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# Lack of effect of topical indomethacin on psoriasis

C. A. GREEN* & SAM SHUSTER
Department of Dermatology, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 4LP

Topical 1% indomethacin had no effect on chronic stable plaque psoriasis in an open controlled study using subjective clinical scores nor in a randomised double-blind inert base controlled study using both subjective and objective measurements of lesional response; nor did it initiate or affect the development of psoriasis after cold injury. Previous studies are reviewed and it is concluded that the evidence does not support the hypothesis which relates psoriasis to eicosanoids produced by lipoxygenase activity.

**Keywords** indomethacin psoriasis

## Introduction

Much contemporary study of psoriasis is concerned with an hypothesis which relates the disease to an abnormality of lipoxygenase production of eicosanoids. A frequently cited item of supporting evidence is a worsening of the lesions of psoriasis by indomethacin (Katayama & Kawada, 1981; Ellis *et al.*, 1983), which is attributed to substrate diversion to the lipoxygenase pathway consequent to cyclo-oxygenase inhibition. Since, in our view, the results of these studies are neither conclusive nor extensive enough to support the importance attributed to them, we reinvestigated the effect of indomethacin on psoriasis using a topical preparation of the drug which has been shown to be an effective inhibitor of UV-B erythema both in normal skin and in clinically normal skin of patients with psoriasis (Lawrence & Shuster, 1985; Farr & Diffey, 1986) using a more varied experimental protocol than in previous studies and with both subjective and objective measures of response.

## Methods

Nineteen patients with stable plaque psoriasis took part in three separate studies. All had received only emulsifying ointment in the preceding 2 weeks and no anti-inflammatory or other drugs. The 1% indomethacin gel (Merck, Sharp & Dohme) was a batch shown to be effectively absorbed by its capacity to inhibit UV-B erythema (Lawrence & Shuster, 1985; Farr & Diffey, 1986).

### *Open study*

There were 11 in-patients (four male, seven female, age range 17–70 years). Two clinically similar plaques on symmetrical opposite sides of the body were selected and treated twice daily, one plaque with 1% indomethacin gel and the other with inert base, using just enough gel to cover the lesions. All other lesions were treated with dithranol. Assessment was made visually and by palpation (0 = not palpable; 1 = just palpable; 2 = easily palpable; 3 = thick) before treatment and 1 and 2 weeks thereafter.

### *Randomised double-blind placebo controlled study*

This was done in eight out-patients (all male, age range 20–58 years). Areas of psoriasis of comparable size and severity were identified on the flexor aspect of the forearms of each patient and three measurements of lesional thickness were made at the centre of each plaque using Harpenden calipers with one spring removed (Cook & Shuster, 1980; Shuster *et al.*, 1980; Marsden *et al.*, 1983) and the mean calculated. The maximum

*Present address: Addenbrooke's Hospital, Hills Road, Cambridge

variation between any three consecutive readings was 0.1 mm. Each subject was then given two tubes, one containing 1% indomethacin gel and the other containing inert gel base of identical appearance. The tubes were labelled 'left-arm' and 'right-arm'; the randomisation code being unknown to both subject and clinician. The patients were instructed to apply enough gel to cover 60 $cm^2$ of each forearm which included the plaque of psoriasis under investigation and normal skin around it, and to wash their hands after application of each gel. Lesion thickness was measured after 7 and 14 days of treatment and the clinical appearance noted.

*Induction of psoriasis by cold* (Farber *et al.*, 1965)

A 1 cm diameter area of skin of normal clinical appearance was selected within the 60 $cm^2$ treatment area on each arm of four of the patients from study 2 above. A Cry-ac gun (Brymill Corp., USA) fitted with the 'C' nozzle was held at a distance of 3 cm from the skin surface and liquid nitrogen was sprayed for 4 s from ice formation, subsequent treatment with indomethacin or inert base was applied as in the previous study. The sites were examined twice weekly for 2 weeks for the development of psoriasis and skin thickness measured.

