A STUDY OF THE USE OF 5 IODO-2′-DEOXYURIDINE IN CUTANEOUS HERPES SIMPLEX*

JOSEPH W. BURNETT, M.D.† AND SAMUEL L. KATZ, M.D.‡

Recent studies of the effects of 5-bromo- and 5-fluoro-2′-deoxyuridine demonstrated that these compounds interfered with both normal deoxyribonucleic acid (DNA) synthesis as well as viral DNA synthesis in animal and bacterial cells (1, 2, 3). A third member of this same series, 5-iodo-2′-deoxyuridine (IDU) was subsequently found to be an effective inhibitor *in vitro* of 2 DNA viruses, vaccinia and herpes simplex (4). With this background, Kaufman *et al* (5) reported in 1962 that when a supersaturated aqueous solution of IDU was placed every two hours in the conjunctival sac of humans and rabbits with herpes simplex keratitis, the viral infection subsided markedly within two days.

This effect of IDU on ocular herpes simplex stimulated a double-blind, controlled study of the therapeutic value of topically administered IDU in *cutaneous* herpes simplex. Twenty-six patients (14 test subjects; 12 controls) with cutaneous herpes simplex were included in the group studied. Nine patients were hospitalized, 17 lived outside the hospital during the course of the investigation. The latter were instructed to apply the test creams to their lesions every two hours while awake for a total of 8–9 applications daily. Hospitalized patients received 12 applications during each 24 hours. On the initial visit, each patient was examined and questioned about the length, frequency and severity of prior attacks of herpes simplex, and a viral culture of the lesion was taken after the involved skin had been washed with alcohol. Thereafter the lesions were inspected daily by one of the authors (JWB) and the degree of progress estimated. A lesion was considered "cured" when the surface of the skin in the infected area was smooth to the touch. The test ointment consisted of a water-soluble cream base containing 0.2% IDU; the placebo ointment consisted of the water-soluble cream base alone. The two preparations looked and felt identical and were packaged in identical one ounce tubes. No patient knew the composition of the cream he was using and, until the study had ended, no examiner knew which cream had been given to any patient. Four patients dropped out of the group after 4, 7, 8, and 20 days of treatment respectively.

In seven patients (3 test subjects, 4 controls) at least one diameter of the lesions was greater than 10 cm. In this group three patients using the test cream were considered "cured" after treatment for 4, 15, and 15 days respectively (average 11.3 days). Three patients using the placebo dropped out of the study after 4, 8 and 20 days of treatment respectively, with only slight improvement. The one control who stayed throughout the study was pronounced "cured" after 11 days of treatment.

In 19 patients (11 test subjects, 8 controls), the greatest diameter in any direction of any lesion was less than 10 cm. One test subject in this group left the study after seven days of treatment, with progress estimated as significant. The herpes lesions of the remaining ten test subjects were considered "cured" between 3 ½ and 13 days after the beginning of treatment (average 7.9 days). This is a significantly shorter "cure time" than that of the controls in this group (2 to 48 days; average 16.2 days). However, the median "cure time" for the test patients (7 days) was almost identical with that of the patients who used placebo (8 days). This suggests that any apparent difference in the average "cure times" reported here for test subjects and for controls may probably be attributed to the small sample of patients studied. Hospital and ambulatory patients did not differ as far as "cure time" was concerned.

The diagnosis of herpes simplex was confirmed by the isolation and identification of the virus in primary human amnion tissue cultures in 19 instances (9 test, 10 control subjects). Five of these patients (2 test, 3 control) had large lesions (diameter greater than 10 cm). There was no significant difference between the "cure times" of the test and control subjects with large lesions. In the remaining 14 patients, whose largest lesions were less than 19 cm in diameter, the average "cure time" was 8.75 days, the median "cure time" 9 days.

Because the response of cutaneous herpes simplex to 0.2% IDU in the cream base was not remarkable, tests were made with the following preparations: 2% IDU in water soluble cream; 2% IDU in a gel; 0.2% aqueous solution of IDU and 10% IDU in water soluble cream. Each of these was used by a single patient only and no corresponding placebos were given to control subjects. The "cure time" of these patients was 4, 6 ½, 6,

* From the Departments of Dermatology and Pediatrics, Harvard Medical School and the Dermatology Service, Massachusetts General Hospital and the Research Division of Infectious Diseases, The Children's Hospital Medical Center, Boston, Massachusetts.

† Chief Resident in Dermatology, Massachusetts General Hospital, Boston, Massachusetts.

‡ Research Associate, Research Division of Infectious Diseases, The Children's Hospital Medical Center and Associate in Pediatrics, Harvard Medical School, Boston, Massachusetts.

Supported in part by Research Grant E-1992, U. S. Public Health Service, Department of Health, Education and Welfare.

Received for publication July 12, 1962.

TABLE I

Cure times (days)

Lesion less than 10 cm.		Lesion greater than 10 cm.	
Trial	Control	Trial	Control
3½	2	4†	4*
5	7	15	8*†
6†	8†	15	11
7*	8		20*
7†	9½		
7†	15		
8½†	23		
9	48		
10			
10			
13			

* Day at which patient lost to follow-up.

† Negative culture, clinical diagnosis only.

and 15 days respectively. The patient who used 10% IDU cream stated that in the past, with different therapy, attacks of cutaneous herpes simplex had subsided within two weeks.

The chief point to emphasize is that no trial patient, in either group, recovered in less than 3 ½ days. These data suggest that when topically applied in water soluble preparations at concentrations of 0.2, 2.0, and 10%, IDU does not dramatically affect the course of *cutaneous* herpes simplex. Until more is known about its effects, this compound should not be made generally available for the treatment of this self-limited disease. Many factors might account for the fact that herpes keratitis responds remarkably well to IDU while cutaneous herpes does not. Among these are the possibility that IDU is not released from the ointment bases used; the permeability to IDU of the skin differs from that of the cornea; and substances which more readily reach the skin than the cornea from the blood stream may inactivate or alter IDU before it has affected viral DNA synthesis.

Summary: A controlled double-blind study of 26 patients with cutaneous herpes simplex treated locally with IDU has failed to demonstrate any therapeutic benefit of this compound in this condition.

REFERENCES

1. Smith, J. D., Freeman, G., Vogt, M. and Dulbecco, R.: The nucleic acid of polyoma virus. Virology, **12:** 185, 1960.
2. Salzman, N. P.: The rate of formation of vaccinia deoxyribonucleic acid and vaccinia virus. ibid. **10:** 150, 1960.
3. Tamm, I.: Metabolic antagonists and selective virus inhibition. Clin. Pharmacol. Ther., **1:** 777, 1960.
4. Herrmann, E. C., Jr., Gabliks, J., Engle, C. and Portman, P. L.: Agar diffusion method for detection and bioassay of antiviral antibiotics. Proc. Soc. Exp. Biol. Med., **103:** 625, 1960.
5. Kaufman, H. E., Nesburn, A. B. and Maloney, E. P.: Treatment of herpes simplex keratitis. AMA Arch. Ophthal., **67:** 583–591, 1962.