Actinic Keratoses in Bantu Albinos

CLINICAL EXPERIENCES WITH THE TOPICAL USE OF 5-FUORO-URACIL

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SUMMARY

Five per cent 5-fluoro-uracil ointment has proved to be highly effective when used topically in the solar keratoses of Bantu albinos. No photoprotective action was noted in the series of 15 patients submitted to the trial, and the response of malignant change was discouraging. The drug may be considered the treatment of choice for actinic keratoses of albinos, particularly in the early stage of the skin disorder.


Dillaha et al. reported that 5-fluoro-uracil ointment (5-FU), topically used, is highly effective in the treatment of certain alterations of the skin induced by exposure to sunlight, mainly solar keratoses, in which the pathological features of anaplastic and proliferative changes are seen. 5-FU for topical application has been extensively used for its efficacy in controlling minor skin malignancies, but recent literature and reports on this drug at the conference held in Rome in 1968, do not mention attempts to treat actinic keratoses in albinos, nor the complications. The purpose of this paper is to report our clinical experience of a series of Bantu albinos treated topically with 5-FU for their actinic keratoses with or without malignant change.

The investigation was undertaken (i) to assess the value of topical 5-FU in these patients; (ii) to investigate whether Bantu albinos have a response different from that of Whites to this treatment; (iii) to gain clinical information about the alleged photoprotective action of 5-FU for Bantu albinos; (iv) to compare the response of tyrosinase-positive and tyrosinase-negative patients to this drug.

MATERIALS AND METHODS

There were 15 Bantu albinos, 9 females and 6 males. All showed evidence of skin changes produced by long exposure to sunlight, i.e. erythema, wrinkling of the skin of the neck and the dorsal aspect of the hands; plaques of scaling on the face; and elements of actinic keratosis distributed on the face and extremities. Besides the above signs which are commonly seen in oculocutaneous or complete albinism, one case also had a squamous cell epithelioma in the temporal region; another had extensive superficial squamous cell epitheliomas on one leg and one upper eyelid; a third had a superficial squamous cell epithelioma on one leg; and a fourth had a basal cell epithelioma on the side of the neck.

Their ages ranged from 7 to 45 years, and they were from the urban community of Soweto. With the exception of 2 patients, a girl of 10 years and a man of 39 years, they were well nourished and without other disease.

Histological investigation of the clinical state was carried out before, during, and after treatment. 5-FU was used as an ointment, containing 5% of fluoro-uracil. It was rubbed into the affected skin which was dressed with tubular gauze on the limbs, but the face was left uncovered. The duration of the treatment was from 3 to 4 weeks for actinic keratoses; 6 weeks for squamous cell epithelioma; and 6 months for basal cell epithelioma. Only 1 patient each with these complications, listed in Table I, was admitted to the trial; while the remaining patients received irradiation or radical surgical treatment. More than 300 actinic lesions were treated.

The clinical effect of 5% 5-FU ointment for each patient was recorded. The grading of results, which applies only to keratotic lesions, was as follows: 'excellent' for complete remission and no relapse on follow-up; 'good' for 70% clearing, a remarkable decrease of the size and hyperkeratosis of the lesions and minimal relapse, with an acceptable cosmetic result.

Only the photoprotective clinical effect of the 5-FU was recorded during the period of the trial. The uncovered face, treated with the ointment, was exposed to the sun for one hour, between 1200 and 1300 each day.

Samples of hair bulbs of 9 patients were sent to the Division of Human and Oral Genetics of the University of Minnesota (Professor C. J. Witkop) for screening for their tyrosinase activity: 6 were found to be tyrosinase-positive, and 3 tyrosinase-negative.

RESULTS

All the patients admitted to the trial showed evidence of local reaction. Usually, an exacerbation of the pre-existing erythema was noted, and this was followed by vesiculation, erosion, and frequently a flare-up of subclinical lesions (marking phenomenon). After 4 days of topical applications, 1 patient developed a severe erythematous reaction on the face, but after a few days' interval and the topical use of steroids, the reaction subsided and treatment was begun again without further side-effects. Another patient with evidence of sunburn, erythema, and cracking of the light-exposed surfaces of
### TABLE I. DETAILS OF BANTU ALBINOS AFFECTED BY SOLAR KERATOSIS

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age</th>
<th>Sex</th>
<th>Distribution of solar keratoses</th>
<th>Tyrosinase activity test</th>
<th>Duration of treatment</th>
<th>Results</th>
<th>Additional lesions, results of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>F</td>
<td>Hands, face</td>
<td>Not done</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>Squamous cell epithelioma left temporal region</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>M</td>
<td>Hands, arms, legs</td>
<td>Not done</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>Squamous cell epithelioma right leg; 5-FU unrespons.</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>M</td>
<td>Face, arms, legs</td>
<td>Not done</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>Face, neck, arms, hands, legs</td>
<td>Negative</td>
<td>4 weeks on rotation</td>
<td>Good to excellent</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>M</td>
<td>Arms, neck</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>Basal cell epithelioma right side neck; 5-FU unrespons.</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>Face, arms, legs</td>
<td>Not done</td>
<td>3 weeks face, 2 weeks legs</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>F</td>
<td>Face, arms, legs (100 lesions)</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Good</td>
<td>Squamous cell epithelioma left upper eyelid and right leg</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>F</td>
<td>Face, neck, arms, legs</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>M</td>
<td>Face, arms</td>
<td>Negative</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>F</td>
<td>Face, neck, hands</td>
<td>Negative</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>F</td>
<td>Face, arms</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>26</td>
<td>F</td>
<td>Arms, legs</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>F</td>
<td>Arms, face, legs</td>
<td>Positive</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>42</td>
<td>F</td>
<td>Face, neck, hands, arms</td>
<td>Not done</td>
<td>3 weeks face, 4 weeks arms</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>52</td>
<td>F</td>
<td>Face, neck, hands, arms</td>
<td>Not done</td>
<td>3 weeks</td>
<td>Excellent</td>
<td>None</td>
</tr>
</tbody>
</table>

The efficacy of 5% 5-FU ointment in the majority of actinic keratotic lesions, variously distributed, may be regarded as excellent, especially from a cosmetic point of view (Figs 3 and 4). It was also effective in controlling the lesions on the limbs.

