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A multiclinic, placebo-controlled, double-blind study of prostaglandin E_1 in Raynaud's syndrome

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SUMMARY Prostaglandin E_1 (alprostadil, Prostin VR Sterile Solution, PGE_1) was evaluated in patients with Raynaud's syndrome in a multiclinic, placebo-controlled, double-blind study. A total of 55 patients with either primary Raynaud's disease or Raynaud's disease secondary to systemic sclerosis were randomly assigned to receive either PGE_1 administered intravenously at 10 ng/kg/min for 72 hours or placebo administered in the same manner. The frequency and severity of Raynaud's attacks were then monitored for up to four weeks by use of in-clinic questionnaires and patients' daily diaries. Haemodynamic assessments included measurements of skin temperature and the finger systolic pressure response to localised digital cooling. Immediately after the infusion the overall symptoms in both the PGE_1 and the placebo group showed marked improvement; by four weeks after infusion, in some cases, values had not returned to pretreatment levels. There was, however, no marked benefit of PGE_1 treatment over that of placebo. Although PGE_1 significantly increased skin temperature during and immediately after infusion, the effect did not persist at two- and four-week follow-up evaluations. The finger systolic pressure response to localised digital cooling (15°C) increased more in the PGE_1-treated group than in the placebo-treated group, but the difference was not statistically significant. There was no difference in ulcer healing between the two treatment groups. These results failed to substantiate earlier open-label reports that a 72-hour intravenous infusion of PGE_1 in patients with Raynaud's syndrome produced significant clinical benefit.

Key words: vasospasm, Raynaud's disease, PGE_1, finger blood pressure, cold hands.

Raynaud's syndrome is an episodic digital ischaemia resulting from vasospasm induced by cold, stress, or medication. It is often associated with connective tissue diseases, such as systemic sclerosis, wherein the vasospasm is superimposed over an already obstructed digital artery. It is more commonly observed as a primary disorder, frequently called Raynaud's disease. At present there is no standard pharmacotherapy for the treatment of patients with the cold-induced digital ischaemia known as Raynaud's syndrome. There have been numerous pharmacological approaches, which include vasodilators, fibrinolytics, and sympatholytics.

Several recent reports have suggested that prostaglandin E_1 (alprostadil, Prostin VR Sterile Solution, PGE_1) can alleviate the symptoms associated with Raynaud's syndrome. Clifford *et al.*[1] reported on 26 patients with severe Raynaud's syndrome who were infused intravenously with PGE_1 (6–10 ng/kg/min) for 72 hours. In 24 of these patients Raynaud's syndrome was secondary to other diseases. An overall subjective improvement was reported by 96% of the patients during PGE_1 infusion, by 81% two weeks later, and by 65% six weeks beyond the infusion period. At six weeks after infusion 63% (five out of eight patients) of ischaemic ulcers were healed. PGE_1 produced a decrease in the Doppler-derived pulsatility index, an increase in pulse volume recording amplitude, and an increase in skin temperature. However, PGE_1 had no effect on the skin temperature response to a standard challenge of hand immersion in cold water.

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Pardy and coworkers[2 3] also reported the open-label use of intravenous PGE_1 (10 ng/kg/min for 72 hours) to treat patients with Raynaud's disease. They found that PGE_1 infusion reduced vasospasticity (as assessed by skin temperature) and increased the number of digital artery segments with Doppler-detectable flow. Moreover, PGE_1 decreased cold sensitivity, as shown by an increase in finger systolic pressure response to localised digital cooling. The beneficial effects extended for weeks beyond the infusion. Red cell flexibility, plasma fibrinogen, euglobulin lysis time, and antithrombin III were all increased after PGE_1 treatment; blood viscosity, plasma β-thromboglobulin, and platelet factor 4 were unchanged. Interestingly, symptomatic improvement (including ulcer healing) was only noted in those patients with ischaemic ulcers. Nearly all of these patients also underwent débridement, abscess drainage, and/or fingernail excision immediately after completion of PGE_1 therapy. Thus the effect of PGE_1 infusion alone, i.e., without the surgical procedures, remains uncertain.