## Results

*Open study*

Of the 11 patients in the open study seven completed 14 or more days of treatment, the four who completed only 8 days were discharged home for reasons unassociated with the study. Both active and inert gels were well tolerated by the patients. After 7 days the lesions in the 11 patients were somewhat better on the indomethacin treated side (Median grade 1) compared with the base treated side (Median grade 2) but this difference was not significant. After 14 days there was no difference between the two groups (Figure 1): in six patients there was no change in either the lesions treated with indomethacin or inactive base; in four patients there was comparable improvement in lesions treated with the active and inert base and in one patient there was improvement of the indomethacin treated lesion whilst the lesion on the side treated with inert base remained unchanged.

*Randomised, double-blind placebo controlled study*

All eight patients completed the double-blind study with apparent good compliance and no adverse reactions. Clinically no difference was apparent between the lesions treated with the active or the inert base (Figure 2). In six patients there was a small increase in lesion thickness on both the indomethacin and inert base treated sides; in two patients there was a small decrease in lesion thickness on the indomethacin treated side, with a slight increase on the inert base treated side in one patient and a slight decrease in one other patient. These changes were not statistically significant. No new lesions developed

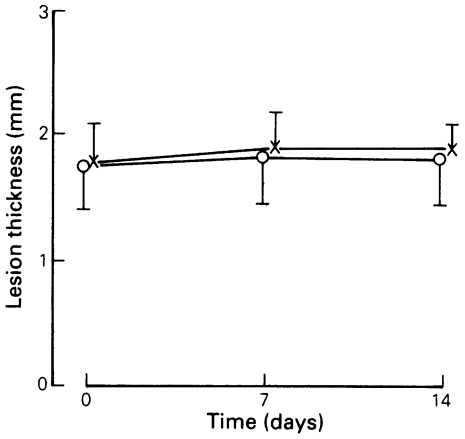


**Figure 1** Clinical response in an open study ($n = 7$) of psoriatic plaques treated with 1% topical indomethacin (×) or insert base (○) assessed as grade of lesion palpability. Four of the patients left the study after 7 days and are excluded.

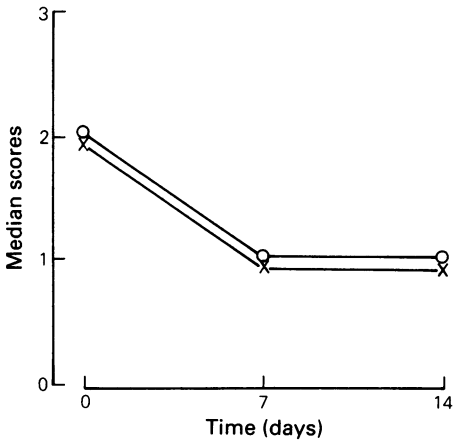


**Figure 2** Response of psoriatic plaques assessed by lesion thickness during treatment with 1% topical indomethacin (×) or inert base (○) in a double-blind study ($n = 8$).

on clinically normal skin treated with indomethacin.

*Induction of psoriasis by cold*

The response of skin treated with liquid nitrogen was no different in indomethacin and inactive base treated sites on opposite arms of the four patients studied. Lesions developed at the site of cold application in two of the four patients after 7 days; they were clinically similar on both indomethacin and inert base treated arms and the lesional thickness was comparable in both (0.7 and 0.6 mm and 1.3 and 1.1 mm). In two patients no lesions developed on either side and there was no difference in skin thickness. No new lesions developed in clinically normal skin between lesions that had been treated with indomethacin.

