Eur J Cancer Clin Oncol, Vol. 19, No. 9, pp. 1201–1205, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00

The Effects of a Novel Potent Oral Retinoid (Ro13-6298) in the Treatment of Multiple Solar Keratoses and Squamous Cell Epithelioma

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Abstract—*Sixteen patients with solar keratoses and/or squamous cell carcinoma were treated for* 4 weeks *with Ro*13-6298, *a potent oral retinoid of the arotinoid series. This treatment caused a small but statistically significant reduction in the mean number and area of the lesions. Tissue measurement and cell kinetic studies demonstrated that the treatment caused significant thickening of uninvolved epidermis but no change in the rate of cell division. Similar side-effects to those occurring with etretinate were experienced.*

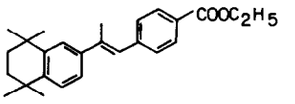
INTRODUCTION

SOLAR keratoses are common premalignant lesions of the skin in fair-skinned individuals past middle age. Multiple lesions are the rule, and even when the surrounding skin appears normal, abnormalities can be demonstrated histologically [1]. Long continued solar exposure is an important aspect of their aetiology and they are particularly common in areas of high isolation such as Australia, South Africa and Southern U.S.A. For a variety of reasons, solar-induced skin tumours of all varieties are becoming more common in North West Europe, and Celtic groups such as those in Wales are especially affected. A small proportion transform to squamous cell carcinoma, but the exact risk is poorly characterized.

Solar keratoses and squamous cell carcinomata are usually treated by excision or destructive therapies including cryotherapy and electrocautery. However, the presence of large numbers of lesions and subclinical dysplasia as well as their predominant localization to exposed sites makes a nondestructive systemic treatment desirable.

Bollag [2, 3] has reported that various synthetic retinoids have an antineoplastic action on induced skin tumours in an animal model. Ro13-6298 arotinoid ethyl ester (Fig. 1) is one of the most potent of the synthetic retinoids [4] in animal experiments, and in this study we have investigated its efficacy in the treatment of multiple solar keratoses and squamous cell epitheliomata, as well as its effects on uninvolved skin.

RO 13-6298



CHEMICAL NAME:
p-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl) propenyl]-benzoic acid ethyl ester = arotinoid ethyl ester.

Fig. 1. *Chemical structure of Ro*13-6298.

MATERIALS AND METHODS

Sixteen patients, 9 male and 7 female, mean age 67 yr, were studied. All had multiple solar keratoses, 5 patients additionally had squamous cell carcinomata and 3 patients also had basal cell carcinomata. The number of lesions and their areas were recorded in each patient. Photographs and biopsies of representative lesions were also taken. To assess the effects of the arotinoid on normal skin a further biopsy was taken from a constant reference site on the inner forearm of each subject. After incubation of fragments of skin in tritiated thymidine and subsequent autoradiography, the number of labelled cells was determined and the labelling index calculated for each specimen (percentage of labelled basal and suprabasal cells of the total number of basal cells).

Accepted 28 March 1983.

The mean epidermal thicknesses were measured automatically using the Quantimet 720 Image Analysis System (Cambridge Instruments).

Each patient was then given arotinoid orally at a dosage of 1 μg/kg/day for 28 days. At the end of the 4 weeks the patients were questioned as to side-effects, the lesions were counted and measured, and lesional and uninvolved skin were biopsied again.

RESULTS

Ten patients improved, showing a decrease in the number and area of the lesions and a reduction in their surface scaliness, and six were unchanged. Figure 2 shows a squamous cell carcinoma and two solar keratoses before and after treatment. Table 1 shows the results of all 16 patients. There was a small but significant reduction in mean number and mean total area of the keratoses. Table 2 refers to the normal forearm skin of the subjects. The mean epidermal thickness (MET) was increased significantly after treatment but there was no significant change in the labelling indices (LI). Table 3 shows the side-effects that occurred—chelitis, pruritus, peeling of the palms and soles or eczema were experienced in 11 cases. No significant change was noted in the blood count, urea and electrolytes, liver function tests and fasting cholesterol or triglycerides during the course of treatment.