The only placebo-controlled study which has been reported was that of Martin *et al.*,[4] who conducted a single-blind, crossover trial in patients with Raynaud's syndrome secondary to systemic sclerosis. For up to two weeks after the infusion period 83% of the PGE_1-treated patients showed an improvement in overall symptoms as compared with 25% of the placebo-treated patients. Subjective improvement was evaluated by reductions in attack frequency, duration, severity, and pain. Healing of ischaemic ulcers was noted by 40% of the patients (two out of five) who had ulcers. Quantified infrared thermography recorded a rise in hand temperature during PGE_1 infusion, which did not occur after placebo administration and which was maintained two weeks after infusion. Despite the increased hand temperature with PGE_1, there was no change in the response of these patients to a standard cold water challenge test. Grip strength and finger goniometry were not affected by either treatment.

In the light of these reports a multiclinic, placebo-controlled, double-blind study was initiated to examine the clinical efficacy of PGE_1 in patients with Raynaud's syndrome. The results are reported herein.

Patients and methods

This double-blind, placebo-controlled, prospective, and randomised study was conducted at four centres, two in the UK and two in the US. Male and postmenopausal or surgically sterile females 18 years of age or older with Raynaud's syndrome were enrolled from November 1982 to June 1983. The Raynaud's syndrome was either primary Raynaud's disease, i.e., not associated with organic arterial obstruction, or secondary to systemic sclerosis. All patients were required to have an abnormal finger systolic pressure response to localised cooling of the digits (i.e., at least a 20% reduction in the pressure response at 15°C from values obtained at 30°C). Patients who had had sympathectomies within the last 12 months were excluded from study. Patients continued their regularly prescribed medications, except that vasodilators, beta blockers, or any platelet-active medication (e.g., aspirin) were discontinued at least two weeks before the start of infusion. A brief medical history, physical examination, cold challenge test (vide infra), 12-lead electrocardiogram (ECG), and safety laboratory evaluations were obtained at the screen. Patients were then randomly assigned to receive either PGE_1 or placebo treatment, with stratification for primary and secondary Raynaud's syndrome.

TREATMENT

PGE_1 was administered by continuous infusion at 10 ng/kg/min via a central venous catheter for up to 72 hours. It was supplied as 2·5 mg active drug in a 5 ml ampoule of anhydrous alcohol and prepared by dilution with one litre of 5% glucose or 0·9% saline. The placebo solution was prepared by adding 5 ml of the placebo ethanol solution to the appropriate diluent and was administered in the same manner as the active drug.

SYMPTOM EVALUATION

Raynaud's symptoms were evaluated by an in-clinic questionnaire completed just before, immediately after, and two and four weeks after infusion. This information was verified by the daily diaries kept by patients throughout the study. The in-clinic questionnaire monitored the frequency and severity of Raynaud's attacks, change in the physical activity, medication usage, and adverse medical events. The frequency of attacks/day was recorded as less than one/day, one/day, two/day, three/day, four/day, five/day, six or more/day, or constant pain in hands. Answers were coded as 0 to 7 respectively. Least square means were calculated and analysed by a three-factor analysis of variance and Student's *t* test. Visual analogue scales (10 cm lines) were used to assess severity parameters such as pain, numbness, stiffness, and coldness.

COLD CHALLENGE

The finger systolic pressure (FSP) response to local digital cooling was measured by a modification of the Nielsen method at least two weeks before, just before, immediately after, and two and four weeks

after PGE_1 infusion. (The FSP measurement made at least two weeks before infusion was used for patient selection, since only those patients with an abnormal response to cooling were enrolled in the study.) The FSP measurement made just before infusion was used as the baseline value. The FSP measurements were performed at an ambient temperature of 23±1°C; the actual room temperature was recorded each time a measurement was taken. A thermostatically controlled room was used whenever possible. The patient was allowed to equilibrate in the room for 30 minutes before determinations were made. FSP was measured with a Medimatic cuff placed on the middle phalanx of the most affected finger and at cuff perfusion temperatures of 30, 15, and 10°C. Two to three determinations were made at each perfusion temperature.

