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Use of prostaglandin E_1 (lipo-PGE_1) to treat Raynaud's phenomenon associated with connective tissue disease: thermographic and subjective assessment

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Abstract—Four patients with connective tissue disease who had been suffering from severe Raynaud's phenomenon were treated with an intravenous infusion of prostaglandin E_1 (PGE_1) and its effectiveness was assessed by thermography and a questionnaire approach. PGE_1 in a lipid microsphere formulation (lipo-PGE_1) produced a significantly greater increase in lesional skin temperature compared with treatment with PGE_1 clathrated in α-cyclodextrin 12 months previously in the same group of patients. These results were supported by the subjective assessment obtained from the patients by questionnaire.

Raynaud's disease associated with connective tissue disease is characterized by cyanosis and severe pain in the extremities. Platelet anti-aggregants and calcium channel blockers have been used in an attempt to treat Raynaud's phenomenon (Franks 1982; Sauza et al 1984; Weksler 1984), but intravenous prostaglandin E_1 (PGE_1) infusion has been considered to be one of the most effective treatments (Belch et al 1983; Langevitz et al 1989). However, this treatment is not suitable for out-patient clinics. In this paper, a formulation of PGE_1 for intravenous infusion, containing PGE_1 dissolved in soybean fat droplets less than 2 μm in diameter (lipo-PGE_1) (Green Cross Corp., Osaka, Japan) was used to treat 4 patients with Raynaud's phenomenon who had been treated with an alternative formulation of PGE_1 12 months previously.

Materials and methods

Four patients who had been suffering from severe Raynaud's phenomenon associated with connective tissue disease were studied. All fulfilled the revised criteria for the classification of systemic lupus erythematosus (Tan et al 1982) and one also showed symptoms of progressive systemic sclerosis. They were all female, age range 18 to 43 years (mean ± s.d., 35·3 ± 5·8). The patients received lipo-PGE_1 (10 μg of PGE_1) once or twice weekly from early January to the end of February in 1989. These four patients had been treated with PGE_1 clathrated in α-cyclodextrin (PGE_1-CD) (60 μg of PGE_1, Ono Pharm., Osaka, Japan) from December 1987 to February 1988, and monitored by thermographic measurement and by a subjective assessment carried out by questionnaire. Both lipo-PGE_1 and PGE_1-CD were dissolved in 100 mL of physiological saline and infused intravenously over a 30-min period.

The patients were rested in bed for 15 min. Skin temperature was monitored before and 10, 30, and 60 min after intravenous infusion of lipo-PGE_1 or PGE_1-CD. Thermographic measurement was assessed in the worst lesion. The efficacy of treatment was assessed by the increase in skin temperature. Differences between the two groups were statistically evaluated by a paired *t*-test. Pain and colour in the worst lesion was monitored and subjectively scored on a scale of 1 to 5, 1 being no symptoms and 5 very severe symptoms. The incidence of side effects was also monitored by the questionnaire survey.

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Results

Assessment by thermography. Fig. 1 shows the mean thermographic responses for each of the four patients monitored for 8 treatments of PGE_1-CD and for 10 treatments of lipo-PGE_1 one year later. Lipo-PGE_1, elicited a significantly greater increase in skin temperature of the worst lesion at 60 min than did PGE_1-CD ($P < 0.05$), and a longer duration of this effect was also suggested.

Assessment by questionnaire survey. Figs 2 and 3 show the results of the scores from the survey on pain and colour of the worst skin lesion in the four patients for 6 treatments of PGE_1-CD and 8 treatments of lipo-PGE_1 one year later. Lipo-PGE_1, appeared to improve lesion colour and pain more effectively than PGE_1-CD 3 and 24 h after infusions. The duration of effectiveness of lipo-PGE_1 seemed to vary considerably with different patients.

Incidence of the side effects. The side effects subjectively encountered are shown in Table 1. No serious reactions were reported.

