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Assessment of possible potentiating action of ultraviolet light on 5 iodo-2' deoxyuridine in superficial herpetic keratitis

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Iododeoxyuridine (IDU), introduced 9 years ago, was the first antiviral drug to be used effectively and without significant toxicity in the treatment of a human viral disease (Kaufman, Martola, and Dohlman, 1962; Kaufman, Nesburn, and Maloney, 1962). Although it has been established as an effective form of therapy in superficial herpes simplex keratitis, IDU is not a panacea (Patterson and Jones, 1967; Patterson, Fox, Davies, MacGuire, Sellors, Wright, Rice, Cobb, and Jones, 1963; Laibson and Leopold, 1964). The inability of this antimetabolite completely to eliminate the virus and viral precursors from cells has stimulated the search for an adjuvant therapy.

The presence of IDU halts the reproduction of herpes simplex virus, presumably by competing with thymidine in the synthesis of the viral desoxyribonucleic acid (DNA), and thereby producing a fraudulent DNA that cannot replicate.

A biological effect of ultraviolet light on DNA is to cause dimerization of thymine molecules and the extrusion of the dimerized molecules from the DNA (Setlow and Carrier, 1964). Theoretically, therefore, the effectivity of IDU could possibly be potentiated by the simultaneous exposure of the DNA virus to ultraviolet light and IDU since more of the thymidine competitive agent would be utilized by the regenerating virus to replace the extruded thymine.

Ultraviolet radiation has other desirable features for the therapy of superficial herpes simplex keratitis, and has been used alone in the treatment of this condition (Hudnell and Chick, 1962; Andrzejewska and Obukowicz, 1966). The advantageous qualities include:

(1) Direct viricidal activity resulting from damage of the exposed viral DNA;

(2) The destruction of diseased epithelial cells in the ultraviolet superficial keratitis. These cells, harbouring virus, subsequently desquamate, giving rise to a photochemical debridement;

(3) The possible stimulation of interferon production.

It has been established that the most effective wavelength of the ultraviolet band to produce damage to DNA in bacteria and viruses is in the vicinity of 2,650 Å, with a small but insignificant decrease at 2,537 Å (Sharp, 1939; Phillips and Havel, 1956; Hudnell and Chick, 1962) (Fig. 1). The spectral limits of the band capable of inducing photochemical keratitis were found to be 2,400 Å and 3,050 Å, with peak effect at 2,880 Å (Cogan and Kinsey, 1946). Kinsey (1948) determined the spectral transmission of the eye to ultraviolet radiations and found that only 26 per cent. of the energy of 2,537 Å incident on the corneal epithelium reached the stroma, and none reached the aqueous humour. Such

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radiations, therefore, should have minimal effect on the deep corneal stroma and none on the iris, lens, or retina. In fact, the first measurable penetration to the lens and retina did not occur until 2,900 Å and 3,200 Å respectively were reached.

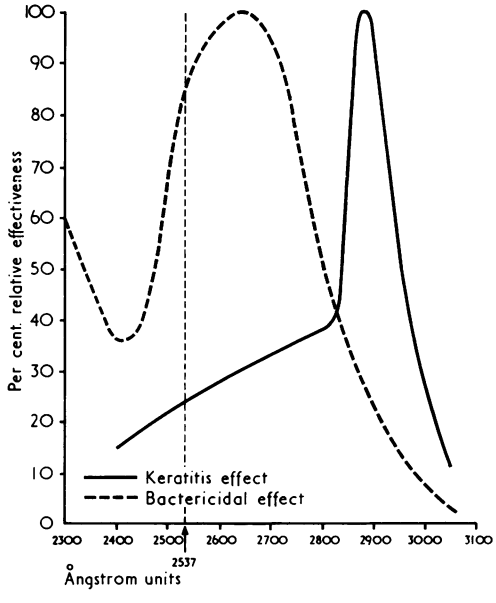

FIG. 1 *Ultraviolet wavelength effective in damaging DNA in bacteria and viruses and wavelength causing keratitis*

