Inhaled iloprost for the treatment of Raynaud's phenomenon

Sirs,

Raynaud's phenomenon (RP) is a significant clinical problem and occurs as an isolated condition or secondary to connective tissue diseases such as systemic sclerosis (SSc). Lifestyle changes and oral vasodilatators are the main treatment but more severe cases may require intravenous prostacyclin. Recently inhaled prostacyclin analogues have been used to treat pulmonary hypertension (1). Studies investigating the efficacy of inhaled iloprost in the treatment of RP have not been reported. In this prospective, open label study, we aimed to evaluate efficacy and tolerability of inhaled iloprost in 20 patients with primary RP or RP secondary to SSc. Among the 20 patients, 17 were female (85%) and 3 were male (15%) with a median age of 50 years (range 28-80). 14 patients had primary RP (70%) and 6 patients had SSc (30%). Each subject received two courses of treatment for 5 days separated by a 5-week interval. Iloprost was administered six times daily by a nebuliser at a daily nebulised dose of 30-60 μg. Symptoms were assessed by weekly diaries including the average weekly frequency and severity of RP attacks on a 100-mm visual analogue scale (VAS) and a 10-point Raynaud's Condition Score (RCS). In addition, thermographies were also performed.

After the first course of iloprost no statistical improvement was seen in any of the patient groups, despite a slight decrease, compared to baseline, in both the frequency (69.3±5.0 mm *vs*. 54.9±11.2 mm, respectively, mean ± SEM) and the severity (62.1±7.1 mm *vs*. 50.7±11.0 mm, respectively, mean ± SEM) of RP attacks in the primary RP subgroup. A similar trend was observed in the frequency of RP attacks in SSc patients (63.5±14.4 mm *vs*. 48.0±16.1 mm, baseline frequency *vs*. post-treatment frequency, mean ± SEM). After the second iloprost treatment course no significant improvement was seen in clinical symptoms in the group of primary RP patients, while SSc patients significantly improved from one week after iloprost inhalation (frequency: 51.0±10.4 mm *vs*. 19.8±6.8 mm, severity: 54.1±11.6 mm *vs*. 19.0±6.4 mm, baseline *vs*. post-treatment, mean ± SEM, $p \leq 0.05$). The RCS, a measurement of overall symptoms, showed a high degree of variability between patients. While 58% of patients with primary RP showed a prompt improvement of at least 25% in the overall symptoms, in the group of SSc patients no immediate beneficial response was seen. However, 2 weeks after treatment, more than 70% of all patients reported an improvement of at least 25%.

Using thermography, mean finger skin temperature showed a consistent increase after the first iloprost treatment. 5 weeks after treatment significantly warmer digits were found in all patients (24.9±1.1°C *vs*. 29.8±1.0°C, baseline *vs*. post-treatment temperatures, mean ± SEM, $p \leq 0.05$). Interestingly, SSc patients showed an additional, but not significant ($p=0.07$) benefit after the second course of iloprost. Similar improvements were observed 10 minutes after cold challenge. Results are shown in Table I.

The major limitation of the study is the small number of patients completing it. Although 20 patients were recruited, 5 patients withdrew for non-study-related reasons at the beginning of the trial and additional 4 patients were withdrawn later due to adverse events. Reasons for withdrawal included gastrointestinal effects (diarrhoea, vomiting) and fainting. Commonly reported adverse events were headaches and nausea (40%), less frequently diarrhoea, dizziness, and flushing (20%). These events were generally mild and intermittent, and no serious or life-threatening event occurred during the study.

Overall, inhaled iloprost was reasonably well-tolerated but treatment response was variable. The main advantage of the inhaled over intravenous iloprost is the easier administration with avoidance of intravenous cannulation that can be a major problem in Raynaud's secondary to systemic sclerosis. In conclusion, inhaled iloprost given 6 times daily for 5 days moderately improved the symptoms of RP in some patients with primary RP and secondary to SSc, although only 4 SSc cases completed treatment, precluding a robust conclusion concerning efficacy.

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Reference

1. OLSCHEWSKI H, SIMONNEAU G, GALIE N *et al.*: Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322-9.

Table I. Efficacy of inhaled Iloprost.

	Primary RP (n=7)			SSc (n=4)		
	Baseline	After treatment	4 weeks later	Baseline	After treatment	4 weeks later
Average frequency (VAS, mm)						
1st treatment phase	69.3 ± 5.0	54.9 ± 11.2	57.9 ± 9.7	63.4 ± 14.4	48.0 ± 16.1	48.8 ± 10.4
2nd treatment phase	56.0 ± 9.9	47.5 ± 13.5	43.5 ± 14.5	51.0 ± 10.4	33.3 ± 13.6	17.0 ± 8.1 *
Average severity (VAS, mm)						
1st treatment phase	62.1 ± 7.0	50.7 ± 11.0	57.8 ± 9.5	54.0 ± 6.7	50.8 ± 13.3	57.3 ± 11.0
2nd treatment phase	54.4 ± 11.2	47.5 ± 12.9	43.5 ± 14.3	54.3 ± 11.6	29.8 ± 13.1	22.0 ± 8.0 *
	Baseline	After treatment	5 weeks later	Baseline	After treatment	5 weeks later
Average baseline FST (°C)						
1st treatment phase	24.2 ± 1.6	28.1 ± 1.6	30.7 ± 1.2 *	26.2 ± 1.4	26.6 ± 1.2	28.1 ± 1.8
2nd treatment phase	30.7 ± 1.2	27.9 ± 1.5	25.7 ± 1.2	28.1 ± 1.8	30.0 ± 1.1	28.4 ± 1.3
FST after cold challenge (°C)						
1st treatment phase	23.5 ± 1.9	27.0 ± 2.1	28.9 ± 1.8	24.3 ± 2.1	24.8 ± 1.9	26.4 ± 2.3
2nd treatment phase	28.9 ± 1.8	24.8 ± 1.6	23.5 ± 1.1	26.4 ± 2.3	26.6 ± 1.0	25.6 ± 1.3

Data represent mean ± SEM, *$p \leq 0.05$
VAS: Visual analogue scale
FST: Finger skin temperatures