Prostaglandin E₁ infusions for vascular insufficiency in progressive systemic sclerosis

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SUMMARY Twelve patients with systemic sclerosis (SS) and severe Raynaud’s phenomenon received infusions of prostaglandin E₁ (PGE₁) at a dose of 6–10 ng/kg/min, with either saline or 5% dextrose, for 72 hours in a single-blind cross-over study. The infusions were administered intravenously by centrally positioned catheters. Infusions were well tolerated with only mild side effects. Following the PGE₁ infusion cold tolerance improved and attacks of Raynaud’s phenomenon were less frequent, less severe, and shorter in duration. This subjective improvement was maintained for several weeks in most patients, and 2 noted healing of ischaemic ulcers. There was no significant change in objective measurements of hand function after either infusion. However, pain measured on a 10 cm visual analogue scale improved 2.19 cm with PGE₁ and only 0.91 cm with normal saline (P<0.05). Temperature of the fingers and hands recorded by thermography did not change significantly with saline infusions, but did rise during PGE₁ infusions (mean rise 2.0°C at 48 hours, p<0.001), and was maintained when measured again 2 weeks later (mean rise 1.56°C, p<0.001). PGE₁ may therefore be suitable treatment for Raynaud’s phenomenon and the vascular insufficiency of systemic sclerosis and other connective tissue diseases.

Prostaglandin E₁ is a potent vasodilator and inhibitor of platelet aggregation¹ which has been used with apparent benefit in patients with peripheral vascular disease²³ and ulceration of the lower limb.⁴ Systemic sclerosis (SS) has been regarded as an abnormality of collagen.⁵⁶ However, there is evidence that the disease has an important vascular component,⁷⁻⁸ the predominantly affected vessels being small arteries, about 150–500 μm diameter.⁸ Over 90% of patients with SS have vascular problems, including severe Raynaud’s phenomenon,⁷⁻⁸⁻¹⁰ but as yet no satisfactory treatment is available.

This report describes the results of a comparative study of PGE₁ and placebo infusions in patients with SS and severe vascular insufficiency leading to ulceration, necrosis, and loss of digits.

Patients and methods

Twelve patients with SS (Table 1) were treated with both PGE₁ and control infusions of either normal saline (7 patients) or 5% dextrose (5 patients), in a single-blind, blind-observer, cross-over trial. Diagnosis was based on a history of severe Raynaud’s phenomenon and sclerodactyly, with or without other systemic features of SS. Three patients had already required digital amputations, and in 5 ischaemic ulceration of the fingers was present.

The patients were admitted to hospital for 5 days, and informed consent was obtained for each infusion which was given over 72 hours. The active and placebo infusions in each patient were separated by a period of 4 to 5 weeks. Infusions were given through a central venous catheter. 1 ml of a cooled (4°C) solution of PGE₁ (Upjohn Ltd) containing 500 microgrammes was added to 9 ml of sterile bacteriostatic water with benzyl alcohol 0.9 w/v for injection, and infused in normal saline or 5% dextrose at an initial dose of 6 ng/kg/min, which was increased after 12 hours to 10 ng/kg/min to minimise any unwanted side effects.

MEASUREMENTS

Measurements were made immediately before an infusion, at 24 hours, 48 hours, on completion of an...
infusion, and again 14 days later. Subjective assessments on a 3-point scale (better, same, worse) were made of the patient's opinion, and preference for either first or second infusion was recorded together with change in hand symptoms, in particular warmth, stiffness, and cold tolerance. In 7 patients pain was assessed on a 10 cm visual analogue scale (VAS). Objective measurements of hand function included grip strength and finger goniometry. Serial lung function tests and diffusion capacity were obtained before and 2 weeks after each infusion.

Quantified infrared thermography was recorded daily during an infusion and again 2 weeks later. Patients were allowed to equilibrate for 15 minutes in a controlled environment. Thermograms were taken from the hands and fingers. A standard cold water challenge was also performed immediately before and after an infusion; an initial thermogram was obtained prior to both hands being immersed in water at 20°C for 1 minute, and recordings were taken at 4 and 10 minutes thereafter.

The thermographic results recorded from both hands during prostaglandin E\textsubscript{1} and placebo infusions were analysed by a paired Student's t test and patient preference was assessed by the χ\textsuperscript{2} test.

