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The Systemic Effect of Dithranol Treatment in Psoriasis

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We have investigated the systemic effect of local treatment with dithranol for one week in psoriasis by a combination of subjective assessment of the severity of individual plaques and more objective assessment of blood flow (measured by laser-Doppler flowmetry) of the centre of the plaque, and at the active edge of the plaque. There is both subjective and objective evidence of an improvement in untreated plaques of psoriasis when dithranol is used on plaques elsewhere on the body. Blood flow falls at the active edge and at the centre of the plaques that are untreated. These findings indicate a systemic effect of local treatment that is more likely to be due to circulating factors, possibly T cells, rather than a direct effect of circulating dithranol. They also suggest that within patient comparisons of topical treatment in psoriasis may be inaccurate.

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The majority of patients with psoriasis respond to simple topical treatments – dithranol, tar preparations or steroids – applied to affected areas of skin. Although it is often suggested anecdotally that topical therapy may induce an improvement in psoriasis in areas to which it has not been applied – implying a humoral, or at least blood-borne, factor which influences the behaviour of psoriatic skin at distant sites – there is no direct evidence of this. Although there is absorption of topical therapies, this is limited by the nature of the drug itself and by the base in which it is applied, and this is particularly true of dithranol (1). It has been generally assumed that there is no distant effect of topical treatment. Indeed, in many clinical trials, the effects of two topical treatments are compared when applied to different halves of the body, implying the absence of a generalised effect.

However, whilst investigating the active extending edges of psoriatic plaques (2), we observed that there was evidence of some systemic effect of treatment. On occasions, after identifying an active edge of a plaque of psoriasis, immediate biopsy was impossible. The chosen plaques were then not treated, although the rest of the body received conventional topical therapy. This appeared to result in loss of the already demonstrated active edge, suggesting that there might after all be a distant effect of topical treatment, and that this might be easily investigated. This we set out to do by a combination of clinical assessment and more objective measurements of skin blood flow.

PATIENTS AND METHODS

Ten patients with stable chronic plaque psoriasis (mean age 35, range 14–66) were investigated. They had all been referred for therapy of their skin disease in the out-patient treatment unit at Leed's General Infirmary. They had used no treatment other than emollients for one week before assessment.

Before starting treatment, the patients were assessed clinically for the extent of disease on arms, legs and trunk according to the system outlined below. In each area, severity of a typical plaque was assessed for erythema, scaling and induration, using a scoring system of 0 = no involvement, 1 = mild, 2 = moderate, and 3 = severe. Thus, the total possible score was 3 for each index of severity, and 6 for disease extent, i.e. 15 in all (Table I).

A typical single plaque on the trunk was selected for more specific assessment. This was scored as above for the three measures of severity, and then blood flow was measured using a laser-Doppler flowmeter (Perimed Pfld) at three sites: the centre of the plaque, the active edge of the plaque, defined as the area immediately adjacent to the plaque at which the blood flow was highest, and thirdly at the inactive edge of the plaque, where laser-Doppler blood flow was lowest. These sites were marked (and re-marked as often as was necessary) with indelible ink to allow remeasurement at a later stage.

Treatment with dithranol in Lassar's paste at concentrations appropriate to the patient's response was then commenced (beginning at 0.125%) to all areas of skin involvement except the plaque on the trunk previously identified for study. Body areas treated ranged from less than 5% of total surface area, up to 30% total surface area. After application, the paste was fixed with talc to prevent spreading and contamination of the untreated site. Ultraviolet therapy was avoided except in 2 cases, and in these the plaque under investigation was covered during ultraviolet exposure but immediately unoccluded thereafter. No plaques were otherwise occluded.

After one week's treatment, the patients were re-assessed both clinically and by blood flow measurement at the marked sites.

Statistics

Changes in clinical state of treated and untreated areas, as well as in the blood flow measurements at each of the marked areas, were analyzed by Wilcoxon's rank sum test for paired samples of non-parametric data.

