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Prostaglandin E_1 infusions for vascular insufficiency in progressive systemic sclerosis

M. F. R. MARTIN,[1] P. M. DOWD,[2] E. F. J. RING,[1] E. D. COOKE,[2] P. A. DIEPPE,[1] AND J. D. T. KIRBY[2]

From the [1]Department of Rheumatology, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW, and the Royal National Hospital for Rheumatic Diseases, Bath BA1 1RL; and the [2]Department of Dermatology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

SUMMARY Twelve patients with systemic sclerosis (SS) and severe Raynaud's phenomenon received infusions of prostaglandin E_1 (PGE_1) 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 PGE_1 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 PGE_1 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 PGE_1 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, $p<0·001$). PGE_1 may therefore be suitable treatment for Raynaud's phenomenon and the vascular insufficiency of systemic sclerosis and other connective tissue diseases.

Prostaglandin E_1 is a potent vasodilator and inhibitor of platelet aggregation[1] which has been used with apparent benefit in patients with peripheral vascular disease[2 3] and ulceration of the lower limb.[4] Systemic sclerosis (SS) has been regarded as an abnormality of collagen.[5 6] However, there is evidence that the disease has an important vascular component,[7–9] 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 PGE_1 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 PGE_1 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 PGE_1 (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

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Correspondence to Dr M. F. R. Martin, Rheumatism Research Unit, University of Leeds, 36 Clarendon Road, Leeds LS2 9PJ.

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_1 with normal saline or 5% dextrose*

No	*Sex*	*Age (years)*	*Duration of Raynaud's phenomenon (years)*	*Mode of onset of disease*	*Clinical features*	*Other vascular features*
1	F	55	22	Raynaud's phenomenon	General scleroderma, C, R, S, T, dysphagia, gastro-intestinal and pulmonary involvement	Mutiple digital amputations
2	F	54	3	Raynaud's phenomenon	Swollen hands and feet, R, Pulmonary involvement	
3	F	63	11	Raynaud's phenomeon	General scleroderma, C, R, S, T, dysphagia, pulmonary involvement	Finger ulceration
4	F	44	9	Raynaud's phenomenon	General and truncal sclεroderma, C, R, S, pulmonary involvement	Finger ulceration, single digital amputation, ECG changes
5	F	69	15	Raynaud's phenomenon	General scleroderma, R, S, T, dysphagia, Sjögren's, pulmonary involvement	
6	F	33	11	Raynaud's phenomenon	General scleroderma, C, R, S, T, dysphagia, gastro-intestinal and pulmonary involvement	Finger ulceration, gangrene, multiple digital amputations
7	M	53	3	Raynaud's phenomenon	General and trunchal scleroderma, C, R, S, T, dysphagia, gastro-intestinal and renal involvement	Severe renal hypertension
8	F	52	7	Raynaud's phenomenon	General scleroderma, R, S, T, dysphagia, pulmonary involvement	
9	F	55	12	Stiffness of hands	General scleroderma, R, T	
10	F	55	12	Raynaud's phenomenon	General scleroderma, R	Finger ulceration
11	F	48	30	Raynaud's phenomenon	Scleroderma hands, R, S, T, dysphagia, renal and cardiac involvement	Finger ulceration, mild renal hypertension, ECG changes
12	F	34	18	Raynaud's phenomenon	General scleroderma, R, S, T, pulmonary and renal involvement	Mild renal hypertension

C=Calcinosis. R=Raynaud's phenomenon. S=Sclerodactyly. T=Telangiectasia.

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_1 and placebo infusions were analysed by a paired Student's *t* test and patient preference was assessed by the χ^2 test.

Results

The PGE_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_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_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_1 therapy to saline; 2 reported no preference for either infusion ($\chi^2 = 14{\cdot}0$, $p<0{\cdot}001$).

Pain (VAS) improved 2·19 cm with PGE_1 and only 0·91 cm with normal saline ($p<0{\cdot}05$). There was no significant change in grip strength, finger goniometry, or lung function with either treatment.

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

	PGE_1			*NaCl*		
	Better	*Same*	*Worse*	*Better*	*Same*	*Worse*
1. Observer	9	3	0	1	11	0
2. Patient	10	2	0	3	9	0
3. Hand symptoms						
(a) Warmth	10	2	0	0	12	0
(b) Stiffness	7	5	0	2	10	0
(c) Cold tolerance	9	3	0	3	9	0

Table 3 *Effect of intravenous PGE1, 10 ng/kg/min, on the thermographic index (TI) of the hand (dorsum) and fingers (PIP) in 4 patients within 10 min of starting on infusion*

Patient	*Dorsum*		*PIP*	
	0 min	10 min	0 min	10 min
1	2·80	3·60	1·30	3·50
2	2·20	3·40	0·75	2·15
3	1·25	2·95	0·35	1·75
4	0·95	2·60	0·15	0·85