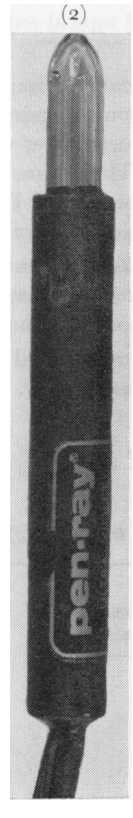

FIG. 2 *Mercury discharge lamp*

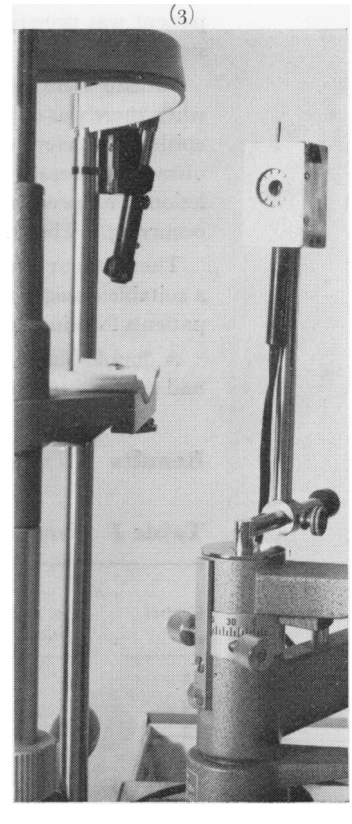

FIG. 3 *Discharge lamp housed in holder and attached to slit lamp*

Material and method

The ideal phototherapeutic waveband is the short-wave ultraviolet band, and this was provided by a miniature low-pressure mercury discharge lamp (Fig. 2). This source emits radiations over the ultraviolet spectrum with over 90 per cent. of the emitted rays being short-wave energy of wavelength 2,536 Å. It was housed in a specially designed lamp-holder that could readily be attached to a slit-lamp (Fig. 3). The housing contained an iris diaphragm to allow variation of the area of exposure.

The source ultraviolet light was used at a distance of 10 mm. from the patient's corneae, and the dose was determined by varying the exposure time, depending upon the individual's biological response. The aim was to achieve an area of confluent fluorescein staining over the whole extent of the superficial herpes simplex keratitis, either with a single exposure or with a second exposure given 24 hours later. To obtain this ideal, the exposure time varied from a single dose of 2 min. to a double dose of 4 min. each.

The total amount of radiant energy given was measured directly by a photoelectric dosimeter with a short-wave ultraviolet sensor cell, the dosage being a product of exposure time (sec.) and flux intensity (measured in microwatts per square centimetre) which for a 1-min. exposure was 38 microwatts per square centimetre.

The combined therapy of IDU and ultraviolet phototherapy was given to 29 patients, and a control group of 25 patients were treated with IDU therapy alone. The IDU was used in ointment form, given five times daily until a clinical cure resulted. All 54 patients were suffering with superficial herpes simplex keratitis with corneal staining of the dendritic or amoeboid configuration. Every patient was prescribed topical antibiotics and mydriatics, together with an eye-pad for 3 days after starting of therapy.

Patients were seen daily to assess progress, and were considered to have achieved a clinical cure when there was cessation of persistent staining with fluorescein and bengal rose. Transient punctate epithelial erosions occurred over the whole area of the cornea in patients who had been exposed to ultraviolet therapy. These punctate erosions persisted for several days and resembled the corneal lesions produced by prolonged IDU treatment. This suggested that a potentiation of IDU was occurring. The transient nature of these erosions indicated their non-infective aetiology.

The first four patients who presented were treated with the combined therapy, in order to establish a suitable dosage; thereafter alternate patients were treated with this form of therapy, the remaining patients forming the control group being treated with IDU alone.

A double-blind controlled trial was not possible as it was obvious to any observer which patients had received ultraviolet therapy.