RESULTS

The clinical scores before and after treatment for the overall extent and severity of the disease are shown in Fig. 1. There was significant improvement in all patients but one, who deteriorated despite treatment and eventually needed systemic therapy. In Fig. 2, the clinical assessments of the plaque left untreated are shown before and after the application of distant therapy. There is a clear and statistically significant fall in disease score in the untreated area.

Table I. *Scaring for extent and severity of disease*

i) Extent of disease	ii) Severity
0 – no involvement	0 – no involvement
1 – <10%	1 – mild
2 – 10–29%	2 – moderate
3 – 30–49%	3 – severe
4 – 50–69%	
5 – 70–89%	
6 – 90–100%	
	for – ERYTHEMA
	INDURATION
	SCALING

i.e. maximum score is 6 for extent + 3 for erythema + 3 for induration + 3 for scaling = 15

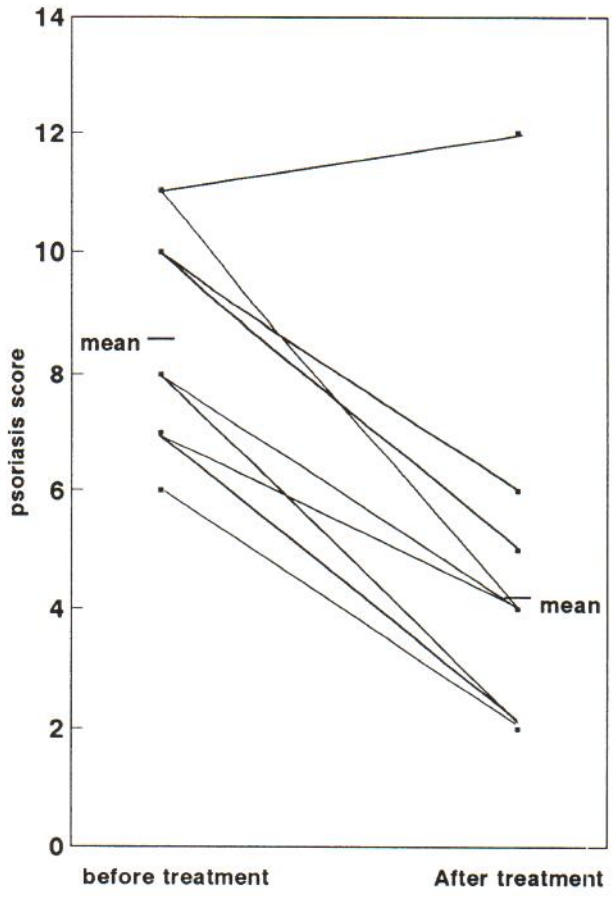

Fig. 1. Overall clinical assessment.

