

Treatment of Ischaemic Digital Ulcers and Prevention of Gangrene with Intravenous Iloprost in Systemic Sclerosis

HUGH ZACHARIAE¹, LARS HALKIER-SØRENSEN¹, PETER BJERRING¹ and LENE HEICKENDORFF²

¹Department of Dermatology, Marselisborg Hospital, and ²Department of Clinical Biochemistry, Aarhus Amtssygehus, University of Aarhus, Aarhus, Denmark

Twelve patients with systemic sclerosis were treated with intravenous infusions of the prostacyclin-stable analogue iloprost 0.5–2.0 ng/kg/min for 6 h from 8 to 13 days. Imminent gangrene was stopped in 2 patients and followed by healing. In 4 of 6 patients iloprost led to complete healing of ischaemic ulcers and in the remaining 2 patients to partial healing. One patient with severe Raynaud's phenomenon discontinued the study after 3 days due to severe headache. The 2 remaining patients with Raynaud's phenomenon as an indication improved, while no improvement was recorded in a patient with vasculitis of the lower leg. Side-effects such as headache, nausea and flushing were the reason that only 5 patients reached the maximum infusion rate. No statistical differences were recorded in digital bloodflow before and after the study or in plasma endothelin in the 9 patients investigated. Three of the 6 patients with healing ulcers, however, showed a pronounced decrease in plasma endothelin. Iloprost appears useful as a treatment of imminent gangrene and ischaemic ulcers in systemic sclerosis. This reparatory capacity could also be of a more general importance in therapy of this disease. *Key words: prostaglandin analogue; bloodflow; endothelin.*

(Accepted November 23, 1995.)

Acta Derm Venereol (Stockh) 1996; 76: 236–238.

H. Zachariae, Department of Dermatology, Marselisborg Hospital, University of Aarhus, DK-8000 Aarhus C., Denmark.

Although the etiology of systemic sclerosis (SS) is unknown, the presence of vascular symptoms in practically all patients together with the fact that these symptoms in general predate the development of fibrosis indicate the importance of keeping vascular damage as minimal as possible in this disease. Besides, painful ischaemic digital ulcers and gangrene are severe complications in SS. Oral vasodilator treatment particularly with calcium channel blockers, such as nifedipine, is commonly used against Raynaud's phenomenon in SS (1, 2) but is often not sufficient against ischaemic ulcers and of little value against gangrene. Infusions of prostacyclin have been used with short-term effect (3), while infusions of the prostacyclin analogue iloprost have been studied against Raynaud's phenomenon. Iloprost is stable and reported to contain both vasodilating and platelet inhibitory effects (4). In some of the studies on Raynaud's phenomenon in SS an effect on ischaemic ulcers was also reported (2, 3). We report on the successful use of iloprost infusions in patients with SS, mainly suffering from ischaemic ulcers, including 2 patients with imminent gangrene.

PATIENTS AND METHODS

All 12 patients met ARA criteria for classification of SS (5). The indications were painful ischaemic digital ulcers in 6 patients, imminent

gangrene in 2 patients, and severe SS vasculitis in 1 patient and pronounced episodes of Raynaud's phenomenon in 3. All patients continued their disease-moderating therapy with immunosuppressives or D-penicillamine together with omeprazol or H₂-blockers against esophagitis. Prior treatment with nifedipine was either kept stable during the study or discontinued at the latest 24 h prior to investigation and therapy. Disallowed medications were anticoagulants and platelet inhibitory agents, except non-steroidal anti-inflammatory drugs.

Digital cutaneous lesions were described and photographed prior to treatment and following therapy, and healing time was recorded together with the patients' observations of pain. In patients with an indication of Raynaud's phenomenon the number and severity of the attacks was the basis for evaluation. Complete healing for patients was defined as healing of all ulcers present at baseline, and partial healing was defined as healing of one or more, but not all ulcers.