SKIN TEMPERATURE

Digital skin temperatures were taken just before, the three days during, immediately after, and two and four weeks after infusion, at approximately the same time of day. The patient rested in the supine position for 30 minutes at an environmental temperature of 23±1°C before skin temperatures were taken. A thermostatically controlled room was used whenever possible. The room temperature was recorded each time a skin temperature measurement was made. Skin temperatures were measured with a thermistor probe on the dorsum of the distal phalanx of the most affected finger, between the distal interphalangeal joint and the nail. Three measurements were made over a one-hour interval (i.e., once every 20 minutes) for each determination.

ULCER EVALUATION

If ulcers were present on the fingers or hands an ulcer evaluation was recorded just before infusion and at two and four weeks after infusion. The location, dimensions, and duration of the ulcers were recorded, and photographs were taken.

Table 1 *Population characteristics*

	No of patients	
	PGE_1	*Placebo*
Total patients	27	28
Females	15	22
Males	12	6
Race: white	26	26
non-white	1	2
Primary disease	11	13
Secondary disease	16	15
Ulcers present	4	10
Sympathectomised	6	9
Age (years), mean±SE	46·9±2·3	43·5±2·3
Duration of disease (years), mean±SE	12·1±1·9	7·2±1·2*

* $p<0.05$ when compared with the corresponding PGE_1 value.

Table 2 *Number of daily attacks*

	Before infusion	*After infusion*		
		Immediately	*2 weeks*	*4 weeks*
All patients				
Placebo	3·9±0·4 (28)	2·0±0·4 (27)	2·9±0·4 (28)	2·8±0·5 (25)
PGE_1	3·0±0·4 (27)	0·9±0·4 (25)	1·8±0·4* (27)	2·8±0·5 (25)
Primary disease				
Placebo	3·8±0·6 (13)	2·1±0·6 (12)	2·4±0·5 (13)	2·3±0·6 (13)
PGE_1	2·6±0·6 (11)	0·1±0·7* (10)	1·5±0·6 (11)	1·8±0·7 (10)
Secondary disease				
Placebo	3·9±0·5 (15)	1·8±0·5 (15)	3·4±0·5 (15)	3·4±0·6 (12)
PGE_1	3·5±0·5 (14)	1·6±0·5 (15)	2·0±0·5 (16)	2·6±0·6 (15)

Values are the mean±SE (n).
*$p<0.05$ when compared with the corresponding placebo value.

SAFETY EVALUATIONS

Safety evaluations consisted of monitoring vital signs and taking standard safety laboratory measurements and electrocardiograms. Vital signs were recorded before and every six hours during infusion, immediately after infusion, and two and four weeks after infusion. Safety laboratory evaluations were obtained just before, immediately after, and two and four weeks after infusion. Cardiac monitoring was performed by obtaining a 12-lead ECG just before and immediately after infusion. An ECG monitor was also displayed throughout the infusion period until cardiac stability was assured.

Results

A total of 55 patients from four centres were randomly assigned to receive either PGE_1 or placebo (Table 1). There were approximately twice as many females as males. Twenty-four patients had primary Raynaud's disease, and 31 patients had Raynaud's disease secondary to systemic sclerosis. The mean duration of disease was approximately 9·5 years, and the mean age was approximately 45 years. There were a number of associated systemic disorders, the most common of which was pulmonary disease (13 patients).

ATTACK FREQUENCY

The mean frequency of attacks/day before infusion

and at various times after infusion is shown in Table 2. The number of attacks was reduced in both placebo and PGE_1 groups after infusion. In the placebo group the reduction from baseline immediately after infusion was approximately 50%. In general the PGE_1 group reported fewer attacks/day than the placebo group. The difference was statistically significant ($p<0.05$) at two weeks after infusion. At four weeks both groups still reported fewer attacks than before treatment but were not statistically significantly different from each other. The statistically significant difference in attack frequency between PGE_1- and placebo-treated patients two weeks after infusion does not allow for group differences in baseline values. When attack frequency was calculated for each patient as the change in frequency from baseline values, PGE_1 and placebo patients did not differ statistically at any time after infusion. An analysis by primary and secondary disease subgroups showed the greatest reduction in attack frequency occurred in patients with primary disease immediately after infusion with PGE_1. These results were supported by data from the daily diaries.