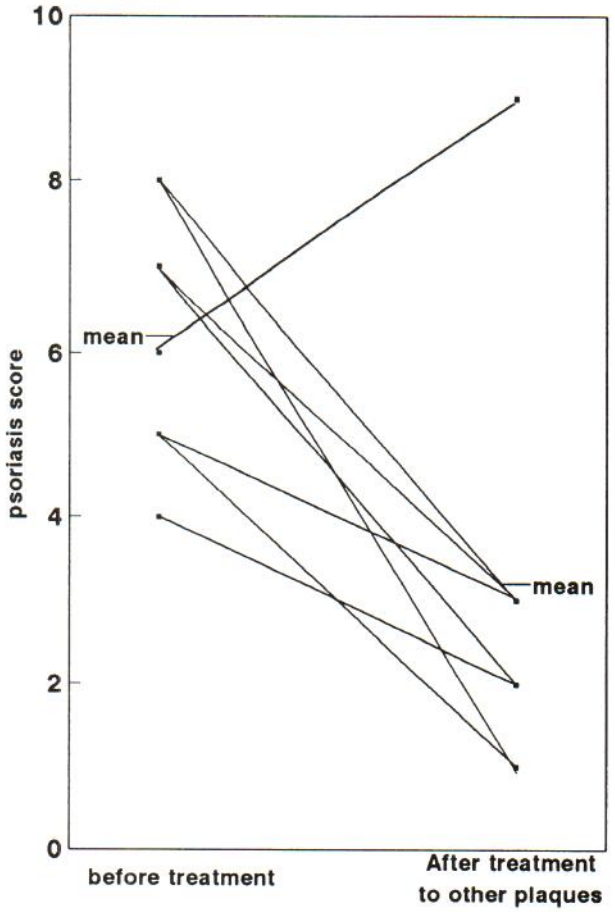

Fig. 2. Clinical assessment.

This is also true of the data shown in Fig. 3 and 4, where the blood flow in the centre of the untreated plaque (Fig. 3) before and after distant therapy and that at the active edge (Fig. 4) are shown. The flow at the active edge is inhibited relatively more than that in the plaque centre. There is no obvious difference in those patients who received additional UVB treatment. The patient who failed to improve with treatment showed deteriorating clinical scores and increased blood flows at the untreated plaque.

DISCUSSION

The results demonstrate that topical treatment produces an improvement in untreated plaques of psoriasis. The clinical improvement is striking, whilst the blood flow studies give objective evidence of what is clinically apparent. The relatively greater inhibition of the most active area of paralesional skin indicates that the effect is not localised to those areas already psoriatic but is manifest in clinically normal, but pre-psoriatic skin.

There may be an element of placebo response here, but we believe it is likely to be a genuine systemic response to therapy. Absorption of topical agents occurs best from true solutions of a compound, supplemented by a reservoir of drug to maintain saturation of the solution (1). This is achieved for ointments containing dithranol, and for paste bases, which differ in absorptive properties only in the maximum concentration of dithranol which can be maintained in solution. Absorption of dithranol is limited from an ointment base (3) and will be similarly limited from e.g. Lassar's paste. It is poorly absorbed when delivered in an ointment base to intact skin, and urinary excretion is rapid, so that significant levels do not accumulate in the blood or other tissues (3). Better penetration occurs if skin barrier function is impaired by trauma or a toxic effect of the drug (3). In this study, the use of a paste base made significant systemic absorption, and hence a direct systemic effect of the dithranol, unlikely. Is also makes contamination unlikely, although we did not specifically assess this. This means that the topical treatment must be inducing changes in a factor or factors as yet unknown in the plaque of psoriasis to which it is applied. There must then be transfer, presumably blood-borne, of these factors to other sites in the body, and these factors are still active when they reach their target. It is possible that there is transport through the skin as well, so that plaques close to those treated may benefit in this way additionally. There are a number of potential candidates, both cellular and humoral, for this role.

The mode of action of dithranol remains unknown. Inhibition of cell growth occurs at pharmacological concentrations (4), possibly due to inhibition of DNA synthesis (5), whilst inhibition of glucose-6 phosphate-dehydrogenase activity also occurs, with a return of elevated formation of cyclic nucleotides to normal levels (6). In addition, the production of free radicals during dithranol auto-oxidation may influence polymorphonuclear cell function (7). Of these actions, the effect on polymorph