Results

The PGE\textsubscript{1} infusions were well tolerated. Initially inflammation at the position of the catheter tip was a problem, with peripherally placed intravenous lines, and 1 patient developed symptomatic postural hypotension. There were no other significant side effects.

After PGE\textsubscript{1} therapy, but not saline, 10 patients reported a marked improvement in hand symptoms, and in 9 of these cold tolerance was especially improved. Attacks of Raynaud's phenomenon were less frequent, less severe, and shorter in duration. Two patients who had painful ischaemic finger ulceration noted healing after PGE\textsubscript{1} infusions, and most recorded improved hand function and a general sense of warmth and well being (Table 2).

Ten of the 12 patients preferred PGE\textsubscript{1} therapy to saline; 2 reported no preference for either infusion (χ\textsuperscript{2} = 14.0, p<0.001).

Pain (VAS) improved 2-19 cm with PGE\textsubscript{1} and only 0-91 cm with normal saline (p<0.05). There was no significant change in grip strength, finger goniometry, or lung function with either treatment.

Table 1  Clinical details of 12 patients with systemic sclerosis who received 72-hour infusions in a single-blind cross-over trial comparing prostaglandin E\textsubscript{1} with normal saline or 5% dextrose

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of Raynaud's phenomenon (years)</th>
<th>Mode of onset of disease</th>
<th>Clinical features</th>
<th>Other vascular features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>55</td>
<td>22</td>
<td>Raynaud's phenomenon</td>
<td>General scleroderma, C, R, S, T, dysphagia, gastrointestinal and pulmonary involvement</td>
<td>Multiple digital amputations</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>54</td>
<td>3</td>
<td>Raynaud's phenomenon</td>
<td>Swollen hands and feet, R, Pulmonary involvement</td>
<td>Finger ulceration</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>63</td>
<td>11</td>
<td>Raynaud's phenomenon</td>
<td>General and truncal scleroderma, C, R, S, pulmonary involvement</td>
<td>Finger ulceration, single digital amputation, ECG changes</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>9</td>
<td>Raynaud's phenomenon</td>
<td>General scleroderma, R, T, dysphagia, gastointestinal and renal involvement</td>
<td>Finger ulceration, gangrene, multiple digital amputations, Severe renal hypertension</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>69</td>
<td>15</td>
<td>Raynaud's phenomenon</td>
<td>General and truncal scleroderma, C, R, S, T, dysphagia, gastointestinal and pulmonary involvement</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>33</td>
<td>11</td>
<td>Raynaud's phenomenon</td>
<td>General scleroderma, C, R, S, T, dysphagia, gastointestinal and pulmonary involvement</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>53</td>
<td>3</td>
<td>Raynaud's phenomenon</td>
<td>General and truncal scleroderma, C, R, S, T, dysphagia, gastointestinal and pulmonary involvement</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>52</td>
<td>7</td>
<td>Raynaud's phenomenon</td>
<td>General scleroderma, C, R, S, T, dysphagia, gastointestinal and pulmonary involvement</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>55</td>
<td>12</td>
<td>Stiffness of hands</td>
<td>General scleroderma, R, T</td>
<td>Finger ulceration</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>55</td>
<td>12</td>
<td>Raynaud's phenomenon</td>
<td>General scleroderma, R</td>
<td>Finger ulceration</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>48</td>
<td>30</td>
<td>Raynaud's phenomenon</td>
<td>Scleroderma hands, R, S, T, dysphagia, renal and cardiac involvement</td>
<td>Finger ulceration, mild renal hypertension, ECG changes</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>34</td>
<td>18</td>
<td>Raynaud's phenomenon</td>
<td>General and truncal scleroderma, C, R, S, T, pulmonary and renal involvement</td>
<td>Mild renal hypertension</td>
</tr>
</tbody>
</table>


Table 2  Subjective results (12 patients) at 14 days after infusion

<table>
<thead>
<tr>
<th></th>
<th>PGE\textsubscript{1}</th>
<th>NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Better</td>
<td>Same</td>
</tr>
<tr>
<td>1. Observer</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2. Patient</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>3. Hand symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Warmth</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>(b) Stiffness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>(c) Cold tolerance</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>
An immediate rise in peripheral temperature was demonstrated thermographically in 4 patients within minutes of starting PGE1 infusions (Table 3).

