.

Throughout the entire study no serious adverse reactions occurred with the use of Acular. One patient did experience an allergic reaction to Voltaren Ophthalmic. This patient was found to have an increase in lid edema, chemosis, conjunctival injection, papillae, follicles, fluorescein staining, and rose bengal staining in the

Voltaren Ophthalmic-treated eye. Upon discovery of the allergic reaction, the patient was withdrawn from the study and instructed to immediately discontinue use of Voltaren Ophthalmic. A follow-up appointment showed a decrease in allergic signs and symptoms within 24 hours after discontinuation of the Voltaren Ophthalmic. Caution should be used when prescribing NSAIDs due to other adverse effects which have been noted including photophobia, gastric sensitivity, and increased bleeding time.[9]

Neither Acular nor Voltaren Ophthalmic was found to have a significant effect on IOP when used in the treatment of ocular surface inflammations. Previous studies have also found no significant difference in the level of intraocular pressure when using Voltaren Ophthalmic[5,8,10] or Acular[4] for the treatment of inflammation following cataract extraction. Both Acular[4] and Voltaren Ophthalmic[11,12] have been found to be as effective as steroids in treating postoperative inflammation after cataract surgery. An advantage of treating such ocular inflammation with these NSAIDs is the fact that they have not been shown to cause the increase in IOP which most steroids are known for.

Conclusion

Although Acular is only indicated for the treatment of allergic conjunctivitis and Voltaren Ophthalmic for postoperative inflammation following cataract extraction, this study suggests that both of these NSAIDs are effective in the treatment of various ocular surface inflammations. This conclusion is supported by others who

have also suggested that these NSAIDs may be useful in a variety of inflammatory ocular conditions.[8,13] Further investigation into this area would prove beneficial to those patients who suffer from various forms of ocular inflammation and to the field of optometry.

Table 1: p-values

	comparison at 1 week- Acular to initial	comparison at 1 week- Voltaren to initial	comparison at 2 weeks- Acular to initial	comparison at 2 weeks- Voltaren to initial
lid edema	0.7532	0.7532	0.1422	0.1422
chemosis	0.0858	0.0972	0.0630	0.0113
conj. injection	0.2787	0.1307	0.0192	0.0268
corneal edema	0.1797	0.1797	0.1797	0.1797
tear debris	0.0535	0.0052	0.0052	0.0373
cells	0.0000	0.0000	0.0000	0.0000
flare	0.3173	0.3173	0.3173	0.3173
papillae	0.1579	0.1166	0.0092	0.0068
follicles	0.0910	0.0330	0.0046	0.0039
NaFl staining	0.1097	0.2026	0.5303	0.7213
rose beng. stain	0.0423	0.1282	0.2936	0.1235
IOP	0.6101	0.7764	0.7299	0.4074

All of the signs listed above, with the exception of cells and IOP, showed a decrease following one and two weeks of treatment.

Table 2: p-values

	comparison at 1 week-Acular to Voltaren Ophthalmic		comparison at 2 weeks-Acular to Voltaren Ophthalmic	
itching immed. before drops	0.5930	A	0.0277	V
itching 1 min. after drops	0.9165	A	0.0759	V
pain immed. before drops	0.1797	A	0.3173	V
pain 1 min after drops	0.4227	V	0.6858	V
stinging caused by drops	0.0192	V	0.0692	V
burning caused by drops	0.0995	V	0.0121	V
excessive tearing	0.0277	V	0.0431	V
photophobia	0.3173	A	0.3173	V
unusual discharge	0.3173	A	1.0000	
halos in vision	0.0000		0.3173	A
excessive blinking	0.0000		0.1797	V
variable vision	1.0000		0.1797	V
overall satisfaction	0.0843	V	0.0010	V

A = Acular
V = Voltaren Ophthalmic
These symbols within the table denote that drop which produced the fewest symptoms, except for overall satisfaction where the symbol denotes that drop which produced the greatest satisfaction.

Table 3

	week 1	week 2
lid edema	A = V	A = V
chemosis	A	V
conj. injection	V	A
corneal edema	A = V	A = V
tear debris	V	A
cells	none reported	none reported
flare	A = V	A = V
papillae	V	V
follicles	V	V
NaFl staining	A	A
rose beng. stain	A	V

A = Acular
V = Voltaren Ophthalmic
The symbols in the chart denote that drop which had the greatest effect on reducing the given signs of inflammation.

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