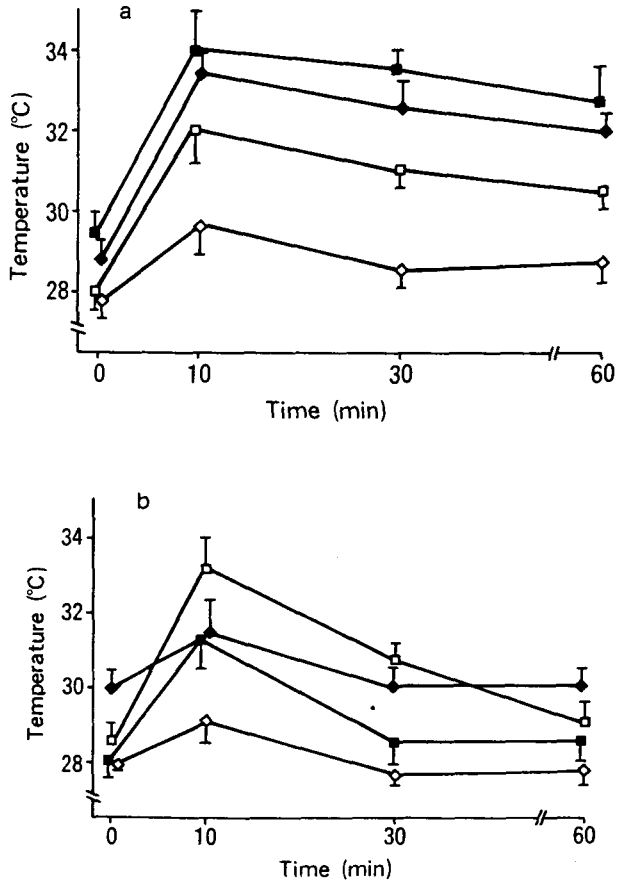

FIG. 1. Skin temperature after treatment with (a) lipo-PGE_1 and (b) PGE_1-CD. $P < 0.05$ at 60 min (paired *t*-test).

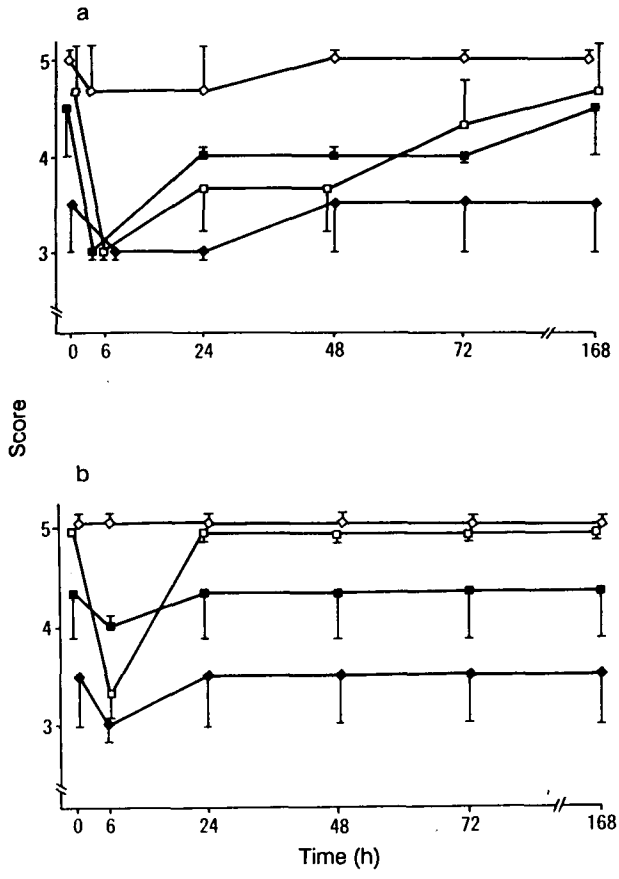

FIG. 2. Pain scores after treatment with (a) lipo-PGE_1 and (b) PGE_1-CD.

