LETTERS TO THE EDITOR

Effect of isradipine on endothelin-1 plasma concentrations in patients with Raynaud’s phenomenon

Raynaud’s phenomenon is a common microcirculatory disorder the pathogenesis of which remains obscure.1 Significantly increased concentrations of plasma endothelin-1 (ET-1), suggesting a possible pathogenetic role of this peptide, have been reported in a majority of patients with Raynaud’s phenomenon.2 Among different agents used to treat the condition, generally with disappointing results,3 calcium antagonists seem to be the most useful.4 We have investigated the effects of a new calcium antagonist (isradipine) on vasopositive episodes and plasma concentrations of ET-1 in patients with primary (type I) and suspected secondary (type II) Raynaud’s phenomenon, using a double blind, placebo controlled, and randomised parallel group trial.

The study was approved by the local ethics committee. In accordance with Kallemberg et al.,5 patients were classified as having type I Raynaud’s phenomenon in the absence of other clinicoanatomical manifestations, and type II when Raynaud’s phenomenon was associated with one or more symptoms of connective tissue disease not fulfilling the American Rheumatism Association criteria for a definite diagnosis. After giving their informed consent, 33 consecutive outpatients (table) with active Raynaud’s phenomenon (14 with type I; 19 with type II), diagnosed according to Allen and Brown,6 were recruited to the study during the winter. The mean duration of their Raynaud’s phenomenon was 6.7 (SD 5) years (range 2–19). Subjects with a history of cardiopulmonary, renal, hepatic, or metabolic disorders, traumatic factors, or those treated with anti-inflammatory drugs were excluded from the trial; patients receiving vasodilator treatment underwent a two week washout period. Initially, each patient underwent careful physical examination, chest radiography, electrocardiography, and routine blood chemistry investigations. In addition, autoantibodies (antineuclear antibody) were sought and capillary microscopy was performed according to techniques described previously7 (table).

Clinicoepidemiological, serological, and capilaroscopic characteristics of 33 patients with Raynaud’s phenomenon (RP)

<table>
<thead>
<tr>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Duration of RP (yr)</th>
<th>Associated clinical features (%)</th>
<th>Auto-antibodies (%)</th>
<th>Nailfold capillary microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary tortuosity (%)</td>
<td>Capillary loss (%)</td>
<td>Enlarged capillaries (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I RP (n = 14)</td>
<td>1/13</td>
<td>38 (15)</td>
<td>6/7 (5-9)</td>
<td>44*</td>
<td>0</td>
</tr>
<tr>
<td>Type II RP (n = 19)</td>
<td>2/17</td>
<td>50 (15)</td>
<td>6/7 (3-9)</td>
<td>90**</td>
<td>85†</td>
</tr>
</tbody>
</table>

Values are number, or mean (SD), as relevant.


Subsequently, patients were allocated randomly to receive, at 08:00, isradipine 5 mg/day (18 patients; eight with type I Raynaud’s phenomenon) or placebo (15 patients; six with type I Raynaud’s phenomenon) for a three week period. Patients treated with placebo were comparable to those in the group treated with isradipine as regards baseline clinicoanatomical characteristics. Each patient received an instruction booklet and a clinical diary for daily recording of episodes of Raynaud’s phenomenon, variations in blood pressure, and possible side effects. Statistical analysis was carried out by means of Student’s t and Wilcoxon’s tests.

At the beginning and the end of the trial, the plasma concentration of ET-1 was measured using a radioimmunoassay kit (Endothelin 1-2 RIA, Biomedica Gesellschaft mbH, Wien, Austria; normal values: mean 0.49 pg/ml (2SD 0.20)) with some modifications. Four of the 33 patients enrolled, one receiving isradipine and three receiving placebo, withdrew after a few days of treatment because of low compliance. In isradipine treated patients only, there was a significant reduction in the number of acute attacks from a mean of 2.6 (SD 1.8, SEM 0.4/day) to 1.5 (0.9, 0.2/day) (p < 0.005); in discomfort score (on a scale of 0–10) from 7.4 (2.0, 0–6) to 5.2 (2.0, 0.5) (p < 0.0005); and in hand disability score (scale of 0–3) from 1.8 (1.0, 0–3) to 1.3 (0.9, 0.2) (p < 0.05). This clinical improvement was mirrored by a significant reduction in plasma concentrations of ET-1 from 1.60 (0.94, 0.25) pg/ml to 1.12 (0.67, 0.18) pg/ml (p < 0.025) (figure) during isradipine treatment. Patients receiving placebo did not show significant variations in any clinical parameter or in ET-1 concentrations. In the isradipine treated group, no differences were demonstrated between patients with type I and type II Raynaud’s phenomenon. In addition, no significant variations in blood mean (SEM) variations in plasma endothelin-1 (ET-1) concentrations in patients with Raynaud’s phenomenon treated with isradipine (%) or placebo (#).
Bone mineral density and bone turnover in spinal osteoarthritis.

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