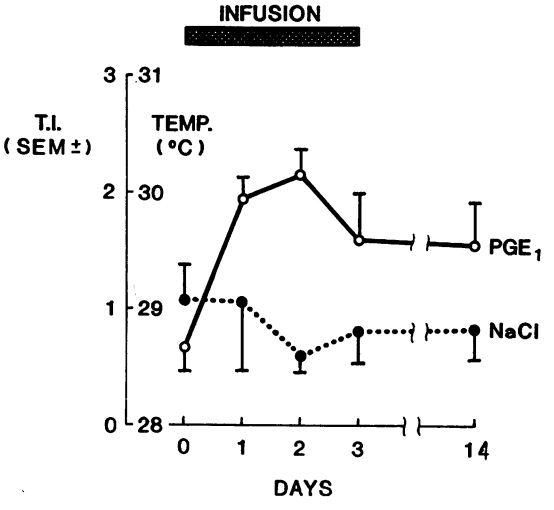

Fig. 1 *Mean thermographic index (TI) of fingers in 12 patients (daily during infusion and 14 days after).*

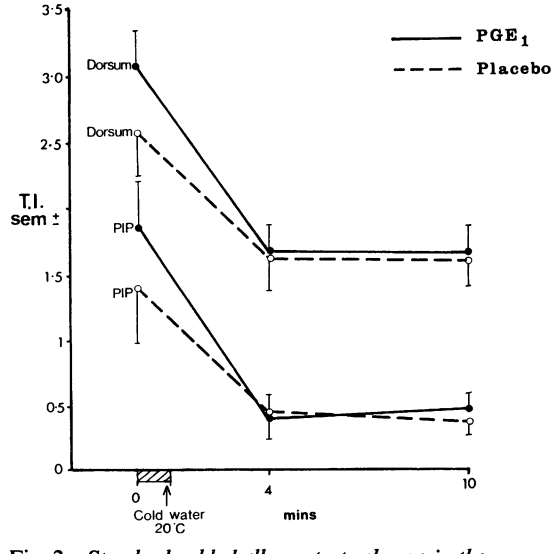

Fig. 2 *Standard cold challenge test: change in thermographic index (TI) of the hand (dorsum) and fingers (proximal interphalangeal (PIP) joints) following immersion in cold water (20°C) for 1 minute.*

An immediate rise in peripheral temperature was demonstrated thermographically in 4 patients within minutes of starting PGE_1 infusions (Table 3).

Thermography of the hands (Fig. 1) did not change significantly with saline infusions, but hand temperature did rise during PGE_1 infusions (mean rise 2·0°C at 48 hours, $p<0·001$). Although no further phermacological treatment was used, thermography recorded a maintained rise in hand temperature two weeks after a PGE_1 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 PGE_1, 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[11] and with single intra-arterial injections of reserpine 0·5 mg.[12,13] Oral vasodilators[14–16] and fibrinolytic agents[17] have also been used but, in general, prolonged benefits have not been reported. PGE_1 is a potent vasodilator and inhibitor of platelet aggregation,[1] and some short-term improvement of peripheral blood flow in systemic sclerosis might therefore be expected.

Intra-arterial and intravenous PGE_1 has been used to treat a variety of vascular disorders. Carlson *et al.*[3] 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, Nielson *et al.*[18] were sceptical about its benefit in severe vascular insufficiency. Sakaguchi *et al.*[4] found intra-arterial PGE_1 helpful in the treatment of ischaemic leg ulcers. In a pilot study one of us (J.D.T.K.) found that intra-arterial PGE_1 produced a sustained improvement in the symptoms of pain, cold tolerance, and hand mobility in 1 patient with systemic sclerosis and that intravenous PGE_1 resulted in a similar beneficial effect in a second patient with severe Raynaud's phenomenon. A formal controlled study of PGE_1 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,[19,20] and quantified infrared thermography is now an accepted technique for measuring changes in peripheral blood flow,[21,22] and we employed it in this study.

The results clearly showed am immediate and sustained improvement in peripheral temperature during the PGE_1 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 PGE_1 is destroyed by a single passage through the lungs.[23] 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 PGE_1. 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 PGE_1 has a very short half life.[23] The standard cold challenge test demonstrated no change in the severity of vasospasm during an induced Raynaud's attack, and the benefits of PGE_1 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[24] or a lasting effect on the vessel walls, perhaps mediated by changes in cyclic nucleotide levels[25] within vascular endothelial cells. PGE_1 is known to influence lyphocyte function, [26 27] and in this way immunological phenomena associated with established systemic sclerosis[28–30] may be altered. Changes in platelet aggregation[1] may also be a factor in the production of an improved peripheral blood flow. Further work on the mode of action of PGE_1 resulting in sustained benefit found in this and other trials is required.

In this study high-dose intravenous PGE_1 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. PGE_1 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.

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