

Plasma Endothelin in Psoriasis: Possible Relations to Therapy and Toxicity

HUGH ZACHARIAE¹, LENE HEICKENDORFF² and PETER BJERRING¹

¹Department of Dermatology, Marselisborg Hospital, and ²Department of Clinical Biochemistry, Aarhus Amtssygehus, University of Aarhus, Aarhus, Denmark

Plasma endothelin levels were studied in 71 patients suffering from severe psoriasis. The psoriatics were treated either with topical therapy alone ($n=18$) or with cyclosporin A ($n=26$), methotrexate ($n=21$), or with hydroxyurea, acitretin or ranitidin ($n=6$) with or without topical therapy. The psoriatics had a significantly higher average plasma endothelin than 40 healthy controls. The patients treated with cyclosporin A had the highest values and these were in contrast to patients on methotrexate and other systemic therapy higher than patients treated with topical therapy alone. There was not significant difference between endothelin levels in patients treated with methotrexate compared to those in patients only receiving topical treatment. Whether the increased endothelin levels in plasma are derived from keratinocytes or enlarged vessels needs to be investigated. An increased plasma endothelin level could be related to therapy and for patients on cyclosporin A be of importance for toxicity. **Key words:** cyclosporin A; methotrexate; topical therapy.

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H. Zachariae, Department of Dermatology, Marselisborg Hospital, University of Aarhus, P.P. Ørumsgade, DK-8000 Aarhus C, Denmark.

Endothelins (ETs) are a family of three newly discovered vasoactive peptides, originally thought characteristically to be synthesized and released by endothelial cells. More recently it has been shown that endothelium is not the only site of synthesis, nor is smooth muscle the only target (1). It has been found that human keratinocytes (2) macrophages and monocytes (3), and several human cancer cell lines produce ETs. ET-1 is one of the most powerful vasoconstrictors known, and renal vessels are particularly sensitive to the effect of ET.

A study by Trevisan et al. from 1994 (4) showed a significant increase of ET-1 and 2 in plasma from psoriatics compared to controls. In the present study, we have evaluated plasma levels in psoriatics during treatment with either topical steroids and/or tar in combinations with systemic therapy with cyclosporin A (CsA) or methotrexate (MTX).

PATIENTS AND METHODS

All 71 patients suffered from pronounced psoriasis which either required systemic therapy or hospitalisation for topical therapy (18 patients). Twenty-six were treated with CsA, 21 with MTX, two with hydroxyurea, two with ranitidine and two with acitretin. CsA doses varied from 2.5 to 5 mg/kg/day and MTX from 7.5 to 15 mg weekly. Hydroxyurea was given as 500 mg daily, ranitidine with a dose of 150 mg twice daily and acitretin 25 mg twice daily. All patients on systemic therapy had been treated for at least 8 weeks, and the majority were in partial remission.

ET was analysed by a radioimmunoassay after preliminary acidification and extraction on C18 columns (Nichols Institute Diagnostic,

Wychen, The Netherlands). This method determines ET-1, ET-2 and ET-3 with relative specificities of 100%, 67% and 84%, respectively. The method was modified to increase sensitivity by diluting antibody and tracer 1:2 with PBS (5). A minimal detectable dose of 0.7 pg/ml was obtained and an interassay CV% of 6%. A normal reference range of 1.4-4.2 pg/ml was established (mean \pm 2 SD) by analysis of samples from 40 healthy individuals.

For statistical analysis Kruskal-Wallis one-way Anova on ranks and Dunn's test were used for comparisons among patient groups and healthy controls. A p value of 0.05 was considered as the limit of significance.

RESULTS

Patients suffering from severe psoriasis had a higher average plasma ET than healthy controls ($p<0.001$) (Table I). Using a multiple comparison procedure, we found significantly elevated levels of ET in all patient groups compared to healthy controls (Fig. 1). The patients treated with CsA had the highest ET values, and plasma ET in this group was significantly higher than in patients treated with topical therapy alone ($p<0.05$). There was no significant difference between ET levels in patients treated with MTX compared to topical therapy alone.

DISCUSSION

In this study, we have supported the data of Trevisan et al. (4), showing increased plasma ET in psoriasis. No information on therapy was given in their paper. One could assume that the highest values would be expected to occur in psoriatics treated with systemic therapy, because these were the most severely affected. On the other hand many of these patients were in partial remission due to the therapy given. Whether the increased ETs in psoriasis are derived from hyperproliferative keratinocytes or from enlarged vessels has not been studied and needs to be investigated.

An increased plasma ET level could also be related to therapy. CsA increases ET plasma levels in patients with solid organ transplants (6), and CsA increases the basal release of ET-1 in human glomerular endothelial cell monolayers (7). It

Table I. Plasma endothelin in patients with psoriasis and in healthy controls

Patient group	<i>n</i>	Plasma Endothelin pg/ml (mean \pm SD)
Psoriasis		
All patients	65	5.4 \pm 1.7
CsA treatment	26	6.3 \pm 1.7
MTX treatment	21	5.0 \pm 1.5
Topical treatment	18	4.5 \pm 1.1
Controls	40	2.8 \pm 0.6

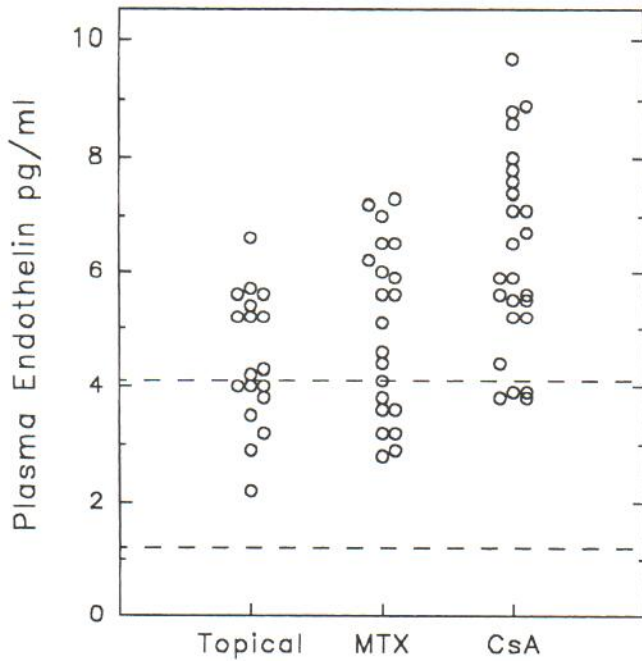


Fig. 1. Plasma endothelin in psoriatics studied during different therapies. Topical therapies were local administration of steroids and/or tar. *MTX*=methotrexate, *CsA*=cyclosporin A. The normal reference range is indicated by dotted lines (mean \pm 2 SD; $n=40$).

is well known that the use of *CsA* is complicated by hypertension, renal vasoconstriction and impaired glomerular filtration (8) and that similar findings can be induced by ET (1). Although endothelin receptor antagonists in rats have not

reversed chronic *CsA* induced renal vasoconstriction (9), it may still be prudent to follow plasma ET's in patients on *CsA* therapy and try to correlate increases in ET with the well known functional and morphological renal abnormalities (8).

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