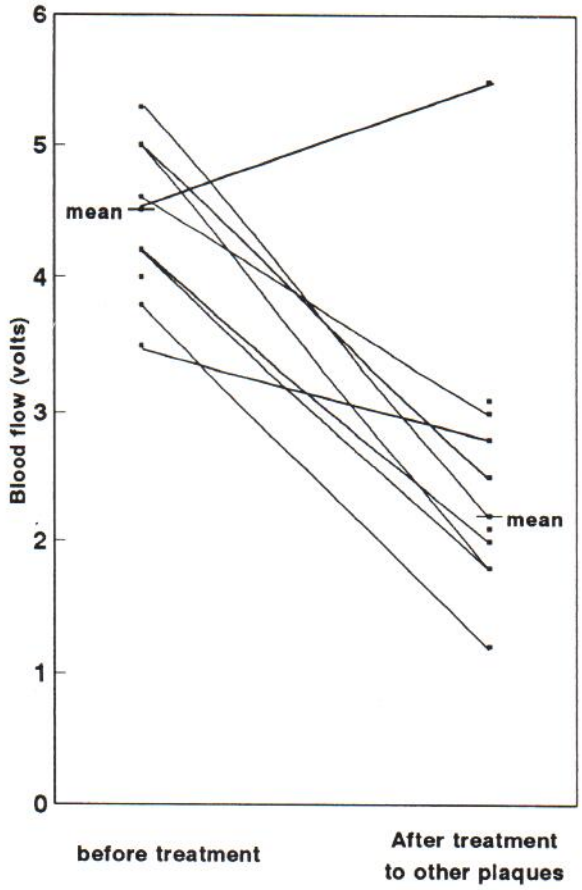

Fig. 3. Change in blood flow at centre of untreated plaque.

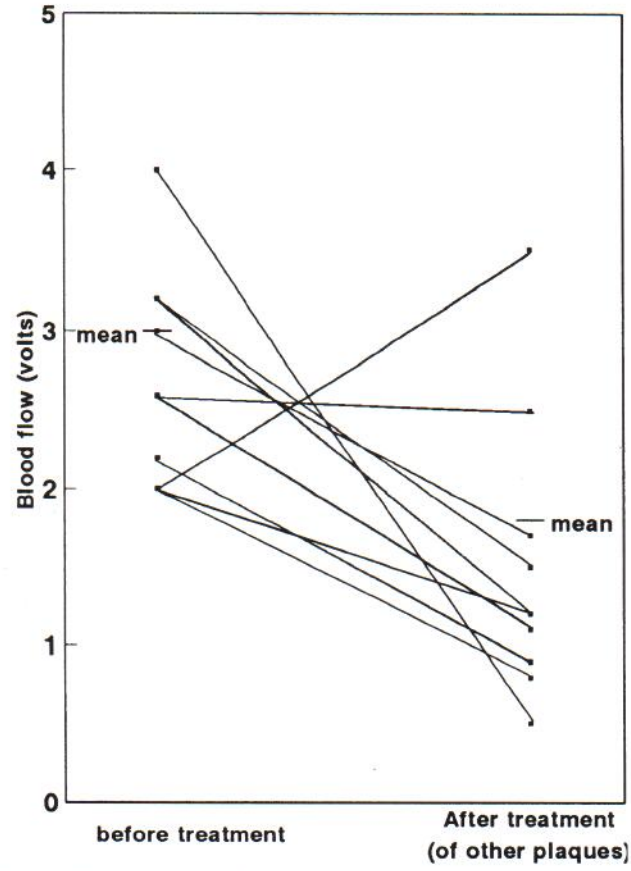

Fig. 4. Change in blood flow: active edge of untreated plaque.

function may be the most relevant, since these cells are free to re-enter the circulation. Alternatively, since it is known that T lymphocytes are intimately involved with the pathogenesis of the psoriatic lesion (8), an indirect effect on these cells is possible.

In the developing psoriatic lesion, changes in cutaneous blood flow occur before any increase in the number of T cells found (2), and some authors, including Bravermann & Sibley (9), believe that the microvascular change is the initiating one in psoriasis. Since many of the peptide-regulating factors have effects on vascular smooth muscle and endothelial function (10), it is possible that one of these peptides, particularly transforming growth factor ß or tumour necrosis factor, is intimately involved in both the initiation and termination of psoriatic lesions. Since transport of both these factors occurs, albeit in an inactive form (10), they could be the humoral agents responsible for the effect documented here.

Whilst such suggestions remain hypothetical, but amenable to confirmation, the practical importance of these findings is apparent. It is likely that the effects demonstrated here would interfere with the assessment of two treatments for psoriasis applied to different sites on the same patient. This is an important point and has implications for many studies already performed and published.

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