Table 1. Mean numbers and areas of solar keratoses, basal cell carcinomata and squamous cell carcinomata before and after treatment with Ro13-6298 in 16 patients

	Mean No. of lesions (± S.D.)	Mean total area of lesions (mm^2) (± S.D.)
Pre-treatment	14 ± 9.6	592 ± 312
Post-treatment	11 ± 8.4	439 ± 388
Significance (Paired *t* test)	$P < 0.02$	$P < 0.001$

Table 2. Mean epidermal thickness and labelling indices in normal forearm skin before and after treatment with Ro13-6298 in 16 patients

	Mean epidermal thickness (μm) (± S.D.)	Labelling indices (%) (± S.D.)
Pre-treatment	57.22 ± 13.87	5.55 ± 3.02
Post-treatment	75.69 ± 19.17	7.22 ± 4.92
Significance	$00.05 > P > 0.02$	N.S.

Table 3. Side-effects in 16 patients treated with arotinoid (Ro13-6298)

	No. affected
Cheilitis	6
Pruritus	6
Exfoliation of palms and soles	5
Eczema	4

DISCUSSION

Vitamin A and the synthetic retinoids have both prophylactic and therapeutic actions in neoplastic disease in animal studies, but there have been comparatively few studies in man documenting their antineoplastic effects. The subject of retinoids and their effects in skin cancer has recently been extensively reviewed [5]. Etretinate has been reported to be effective in the treatment of solar keratoses in a double-blind study by Moriarty *et al.* [6]. Other studies have demonstrated the potential usefulness of this compound and another, 13-*cis*-retinoic acid (isotretinoin), in the treatment of basal cell carcinoma.

The compound used in this study, Ro13-6298, has been used previously to treat patients with psoriasis [7], but its use in human skin tumours has not been documented until now. Its activity as assessed in the present report is definite but not great. It is likely that a protocol involving a 2-month period of study or increased dosage would have demonstrated a greater benefit from using the drug and further studies are in progress.

The way in which the retinoids exert their antineoplastic effects is unclear. It does not appear that an antimitotic effect is involved [8], and a variety of other mechanisms have been proposed, including blockage of ornithine-decarboxylase induction [9], a change in the pattern of differentiation and alteration of the surface receptors and immunomodulation via increase in NK lymphocytes and increase in macrophage activity [10].

The increase in epidermal thickness recorded here parallels previous results in patients with disorders of keratinization treated with etretinate [11, 12], and the experimental findings of Fritsch *et al.* [8] in mice after treatment with the same drug.

Although the present studies confirm the lack of an antimitotic effect of the retinoids when used *in vivo*, they do not indicate a likely mode of action in neoplasia.

Acknowledgements—We are grateful to Dr. Alan Miller of Roche Products Ltd., Welwyn Garden City, Herts for supplies of the drug and help with the study.

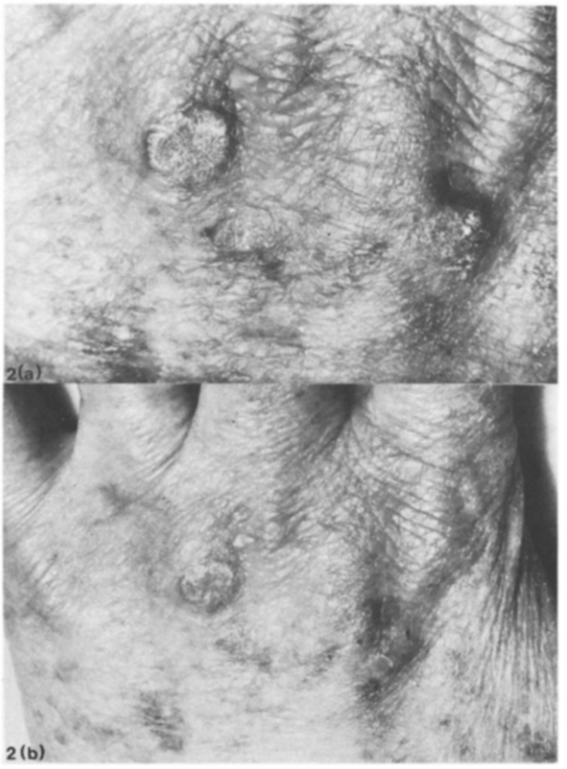


Fig. 2. Squamous cell carcinoma and solar keratoses (a) before and (b) after 4 weeks *of treatment with Ro*13-6298.

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