ATTACK SEVERITY

The mean values for the severity of Raynaud's attacks are shown in Table 3. The values for severity of hand coldness, numbness, pain, and stiffness were derived from the in-clinic questionnaire and were corroborated by information in the patients' daily diaries. The marked reduction in severity of coldness in both PGE_1 and placebo patients immediately after infusion did not persist at two and four weeks after infusion, though mean values at two and four weeks were slightly below pretreatment means. At no time did PGE_1 values differ statistically from placebo values, nor were there appreciable differences in the severity of the coldness symptom between groups with primary and secondary Raynaud's disease.

The severity of numbness decreased substantially in both PGE_1 and placebo groups immediately after infusion and gradually approached baseline values at two and four weeks after infusion. An analysis of the subgroups of patients with primary and secondary Raynaud's disease showed that most of this immediate effect was in the latter group. At no time was there a statistically significant difference in degree of numbness between the PGE_1 and placebo treatment groups.

The severity of pain immediately after PGE_1 or placebo infusion was reduced from baseline by about 50%. At two and four weeks values in the placebo group returned to near normal, while values in the PGE_1 group remained at approximately 60% of baseline. Even so, at no time did the treatment groups differ significantly. Subgroup analysis of this factor showed that the group of patients with secondary disease had the greatest reduction in pain immediately after infusion.

Hand stiffness did not follow the pattern observed with coldness, numbness, and pain immediately after infusion. The severity of stiffness was the same in the PGE_1-treated group immediately after infusion as it was before infusion but was reduced in the placebo group. This made PGE_1 appear to worsen hand stiffness when compared with placebo immediately after infusion, though the difference was not statistically significant. At two weeks after infusion, however, there was statistically significantly less stiffness in the PGE_1 group than in the placebo group ($p<0.05$). At four weeks PGE_1 patients still had less stiffness than placebo patients, but the difference was no longer significant. The subgroup analysis for this symptom did not show any

Table 3 *Severity of Raynaud's symptoms (mean±SE) evaluated on visual analogue scales (cm)*

Symptom	*Treatment*	*Before infusion*	*After infusion*		
			Immediately	*2 weeks*	*4 weeks*
Coldness	Placebo	6·1±0·5	3·1±0·5	4·9±0·5	4·8±0·6
	PGE_1	6·6±0·5	2·6±0·6	5·0±0·5	4·8±0·6
Numbness	Placebo	5·2±0·5	2·6±0·5	3·9±0·6	4·8±0·6
	PGE_1	5·5±0·5	2·3±0·6	3·8±0·7	4·1±0·7
Pain	Placebo	5·6±0·5	2·8±0·5	4·5±0·6	5·0±0·6
	PGE_1	5·7±0·5	2·6±0·5	3·6±0·6	3·6±0·6
Stiffness	Placebo	5·1±0·5	3·3±0·6	4·5±0·5	4·3±0·6
	PGE_1	4·6±0·5	4·7±0·6	2·8±0·6*	3·4±0·6
	Placebo n=	28	28	28	25
	PGE_1 n=	27	26	25	23

* $p<0.05$ when compared with the corresponding placebo value.

Table 4 *Skin temperature (°C)*

Treatment	*Before infusion*	*During infusion*			*After infusion*		
		Day 1	*Day 2*	*Day 3*	*Immediately*	*2 weeks*	*4 weeks*
Placebo	26·9±0·6 (28)	27·8±0·6 (20)	28·2±0·6 (23)	28·1±0·6 (23)	27·6±0·6 (28)	26·7±0·5 (28)	26·5±0·7 (24)
PGE_1	26·7±0·5 (27)	28·6±0·6 (22)	30·5±0·5† (22)	30·8±0·6† (22)	29·3±0·6* (26)	26·9±0·5 (27)	26·8±0·6 (25)

Values are the mean±SE (n).
* $p<0·05$ when compared with the corresponding placebo value.
† $p<0·005$ when compared with the corresponding placebo value.

striking dissimilarities between the groups of patients with primary or secondary Raynaud's disease, though at two weeks the stiffness appeared to somewhat greater in the latter group.