Thermography of the hands (Fig. 1) did not change significantly with saline infusions, but hand temperature did rise during PGE1 infusions (mean rise 2.0°C at 48 hours, p<0.001). Although no further pharmacological treatment was used, thermography recorded a maintained rise in hand temperature two weeks after a PGE1 infusion (mean rise 1.56°C, p<0.001).

Cold challenge measured immediately on completion of an infusion and again 14 days later was unaltered despite an initially increased hand temperature following PGE1, but thermographic recordings were not continued beyond the standard 10 minutes of the test (Fig. 2).

**Discussion**

A number of vasodilators have been used in patients with systemic sclerosis and vascular insufficiency. Short-lasting benefit has been reported with intravenous low molecular weight dextran and with single intra-arterial injections of reserpine 0.5 mg. Oral vasodilators and fibrinolytic agents have also been used but, in general, prolonged benefits have not been reported. PGE1 is a potent vasodilator and inhibitor of platelet aggregation, and some short-term improvement of peripheral blood flow in systemic sclerosis might therefore be expected.

Intra-arterial and intravenous PGE1 has been used to treat a variety of vascular disorders. Carlson et al. infused 2–4 ng/kg/min intra-arterially for 10 min every hour for 3 days and alleviated rest pain for several weeks in patients with arteriosclerosis obliterans. However, Nielsen et al. were sceptical about its benefit in severe vascular insufficiency. Sakaguchi et al. found intra-arterial PGE1 helpful in the treatment of ischaemic leg ulcers. In a pilot study one of us (J.D.T.K.) found that intra-arterial PGE1 produced a sustained improvement in the symptoms of pain, cold tolerance, and hand mobility in 1 patient with systemic sclerosis and that intravenous PGE1 resulted in a similar beneficial effect in a second patient with severe Raynaud's phenomenon. A formal controlled study of PGE1 in systemic sclerosis was therefore undertaken.

The problem with previous studies of new therapies in Raynaud's phenomenon has been the lack of methods to measure change in blood flow to the extremities. Various methods have been used, and quantified infrared thermography is now an accepted technique for measuring changes in peripheral blood flow, and we employed it in this study.
The results clearly showed an immediate and sustained improvement in peripheral temperature during the PGE₁ infusion period. It is presumed that this was due to improved peripheral blood flow. This was accompanied by a far greater symptomatic improvement than that obtained by the placebo infusions. Huge intravenous doses were used, because a large percentage of circulatory PGE₁ is destroyed by a single passage through the lungs. However, the immediate rise in hand temperature that was recorded indicated that a therapeutic dose was reaching the systemic circulation.

This trial also demonstrated a sustained beneficial effect from an infusion of PGE₁. Patients reported a maintained general symptomatic improvement, attacks of Raynaud’s phenomenon were less severe, and these benefits lasted for a period of several weeks following an infusion. It is hard to explain the changes in terms of a pure vasodilator effect, as PGE₁ has a very short half-life. The standard cold challenge test demonstrated no change in the severity of vasospasm during an induced Raynaud’s attack, and the benefits of PGE₁ were not immediately obvious during the 10 minutes of the test, but if measurements had been continued for longer a difference in the pattern of rewarming may have become apparent. Possible mechanisms include the promotion of tissue revascularisation or a lasting effect on the vessel walls, perhaps mediated by changes in cyclic nucleotide levels within vascular endothelial cells. PGE₁ is known to influence lymphocyte function, and in this way immunological phenomena associated with established systemic sclerosis may be altered. Changes in platelet aggregation may also be a factor in the production of an improved peripheral blood flow. Further work on the mode of action of PGE₁ resulting in sustained benefit found in this and other trials is required.

In this study high-dose intravenous PGE₁ was well tolerated and resulted in marked symptomatic benefit. Quantified thermography showed unequivocal evidence of a significant rise in peripheral temperature during the infusion, and this effect was sustained for several weeks. PGE₁ may therefore be suitable treatment for Raynaud’s phenomenon and vascular insufficiency of systemic sclerosis and other connective tissue diseases. Further investigations are under way.

We are glad to acknowledge the support of the Arthritis and Rheumatism Council for this work, and would like to thank Dr B Copley, Upjohn Ltd., Crawley, Sussex, UK, for supplying the prostaglandin E₁, and both Sally Bowcock and Sharon Martin who obtained and recorded the thermographic data.

References

Martin, Dowd, Ring, Cooke, Dieppe, Kirby


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