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**Fig. 1.** Patient with severe solar keratosis of the face — before treatment.

**Fig. 2.** The same patient as shown in Fig. 1, after 4 weeks of treatment with 5-FU.
Follow-up of the majority of our cases, ranging from 6 to 14 months, showed minimal relapses (from 3 to 5 keratotic lesions) on exposed areas, in patients who neglected the protective measures suggested, such as the use of sun-screening creams, or lotions. On the other hand 5-FU did not have any light-protective action; in fact, the uncovered treated face, exposed to sunlight, showed a more intense reaction than did the limbs protected by a dressing during exposure to the sun.

No difference in response to the drug was noticed in either the tyrosinase-positive or the tyrosinase-negative groups of patients. The treatment of a superficial squamous cell epithelioma was extremely disappointing (case 2). A marked decrease in the size of the ulceration was noted, but biopsy 3 months later showed evidence of activity in the nature of wandering islands of squamous cells in the subpapillary dermis.

A superficial, nodular, basal-cell epithelioma (case 6) was also disappointing in its response to long-term topical treatment with the ointment. The ulceration was unresponsive, and biopsies at intervals of 3 and 6 months, showed isolated islands of basal cells in mid-dermis. Clinically there was evidence of pearluceous nodules at the periphery of the ulcer, which remained unaffected by the treatment; radical surgical treatment and skin grafting led to complete healing.

**COMMENT**

As an antagonist of cellular pyrimidine, 5-FU acts by blocking the production of thymine (5-methyluracil) and so blocks the DNA synthesis, stopping the biological growth at the macromolecular level. This action leads to the inhibition of growth of rapidly proliferating tissue, mainly those characterized by a high rate of mitosis, including the haemopoietic system. The affinity of 5-FU for tumour tissue has been proved in animal experiments: by using radioactive 5-FU, the distribution pattern showed that the mouse sarcoma S-180 accumulates more labelled material than other proliferative tissue such as bone marrow and intestinal mucosa. Nevertheless, 5-FU may act on other tissue such as the germinal epithelium and the gastro-intestinal mucosa. Cutaneous absorption of $[^6]$C-5-FU from a 5% ointment applied to healthy and diseased skin, has been studied by Erlanger et al., on the basis of the urinary excretion of the drug and its metabolites. The authors found that in diseased skin the rate of absorption was about 15 - 75 times as rapid as that of healthy skin, but so far no systemic effects from the topical use of 5-FU have been reported.

In our experience, the use of topical 5-FU in a 5% ointment, in a series of Bantu albinos suffering from actinic keratoses, has proved its remarkable efficacy in controlling these skin disorders; and it was also efficient in controlling keratotic lesions localized to the limbs. This result contrasts with that reported by Dillaha et al., but agrees with the finding of Schultz and Falkson in their series of White patients.

In accordance with our experience we wish to stress that in our Bantu albinos, 5-FU, topically used, has failed to prove that it has any light-protective action. In 6 patients who submitted to an empirical test, i.e. exposure to the sun of their uncovered but topically treated skin, we noted an extraordinary increase of the well-known
reaction of intense erythema and oedema which contrasted with the minimal signs in the protected and unexposed treated skin of the same patient. Our observation seems to contrast with Ippen's experimental results on the photoprotective action of 5-FU, but not with those of Klein and Scarpa, outlined by Serri. Nevertheless, in commenting on our findings, we must take into consideration the high vulnerability of the albino's skin when it is exposed to sunlight and therefore the severity of the response may in some way be related to a particular degree of hypomelanosis.

It may also be said that although we have treated only 1 case of basal cell epithelioma and 1 case of squamous cell epithelioma complicating the solar keratoses of our Bantu albinos, the effectiveness of 5% 5-FU ointment does not appear convincing.

On the other hand, this group of albinos has not reacted any differently to the contact chemotherapy than the other series of patients mentioned in the literature.

To conclude: although our trial was of a limited number of cases of albinism, we are in a position to state that 5% 5-FU ointment should be used at the earliest stage of solar keratosis in albinos, so that the serious complications, seen in 4 of 15 cases and in the age range 10-32 years in our series may be prevented; this treatment should be confined to solar keratosis rather than its complications; and long-term benefits are better achieved when the post-treatment use of sun-screening preparations, mainly methylbenzophenone and PABA 10% lotions, is adopted.

There is no doubt that we have the opportunity of adding another variety of treatment to our dermatological armamentarium for Bantu albinos' solar keratoses, and by using 5% 5-FU topically, we can offer them a far better prognosis than we have previously been able.

I should like to thank Dr C. H. Kniep, Superintendent of Baragwanath Hospital, for permission to publish; Dr I. Caro, for his collaboration; the Photographic Unit of the University of the Witwatersrand; and Roche Products (Pty) Ltd for the supply of Efudix for the trial.

REFERENCES

Books Received : Boeke Ontvang