Iloprost (0.5–2.0 ng/kg/min) was administered for 6 h by continuous intravenous infusion using an Infusomat[®] infusion pump. The dose was started at 0.5 ng/kg/min and increased by increments of 0.25–0.5 ng/kg/min until the patient developed side-effects or a maximum dose of 2.0 ng/kg/min. If adverse symptoms occurred, the dose was reduced step-wise. The therapy was given for 8 to 13 days (mean 9.3 ± 2.8 days). Baseline laser Doppler skin blood flowmetry (Periflux, Perimed, Sweden) (6) on finger skin perfusion was measured on the dorsal side of all fingers at the midpoint between the proximal interphalangeal joint and the distal interphalangeal joint and repeated after determination of therapy.

Endothelin, which may contribute to vasospasms in SS (7), was studied in plasma from 9 patients by radioimmunoassay (8) prior to and after treatment. Three patients were only studied either prior to or after therapy.

RESULTS

One patient with pronounced Raynaud's phenomenon as indication discontinued the therapy due to severe headache. All remaining patients completed the planned course of infusions. However, only 5 patients reached the maximum infusion rate of 2.0 ng/kg/min due to either headache or nausea. Flushing was also a common side-effect. The average tolerable dose of iloprost was 1.3 ng/kg/min. All patients who completed the study gave an overall positive assessment of therapy. The 2 remaining patients with Raynaud's phenomenon noted a temporary improvement lasting several weeks. The imminent gangrene was arrested and followed by total healing (Fig. 1). All ischaemic ulcers healed in 4 of 6 patients, while the remaining 2 patients experienced partial healing. No change was observed in the patient with a clinical vasculitis of the lower leg.

No statistically significant differences in skin bloodflow were found comparing the data before and after iloprost infusion series ($p=0.219$). Neither was there a significant change in plasma endothelin, although 3 of 6 patients with healing ulcers had a pronounced decrease. This included 2 of the 3 patients with high plasma endothelin values. The third patient with increased plasma endothelin was the patient with a vasculitis, which did not heal. Increased plasma endothelin levels were

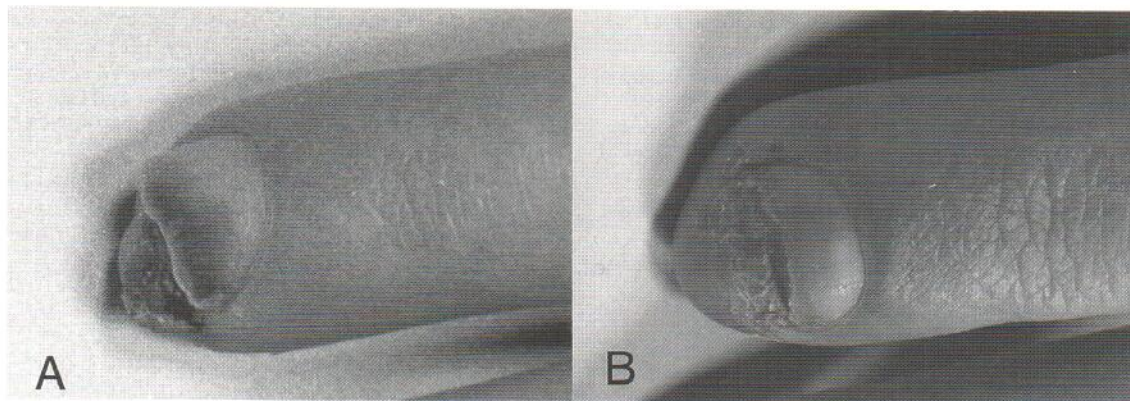


Fig. 1. (A) Imminent gangrene in patient prior to iloprost. (B) Same finger as in A 6 weeks later.

Table I. Results of clinical data and plasma endothelin prior to and after therapy with iloprost infusions for 8–13 days

I.U. = ischaemic ulcers, I.G. = imminent gangrene, V = vasculitis, R = severe Raynaud's phenomenon.
+ = total healing, (+) = partial healing, - = no healing, N.U. = no ulcers.

