
Ara-A ointment was compared to IDU ointment in patients with dendritic herpes simplex virus infection of the corneal epithelium. Twenty-eight patients were treated with Ara-A ointment and twenty-four with IDU ointment. The lesions healed in 5.1 days with Ara-A and in 6.9 days with IDU. This drug was given in a double-controlled manner, so that neither the patient, nor the investigator knew which drug the patient was receiving. The patient groups were comparable as to length of the dendritic lesion and duration of symptoms. The adverse reactions to each of these drugs were comparable and in no case was there any permanent ocular change from drug use.

IDU, the only drug approved by the Food and Drug Administration for use in human herpetic keratitis is not effective in all cases of this disease. There is occasionally toxicity after prolonged IDU use, and rarely viral resistance.

A new antiviral, adenine arabinoside (Ara-A) will soon be available for the treatment of herpes simplex keratitis. Ara-A is a nontoxic inhibitor of viral replication which acts intracellularly but does not incorporate into the DNA molecule as does IDU. Earlier studies found it equally effective to IDU in human herpetic keratitis and possibly useful for adenovirus keratoconjunctivitis. Recent reports documented its efficacy in IDU unresponsive or IDU toxic cases, but ineffective-ness for the treatment of various strains of adenovirus infection treated in the acute stage.

In order to more accurately determine the efficacy of (Ara-A) for corneal epithelial herpetic disease we compared it to IDU, the current drug of choice for this disease, in a double-controlled clinical trial. Patients with dendritic lesions and small geographic ulcers seen in superficial herpetic keratitis were selected for "double-blind" treatment since the end-point of epithelial healing could be judged most clearly in these cases. Sixty-four patients were studied. Each had a typical dendritic or small geographic ulcer pathognomonic of herpetic simplex keratitis. Thirty-one patients received 3.0 per cent Ara-A ointment and thirty-two patients were given 0.5 per cent IDU ointment. No one was included who had been taking an antiviral drug or corticosteroid topically in the preceding months before entering the study. Half the patients in each treatment group had a past history of ocular herpetic keratitis, but there was no active disease in any patient for the prior three months before entering the study.

The corneal ulcer area was measured with the Haag-Streit slit lamp vernier scale and the findings were drawn on a protocol sheet. The patient was instructed to use the antiviral ointment every four hours while awake and shown the exact means of application to the eye by pulling down the lower lid and placing the ointment in the lower cul-de-sac. The lid was held down for thirty seconds so that the ointment had a chance to melt and layer across the cornea. Visual acuity and intraocular pressure were documented.

Healing of the epithelial lesion by day fourteen, was the chief criteria for judging successful treatment. A failure was defined as (1) no improvement, (2) epithelial ulcer enlargement by day seven, (3) failure to re-epithelialize by day fourteen or, (4) breakdown of healed epithelium after tapering the drug between day fourteen and day twenty-one.

Patients were examined just prior to drug use, two days after treatment began, and then every three or four days for two weeks. They were also examined three weeks from the start of treatment at which time therapy was discontinued if it had not been completed, or the patient was switched to known IDU if there was still corneal staining and medication was required.

Results. Upon opening the code at the completion of the study, thirty-one patients had used Ara-A initially, and thirty-three IDU ointment. Twenty-eight patients in the Ara-A group had had dendritic lesions which averaged 4.8 mm. in length, while twenty-six patients in the IDU treatment group had dendritic lesions measuring 3.7 mm. in length. Two patients treated with Ara-A ointment, had dendritic geographic ulcers and one a geographic ulcer alone. Five patients in the IDU group had dendritic geographic ulcers, while two had only geographic lesions.

In the Ara-A dendritic lesion group, duration of symptoms was 5.7 days, while in the IDU series it was 4.6 days.

Since there were few patients with geographic or dendritic geographic ulcers in each treatment group, comparison of IDU and Ara-A treatment in these patients was not undertaken. There were twenty-eight patients with dendritic lesions who were treated with Ara-A and twenty-six patients who were treated with IDU. The average days to re-epithelialization in the Ara-A group was 5.1 while in the IDU group, it was 6.9. The end-point of healing was taken as the day that no epithelial ulcer staining was noted in the dendritic bed. Punctuate epithelial staining with fluorescein or Rose Bengal was not considered in this end-
point as most patients had lingering superficial punctuate epithelial stain for several days after healing of the epithelial ulcer. In several patients the stain did not disappear until medication was discontinued.

There were few adverse reactions in each treatment group. In the Ara-A treatment group, one patient developed marked superficial punctate staining after seven days of topical Ara-A ointment. When Ara-A was discontinued, the superficial staining disappeared. A second patient on Ara-A developed secondary glaucoma and anterior uveitis while on therapy fourteen days after initiation of the drug. The reaction could have been caused from herpes simplex virus or reaction to virus, however, this was included as a possible adverse reaction to Ara-A. Using diamox, and later IDU and low-dose topical steroids, the eye quieted. A third patient on Ara-A developed a punctate occlusion. This disappeared on cessation of drug. A fourth patient developed stromal edema while on therapy. The edema could have been a result of the herpes simplex virus invading stroma, or a stromal reaction to toxic or other products. This may also have been an immunologic manifestation of the disease which could not be helped by Ara-A.

In the IDU treatment group, two patients developed stromal edema while under therapy, one patient had a recurrence of herpes simplex virus infection in a dendritic pattern, nineteen days after initiation of IDU. A fourth patient had increased corneal edeema or enlargement of the dendritic lesion nine days after the IDU was started. This patient was switched to known IDU and dendritic lesions finally resolved one week later.

Discussion. Epithelial herpes simplex virus infection in man is a variable disease which clears spontaneously in approximately one quarter of the cases on just placebo therapy.5 Double-controlled studies, therefore, are necessary to effectively evaluate new modes of therapy in the disease. Comparing new drugs to the standard of therapy, IDU ointment, is a convenient way to plan a controlled study of a new antiviral agent. It is preferable for the new agent to be in ointment form, so that the investigator and the subject recognizes no difference in medication. Every superficial herpetic lesion in man, eventually does clear, but the goal is to have rapid clearing of the surface lesion without stromal involvement, vascularization, thinning, or recurrent herpetic keratitis.

Ara-A was as effective as IDU in the treatment of superficial dendritic herpetic simplex virus infection in this study. Patients on Ara-A did not complain of burning or irritation. The only sign of a possible toxic reaction was the development of punctate occlusion in one patient. This subsided when the drug was discontinued. In some patients, there was a mild opacity or anterior stromal ghost figure beneath the dendritic lesion. This had been previously seen in patients treated with IDU or who underwent mechanical or chemical debridement. These changes also occurred in patients receiving Ara-A. We attribute these superficial stromal changes to the disease, and not to antiviral therapy. New derivatives of Ara-A are under investigation, (adenine arabinoside monophosphate Ara-AMP) which have far greater solubility and may be more effective in man.5

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REFERENCES

Ascorbic acid stimulates chloride transport in the amphibian cornea. WALTER N. SCOTT* AND DEBORRA F. COOPERSTEIN.**

Ascorbic acid stimulates chloride transport in the amphibian cornea. Walter N. Scott* and Deborra F. Cooperstein.**

The cornea of the toad, Bufo marinus, actively transports chloride from the endothelial to the epithelial surface. This transport process has been related to the maintenance of the normal transparency of the cornea. Ion transport, as evidenced by the short-circuit current (SCC), is markedly

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