SKIN TEMPERATURE

In the PGE_1 treatment group a statistically significant increase in skin temperature was observed on day two and three of infusion, with respective mean values of 30·5 and 30·8°C (Table 4). Temperatures declined sharply immediately after infusion, though values in the PGE_1 group remained statistically significantly greater than those in the placebo group. The effect of PGE_1 on skin temperature did not persist at two and four weeks after infusion.

ULCERS

There were few ulcers in the study: 27 among 10 placebo patients and 13 among four PGE_1 patients. Three ulcers in placebo patients and one in a PGE_1 patient developed during the study. There was no difference between placebo and PGE_1 patients with respect to ulcer healing (26 and 23%, respectively).

FINGER SYSTOLIC PRESSURE

The finger systolic pressure (FSP) response to localised cooling (15°C) before and after treatment is shown in Table 5. The values were obtained by taking the median of three determinations for each patient at each time point. The mean (±SE) of these median values for the patient population was then determined. Only those patients whose FSP for the 15°C cuff temperature just before infusion was less than or equal to 80% of their 30°C FSP were included in the calculations. Immediately after infusion PGE_1 produced a statistically significant increase in the FSP when compared with the preinfusion mean; this increase did not persist at two and four weeks. There was no statistically significant difference between PGE_1 and placebo values at any of the evaluation periods.

OTHER EFFICACY MEASUREMENTS

The medication used in addition to PGE_1 and placebo was reduced similarly in placebo and PGE_1 groups at two and four weeks after infusion. The limitation of physical activities was not appreciably altered throughout the course of the study in either group. A generic question on the frequency of any Raynaud's symptoms also showed no statistically significant differences between the PGE_1 and placebo groups when baseline values were equalised. As can be seen from the global assessment (Table 6) a slightly greater percentage of PGE_1

Table 5 *Finger systolic pressure at 15°C cuff temperature (mmHg)*

	Before infusion	*After infusion*		
		Immediately	*2 weeks*	*4 weeks*
Placebo	13·9±9·3 (11)	30·0±13·1 (10)	25·8±11·5 (10)	16·9±10·4 (10)
PGE_1	15·3±7·1 (16)	57·7±10·7* (15)	26·6±11·3 (14)	26·8±9·5 (15)

Values are the mean±SE (n) of patients with a ≤20% decrease from the before-infusion 30°C cuff value.
* $p<0·05$ when compared with PGE_1 before-infusion value.

Table 6 *Global assessment*

	Effective (%)	*Ineffective (%)*
Patient's evaluation		
Placebo	48	52
PGE_1	63	37
Investigators' evaluation		
Placebo	18	71
PGE_1	48*	33*

*$p<0·05$ when compared with investigators' placebo values. n=28 for placebo, 27 for PGE_1 per value.

Table 7 *Number of adverse medical events reported*

	PGE_1	*Placebo*
Total	78	40
Severe	5	4
Most common:		
Injection site problems (includes oedema, inflammation, pain, vasodilatation)	10	10
Headache	10	11
Oedema	9	2
Flushing	9	4
Nausea and/or diarrhoea	6	3
Arthralgia and/or myalgia	6	2

patients than placebo patients found treatment effective; the clinical investigators thought more patients benefited from PGE_1 than from placebo treatment.

SAFETY

A total of 78 adverse medical events were reported for patients in the PGE_1 group and 40 for patients in the placebo group (Table 7). Most of these occurred during infusion (55 with PGE_1 and 11 with placebo). The 10 injection site problems occurred in six patients and were due in part to the use of a peripheral line in some of these patients. Although headache was equally prevalent in both treatment groups, more headaches during infusion were reported in PGE_1 patients (nine) than in placebo patients (five). There were five severe events in the PGE_1 group and four in the placebo group. The severe events during infusion were peripheral oedema, headache, flushing, and inflammation and pain at the injection site. One of the four severe events in the placebo group was a death that occurred at the two-week follow up and was of cardiovascular origin. It was the only death reported throughout the study.

The only appreciable differences in laboratory abnormalities between PGE_1 and placebo patients occurred immediately after infusion, at which time the PGE_1 group had three to five more occurrences of (*a*) low values of serum albumin, red blood cells, haemoglobin, and prothrombin time and (*b*) high values of glucose, monocytes, and white blood cells.