Sex/Age	Length of therapy (days)	Indication of therapy	Healing of ulcers	Plasma endothelin $\mu\text{g/l}^a$	
				before	after
F/48	13	I.U.	+	4.4	4.6
F/57	8	V	-	8.2	8.3
F/60	10	I.G.	+	-	6.5
M/73	8	I.U.	+	7.9	4.0
F/26	10	I.G.	+	6.6	8.0
F/50	10	I.U.	+	10.3	5.1
F/42	10	I.U.	+	4.2	2.3
F/39	10	R	N.U.	1.8	-
F/48	10	R	N.U.	3.5	3.2
F/31	3 ^b	R	N.U.	2.2	3.7
F/61	13	I.U.	(+)	3.0	3.3
F/48	10	I.U.	(+)	-	5.7

^aNormal values: 2.0–5.3 $\mu\text{g/l}$.

^bDiscontinuation due to side-effects.

recorded in 5 of the 12 patients. The individual data on the patients appear from Table I.

DISCUSSION

Our studies support the data of Wigley et al. (2) and Rademaker et al. (1) for treatment of ischaemic ulcers in SS, while it is in contrast with the results of McHugh et al. (9), who found no difference between iloprost and placebo in healing. Their study was, however, mainly designed for studying Raynaud's phenomenon. The benefit of iloprost has been proposed to be due to vasodilation, inhibition of platelet activation, and leukocyte adherence to endothelium. In their study Wigley et al. (2), however, were unable to attribute healing to effects on platelet activation. In our study, it is unlikely that a local vasodilatation was the reason for healing. Rademaker et al. (1) suggested that iloprost promoted repair of damaged endothelium, which could explain vascular effects and clinical improvement weeks after therapy. The vascular endothelium is of importance not only for the vascular tissue, but also for perivascular tissue. The pronounced decrease in plasma endothelin observed in 3 of the 5 patients with healing ulcers who were studied could be both a consequence of

healing and a contributing factor to healing. This should be elucidated in further studies. We have previously demonstrated a positive correlation between plasma endothelin and serum PIIINP, a marker of fibrogenesis of type III collagen in SS, and suggested that endothelial cell damage could lead to increased secretion of endothelin and subsequent fibrosis in SS (10).

REFERENCES

1. Rademaker M, Cooke E, Almond N, Beacham J, Smith R, Mant T, et al. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double-blind randomized study. *BMJ* 1989; 298: 561–564.
2. Wigley F, Seibold J, Wise R, McCloskey D, Dole W. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. *J Rheum* 1992; 19: 1407–1414.
3. Belch J, Newman P, Drury J, McKenzie F, Capell H, Leiberman P, et al. Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome: a double-blind controlled trial. *Lancet* 1983; 1: 313–315.
4. Ylitalo P, Kaukinen S, Seppälä E, Nurmi A, Pessi T, Kraiss T, et al. Pharmacological effects of iloprost (ZK 36374), a stable

- prostacyclin analogue in man. *Biomed Biochem Acta* 1984; 43: 399–402.
5. Subcommittee for Scleroderma Criteria of the American Rheumatism Association. *Arthritis Rheum* 1980; 23: 581–590.
 6. Tenland T. On laser Doppler flowmetry. Methods and microvascular applications. Linköping University Medical Dis. University of Linköping, 1982.
 7. Kahaleh M. Endothelin an endothelial-dependent vasoconstrictor in scleroderma. *Arthritis Rheum* 1991; 34: 978–983.
 8. Vorman H, Stehouer C, van Kamp G, van Schijndel R, Grone A, Thijs L. Plasma endothelin levels are increased during septic shock. *Crit Care Med* 1992; 20: 1097–1101.
 9. McHugh N, Suka M, Watson H, Belcher G, Amadi A, Ring E, et al. Infusion of iloprost, a prostacyclin analogue for treatment of Raynaud's phenomenon in systemic sclerosis. *Ann Rheum Dis* 1988; 47: 43–47.
 10. Zachariae H, Heickendorff L, Bjerring P, Halkier-Sørensen L, Søndergaard K. Plasma endothelin and the aminoterminal propeptide of type III procollagen (PIIINP) in systemic sclerosis. *Acta Derm Venereol (Stockh)* 1994; 74: 368–370.