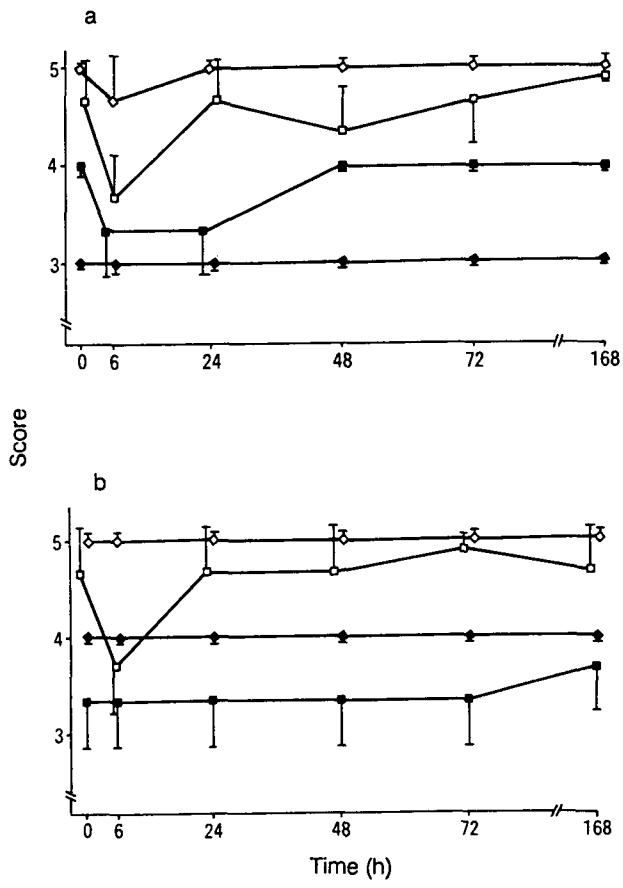

FIG. 3. Colour scores after treatment with (a) lipo-PGE_1 and (b) PGE_1-CD.

Two patients showed gastrointestinal complaints such as diarrhoea, but none discontinued treatment. The incidence of side effects was similar between PGE_1-CD and lipo-PGE_1 in this small-size population.

Table 1. Frequency of side effects in four patients treated 8 times with lipo PGE_1 and 6 times with PGE_1-CD.

	Lipo PGE_1 (n = 8)	PGE_1-CD (n = 6)
Diarrhoea	1	2
Constipation	1	0
Nausea	0	1
Palpitation	1	2
Flushing	0	1

Discussion

Objective assessment of the improvement in Raynaud's phenomenon is difficult since diverse factors, such as ambient temperature, humidity, emotions, and mental stress are involved in this disorder. The present study attempted to quantify the efficacy of the vasodilator treatment for Raynaud's phenomenon by thermography and by subjective assessment.

PGE_1, a potent vasodilator and an inhibitor of platelet aggregation, has been reported to be useful in the treatment of severe Raynaud's phenomenon. Recently, Yoshikawa et al (1990) suggested that continuous intravenous infusion of PGE_1 is effective in reducing levels of circulating immune complexes in patients with connective tissue disease as well as improving ischaemic skin ulcers. In preclinical studies it was found that lipo-PGE_1 had a stronger vasodilating effect than PGE_1-CD (Mizushima et al 1983). A similar effect has been seen in diabetic rats which are known to be poorly responsive to PGE_1 and other vasoactive substances (Hamano et al 1986). According to Sim et al (1986), lipo-PGE_1 had a more potent and sustained antithrombogenic effect in the microvasculature of the hamster cheek pouch and this was potentiated in the damaged vessels.

In our study, a once- or twice-weekly regimen of lipo-PGE_1 in out-patient clinics appeared to be of some value in the management of Raynaud's phenomenon associated with connective tissue disease. Intravenous infusion is probably preferable to bolus injection in view of the increased risk of adverse reactions associated with the latter. Further studies will be necessary in a larger patient population.

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References

Belch, J. J. F., Drury, J. K., Capell, H., Forbes, C. D., Newman, P., Mckenzie, D., Leiberman, P., Prentice, C. R. M. (1983) Intermit-

tent eroprostenol (prostacyclin) infusion in patients with Raynaud's phenomenon. Lancet i: 313–315
Franks, A. G. (1982) Topical triglyceryl trinitrate as adjunctive treatment in Raynaud's disease. Ibid. i: 76–77
Hamano, T., Shintome, M., Watanabe, M. (1986) Lipo PGE_1: vasodilating action. Clin. Report 20: 5145–5154 (in Japanese)
Langevitz, P., Buskila, D., Lee, P., Urowitz, M. B. (1989) Treatment of refractory ischemic skin ulcers in patients with Raynaud's phenomenon with PGE_1 infusions. J. Rheumatol. 16: 1433–1435
Mizushima, Y., Yanagawa, A., Hoshi, K. (1983) Prostaglandin E_1 is more effective, when incorporated in lipid microspheres, for treatment of peripheral vascular diseases in man. J. Pharm. Pharmacol. 35: 666–667
Sauza, J., Kraus, A., Gonzalez-Amaro, R., Alarcon-Segovia, D. (1984) Effect of the calcium channel blocker nifedipine on Raynaud's phenomenon. A controlled double blind trial. J. Rheumatol. 11: 362–364
Sim, A. K., McCraw, A. P., Cleland, M. E., Aihara, H., Otomo, S., Hosoda, K. (1986) The effect of Lipo PGE_1 on thrombus formation and thrombus disaggregation and its potential to target to the site of vascular lesions. Arzneim.-Forsch. 36: 1206–1209
Tan, E. M., Cohen, A. S., Fries, J. F., Masi, A. T., McShane, D. J., Rothfield, N. F., Schaller, J. G., Talal, N., Winchester, R. J. (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 25: 1272–1277
Weksler, B. B. (1984) Prostaglandins and vascular function. Circulation 70 (Suppl. III): 63–71
Yoshikawa, T., Suzuki, H., Kato, H., Yano, S. (1990) Effects of prostaglandin E_1 on collagen diseases with high levels of circulating immune complexes. J. Rheumatol. 17: 1513–1514