## Discussion

We found no evidence that topical indomethacin has any effect on established psoriasis, nor on its development or severity after cold injury. The dose and percutaneous delivery of the indomethacin was satisfactory because the topical preparation used was shown to inhibit UV erythema in normal subjects and in patients with psoriasis (Lawrence & Shuster, 1985; Farr & Diffey, 1986). Our first study was open with a simple clinical assessment and therefore has only a limited discriminatory power: nevertheless, indomethacin had no obvious deleterious effect on the plaques of psoriasis. The similar results of the second study are more conclusive because the response was measured objectively by lesion thickness (Shuster *et al.*, 1980; Marsden *et al.*, 1983) as well as clinically, and the experimental design was double-blind and randomised with same patient (opposite arm) inert base control. Furthermore, the 2 week period of study was adequate as the worsening originally reported after indomethacin (Katayama & Kawada, 1981) occurred during this period as do responses to other agents. Although our findings exclude a worsening of the lesions of psoriasis by topical indomethacin it could of course be that initiation of lesions by indomethacin is more important than the worsening of chronic plaques. However, like Ellis *et al.* (1983) we found no evidence of development of new lesions after indomethacin, and we found no facilitation of initiation by cold injury in the four subjects studied: thus topical indomethacin neither elicited a Koebner response (locally induced psoriasis) nor worsened the response when it occurred after cold injury. We therefore conclude that inhibition of cyclooxygenase activity by topical indomethacin neither initiates the development of psoriaisis nor exacerbates the condition of the developed plaques.

Although our findings are therefore at variance with Katayama & Kawada (1981) and Ellis *et al.* (1983) the first of these two studies was a simple open investigation of 11 patients, and the efficacy of the 0.5% indomethacin in 50% ethanol was not established. Moreover, in an earlier placebo controlled study of 12 patients with psoriasis (Kern, 1966) there was improvement with indomethacin in four patients and deterioration in none (one had the side effect of a generalised eruption), but there was no difference overall compared with the response to placebo. The most frequently quoted study is that of Ellis *et al.* (1983), and although this report is a summary the essential details of which are not entirely clear, it is apparent that indomethacin treated lesions did not actually deteriorate but simply did not improve as much as did the lesions treated with inert base. Thus it appears that the results of this study have been seriously and repeatedly misquoted both by the authors themselves (e.g Anderson & Voorhees, 1986) and by many others (e.g. Maurice *et al.*, 1986) as showing a worsening of the lesions of psoriasis with topical indomethacin. What appears to be a full paper on this work has only recently appeared (Ellis *et al.*, 1986) and the account is in many ways less satisfactory than the earlier summary. Thus whereas the essential data appears to be the same, some of the authors are different and the title is very significantly different from that of the earlier summary. Neither the precise nature of the clinical measurement is given nor are the results: the paper simply says that the placebo (vehicle) treated lesions improved minimally whilst those treated with indomethacin remained unchanged. Therefore we can only conclude from this published data that topical indomethacin had no worsening effect on the lesions of psoriasis.

Although worsening of lesions by indomethacin would have been a powerful argument in support of an abnormality of lipoxygenase eicosanoids in psoriasis, the absence of worsening by no means excludes it. Nevertheless, the evidence for the hypothesis is poor. The polymorphonuclear microabcesses caused by topical leukotriene $B_4$ (Camp *et al.*, 1984) make a dramatic contrast to the lesions of psoriasis in which, textbook descriptions notwithstanding, polymorphonuclear infiltrates and microabscesses are far less common and extensive than in other dermatoses. Furthermore, despite the poly-

morphonuclear infiltrate produced by leukotriene $B_4$ application, the lesions of psoriasis are not induced. Likewise the effect of benoxaprofen, the clinical efficacy of which was not clearly established before the drug was withdrawn, cannot continue to stand as evidence for the hypothesis since it is now known to be a not particularly potent inhibitor of lipoxygenase activity. Too much emphasis has been placed on the isolation of lipoxygenase eicosanoid products in psoriasis in the absence of evidence of causation by introduction and improvement by removal.

In conclusion, none of the individual items of evidence cited is adequate to validate the hypothesis which relates psoriasis to an abnormality of lipoxygenase eicosanoid products. Our experimental refutation of one piece of that evidence and the theoretical doubts about the others therefore suggest that unless the hypothesis finds new supporting evidence it should be abandoned.

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