Discussion

There have been several reports[1–4] of clinical improvement in patients with Raynaud's disease after treatment with PGE_1 infusion. This improvement has been both subjective, such as a reduction in attack frequency and severity, and objective, such as changes in hand haemodynamic/rheological measurements and ulcer healing. The results of the present study do not agree with these reports, rather they show that a 72-hour infusion of PGE_1 does not provide a statistically significant clinical benefit over that of placebo treatment. Nevertheless, many of the parameters measured showed an appreciable improvement over pretreatment values in both placebo- and PGE_1-treated patients. Thus this 'placebo effect' may account for the beneficial effect reported in a number of the earlier studies. Although the source of such improvement remains obscure, it may be that the hospitalisation of patients in a controlled environment for three days to administer PGE_1 provides some degree of short-term relief of symptoms.

This is not to say that there is no therapeutic potential for PGE_1 in the treatment of Raynaud's syndrome. In the present study PGE_1 was given for only 72 hours. It may be that administration of PGE_1 over a longer time period could provide a greater and more prolonged benefit. Also there was some reduction in the severity of Raynaud's symptoms after infusion of PGE_1 in the present study. The coldness experienced immediately after infusion was somewhat less in PGE_1 patients than in placebo patients. The severity of pain and stiffness in the hands was also less in PGE_1-treated patients than in placebo patients at two and four weeks after infusion. The differences, however, were rarely statistically significant and were not clinically significant. (The PGE_1-treated patients actually experienced more stiffness than placebo patients immediately after infusion. This is consistent with the vasodilatation and peripheral oedema that PGE_1 can produce.) Moreover, a significant increase was observed in skin temperature and finger systolic pressure to localised cooling during and immediately after infusion.

The results of the present study agree in part with some earlier reports that PGE_1 can increase skin temperature[1 4] and decrease the vasospasm that results from localised digital cooling.[2] The results do not, however, support the contention that a significant effect persists well beyond the infusion period. Other methods of 'experimentally induced' vasospasm, such as hand immersion in cold water, also have failed to show an effect with PGE_1 in patients with Raynaud's disease.[1 4]

There have been several reports of ulcer healing after PGE_1 treatment.[1–4] This, too, was not substantiated in our study, though there were only a few ulcers in the study. Our observation that ulcer healing can occur in placebo-treated patients may indicate that the healing observed in other studies may, again, have been due to a 'placebo effect'.

In summary, in patients with Raynaud's syndrome, a 72-hour infusion of PGE_1 failed to provide a more marked improvement than a 72-hour infusion of placebo. There was, however, a statistically significant improvement from preinfusion values in both placebo- and PGE_1-treated patients.

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Book review

Occupational Low Back Pain. Eds. M H Pope, J W Frymoyer, G Anderson. Pp. 348. £48·00. Praeger: New York. 1984.

This book considers low back pain from the occupational viewpoint. However, in addition to sections on ergonomics, biomechanics, finance, and legal problems, which would be expected in such a work, consideration is also given to the structure of the low back, disease classification, therapy, and epidemiology in general terms. Thus the book takes a wide look at the problem of those affected by back pain, including causal factors (or at least those factors which may lead to an earlier onset of the disease than might otherwise have occurred) and management. What is perhaps more important is that consideration is given to the restoration of best possible health to those who cannot be cured in the light of our present knowledge. Restoration not only in social terms but also in the working situation best suited to their limitations.

The sections containing two chapters on aetiology and five chapters dealing with prevention covering the traditional aspects of both personal and environmental prevention may be of particular interest to occupational physicians, while the chapters in the sections on patient care may be of greater interest to rheumatologists, orthopaedic surgeons, and general practitioners. However, anyone concerned with the back pain problem and those afflicted will find the book interesting, readable, and encouraging, while not unrealistically optimistic. The three editors are to be congratulated on achieving this with the help of 12 other authors without losing continuity or style.

Inevitably the sections dealing with the legal aspects of the problem, including compensation and some of the statutory services concerned with rehabilitation and welfare, reflect the American base of the authorship. Thus readers from the UK or Western Europe must be prepared to interpret these sections in the light of the situation prevailing in their own countries.

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