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Iontophoretic permeation of sodium cromoglycate through synthetic membrane and excised hairless mouse skin

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Abstract—The iontophoretic transport properties of sodium cromoglycate were characterized using a synthetic membrane and excised hairless mouse skin. The permeation rate of sodium cromoglycate through the synthetic membrane was found to be linearly dependent on the density of electrical current applied. Passive diffusion through the excised hairless mouse skin was not demonstrated for sodium cromoglycate; however, under iontophoresis, an appreciable permeation was exhibited by the drug through the animal skin, which was also found to be a function of the electrical current density.

Sodium cromoglycate is used primarily in the prophylactic treatment of bronchial asthma (Altounyan 1967). Due to its highly polar properties, sodium cromoglycate has poor bioavailability when administered orally or by inhalation. Topical application of sodium cromoglycate was reported to be effective in the treatment of atopic eczema in children (Haider 1977). However, the highly polar nature of the drug makes it difficult for it to be absorbed through skin. Lipophilic prodrugs of cromoglycate have been developed to facilitate the topical absorption of such a polar drug (Bodor et al 1980).

Iontophoresis is a unique transdermal process by which ionic molecules may penetrate through skin. The iontophoretic technique involves transport of selected ions by passing a direct electrical current between a drug solution and the patient's skin using a selected electrode polarity (Banga & Chien 1988). Sodium cromoglycate is an ionic compound which has an aqueous solubility of 100 mg mL^{-1} at 20°C. Taking advantage of the highly polar structure of sodium cromoglycate, iontophoresis may be used to enhance the bioavailability of the drug through transdermal application. The main objective of the present study was to characterize the iontophoretic transport of sodium cromoglycate using a synthetic microporous membrane, and to investigate the effect of iontophoresis on the permeation of such a drug through the excised skin of hairless mice.

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Materials and methods

Materials. Sodium cromoglycate, USP was purchased from Sigma Chemical Company, MO, USA. Sodium chloride and potassium chloride, both reagent grade, were obtained from Merck & Co., NJ, USA. Microporous polyolefin membranes (MSX #640, void volume 60–70%) having pores (maximum effective pore diam. of 0·15–0·2 μm) filled with a hydrophilic urethane polymer and a mean thickness of 25·3 μm were provided by the Health Care Specialties Division/3M Center. MI, USA. The platinum wires (99·9% purity, 0·25 mm in diam.) and silver wires (99·9% purity, 0·5 mm in diam.) were obtained from Aldrich Chemical Co. Inc., WI, USA. Hairless female mice, homozygous, 56–63 days old, and weight 22 g were purchased from Sasco Inc., NE, USA.

Synthetic membrane permeation studies. A side-by-side glass diffusion cell (Crown Glass Co. Inc., NJ, USA) equipped with a plastic membrane holder, specially designed for iontophoresis, was used in all permeating studies. A constant stirring rate of 600 rev min^{-1} in both half-cells was provided using a revolving Teflon-coated magnet and an electrical drive unit. The orifice opening between two diffusion cells was 1·7 cm in diameter, which provides a membrane surface area of 2·27 cm^2, exposed to the solution in both donor and receptor cells. Each side of the diffusion cell contained 9·0 mL of solution. Oval-shaped platinum loops, formed using 10 mm × 5 mm (i.d.) platinum wires, were used as electrodes. A constant current was applied through the two electrodes from a constant current source (Keithley 224 programmable current source, Keithley Instrument, Cleveland, OH, USA). The cathode was placed in the donor cell which contained the sodium cromoglycate solution and the anode was inserted in the receptor cell which held the sodium chloride solution. The concentration of sodium chloride in both cells was 0·02 M. The synthetic membrane was soaked in deionized water at room temperature (21°C) overnight to allow complete hydration of the membrane before use. A 2·0 mL sample solution was taken from the receptor cell at 10 min intervals for 1 h. An equal volume of fresh receptor solution was replaced after