Results (Tables I and II)

Table I *Results of treatment of ulcers with IDU alone in 25 control subjects*

Control No.	*No. of previous attacks of dendritic ulcers*	*Stromal involvement*	*No. of days for clinical cure*	*Recurrence*
1	3	No	5	Yes
2	3	No	20	Yes
3	2	No	20	No
4	3	No	9	No
5	0	Yes	8	No
6	2	Yes	22+	Yes
7	4	Yes	14	No
8	3	No	10	No
9	2	No	14	No
10	0	No	18	No
11	3	Yes	12	No
12	1	Yes	Increase in size-debrided	No
13	1	Yes	14	No
14	0	No	11	No
15	5	No	7	Yes
16	3	No	Debrided after 14 days	No
17	2	No	22	No
18	2	Yes	30	No
19	0	No	14	No
20	2	No	14	No
21	0	No	2	Yes
22	2	No	14	No
23	2	Yes	Increase in size-debrided	No
24	3	Yes	14	No
25	1	No	7	Disciform

Table II *Results of treatment of ulcers with ultraviolet light and 5 iodo-2′ deoxyuridine in 29 patients*

Patient No.	*No. of previous attacks of dendritic ulcers*	*Stromal involvement*	*Ultraviolet exposure (min.)*	*Confluent stain*	*No. of days for clinical cure*	*Recurrence*
1	0	Yes	3	Yes	7	No
2	6	No	½	No	3	No
3	0	No	4	Yes	9	No
4	1	No	4	Yes	9	No
5	5	No	3	Yes	4	No
6	1	No	2	Yes	10	Yes
7	1	No	3	Yes	3	No
8	4	Yes	3½	Yes	4	Disciform
9	0	No	8	Yes	6	No
10	0	No	4	Yes	7	Yes
11	3	No	4	Yes	10	Disciform
12	0	Yes	3	Yes	9	No
13	3	No	4	Yes	40	(Metaherpetic)
14	2	No	3	Yes	13	Yes
15	6	Yes	3	Yes	12	Yes
16	1	No	6	Yes	Increasing size-debrided	No
17	0	No	9	Yes	4	No
18	0	No	4	Yes	9	Yes
19	5	No	5	Yes	3	No
20	6	Yes	6	Yes	10	Yes
21	1	No	3	No	Increasing size-debrided	No
22	0	No	3	Yes	3	No
23	1	Yes	4	Yes	8	No
24	5	No	4	Yes	20	No
25	0	No	4	Yes	5	No
26	0	No	6	Yes	15	No
27	0	Yes	7	Yes	8	Disciform
28	0	No	4	Yes	6	No
29	0	No	8	Yes	6	No

A clinical cure within 2 weeks of starting treatment was considered as successful therapy, and if therapy was required for more than 2 weeks it was considered as a failure. On this basis 85 per cent. of the 29 patients treated with ultraviolet were cured, compared to 58 per cent. of patients in the control group.

The average time required for a cure to result with the combined therapy was 7 days, whereas patients receiving IDU alone required an average of 10 days to achieve a clinical cure.

This study was made between April, 1970, and May, 1971; during this period there was a recurrence rate of 34 per cent. in patients treated with phototherapy compared to 20 per cent. in those not treated.

There was no significant difference between the two groups in the appearance of the corneae and in the visual acuity at the time of cessation of treatment. In both groups, when there was superficial stromal involvement, permanent superficial opacities resulted.

Three patients (10 per cent.) in the combined therapy group developed deep stromal keratitis.

One patient (4 per cent.) in the control group developed this complication.

Considerable pain resulted from the phototherapy, because of the resulting photochemical keratitis. This pain lasted for 8 to 12 hours, having started after a latent period of 4 to 6 hours. It was possible to alleviate it with analgesics and hypnotics. In some patients pain prevented the further exposure that was necessary to achieve a confluent corneal stain.

Discussion

The evaluation of the possible clinical effectiveness of different treatments is difficult in this condition because of its clinical variability.

It appears that ultraviolet light does potentiate the therapeutic effect of iododeoxyuridine in the majority of cases, but it unfortunately results in a higher recurrence rate and possibly an increase in the incidence of stromal keratitis, than when IDU is the sole method of treatment. The incidence of stromal keratitis resulting from this combined therapy was no greater than that found in cases treated by chemical debridement by Gundersen (1936).

Conclusion

It is felt that the treatment of superficial herpes simplex keratitis with ultraviolet phototherapy in addition to IDU is not merited because of the pain induced, the higher recurrence rate, and the possibility of an increase in the incidence of stromal keratitis.

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