Rheumatology 2004;43:229–233 doi:10.1093/rheumatology/keg480
Advance Access publication 15 August 2003

Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases

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Objective. **We analysed our experience with the use of iloprost for the treatment of critical ischaemic digits (ID) in children with connective tissue diseases (CTD) in order to assess its safety and efficacy.**
Methods. **This was a retrospective analysis of paediatric patients with CTD who were treated with iloprost for critical ID resistant to conventional therapy. Information on demographics, clinical and laboratory features, the regimen of iloprost treatment and outcome were collected.**
Results. **Fifteen patients (10 female, five male) treated one or more times with iloprost were included (total of 19 treatments). Six had juvenile systemic sclerosis, five had systemic lupus erythematosus, three had mixed connective tissue disease and one had cutaneous polyarteritis nodosa. Thirteen patients were already taking calcium channel blockers with no improvement; in two patients ID were the presenting signs of the disease without prior treatment. Eleven patients had more than two fingers involved; one child had involvement of all 10 fingers. Normal digital blood flow was achieved in 74% of treatments and significant improvement was noted in 26%. Fingertip necrosis was present in 11 patients (14 treatments). It healed completely in seven, improved in one and remained unchanged in six. Raynaud's phenomenon (RP) was present in 14 patients (17 treatments): in two no RP attack occurred during the follow-up period, eight improved both in the number of attacks per week and in the duration of each attack. Complete pain relief was observed in 10/17 treatments (59%) and there was a significant decrease in pain in the remaining seven. No major side-effects or withdrawal symptoms were reported. Minor side-effects reported include reversible headache (seven patients), hypotension or irritability (three), nausea/vomiting (two) and injection site reaction (one).**
Conclusions. **Iloprost appears to be a safe and effective treatment for ischaemic digits and digital ulcers in children with CTD. In conjunction with immunosuppressive drugs, it has a potential role in preventing irreversible complications, such as digital gangrene and amputation.**

KEY WORDS: Iloprost, Necrotizing vasculopathy, Ischaemic digits, Paediatric CTD.

Systemic necrotizing vasculopathy is a relatively uncommon condition in children, and the condition has potential for serious morbidity and life-threatening complications [1, 2]. It can be a primary vasculitic syndrome or a clinical manifestation of various conditions, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polyarteritis nodosa (PAN), Wegener's granulomatosis and mixed connective tissue disease (MCTD).

Immunosuppressive treatment in combination with vasodilators, such as calcium channel blockers (CCB), can control both the inflammatory and the ischaemic processes and help prevent vascular occlusions in most situations [2]. Sometimes this combination therapy fails and other agents are needed.

Iloprost, an analogue of natural prostacyclin (PGI_2), has been used successfully in adults for the treatment of critical leg ischaemia [3–5], Raynaud's phenomenon (RP) [6–8] and ischaemic ulcers secondary to connective tissue diseases (CTD) [9, 10]. Its major pharmacological functions include reduction of vascular resistance in peripheral arteries, inhibition of platelet aggregation, anti-inflammatory properties (such as leukocyte inhibition) and reduction of tumour necrosis factor production and inhibition of fibrosis [11, 12].

While the use of iloprost in adults is well established, experience in children is limited and anecdotal. We retrospectively evaluated the safety and efficacy of iloprost for the treatment of critical ischaemic digits (ID) and RP resistant to common vasodilators in children with CTD.

Methods

We performed a retrospective analysis of paediatric patients with documented CTD, treated with iloprost for critical ischaemic digits due to vasculitic processes and resistant to conventional immunosuppressive and vasodilator treatment.

Five tertiary care paediatric rheumatology units took part in the study. We collected clinical information on gender, race, disease,

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Submitted 6 February 2003; revised version accepted 3 July 2003.

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age at onset, disease duration at the time of first iloprost treatment, symptoms, internal organ involvement, and concomitant immunosuppressive and vasodilator treatment.

Response to treatment was assessed by documenting the following features before and after treatment: number of ischaemic digits, number of instances of fingertip necrosis (FN), degree of pain (visual analogue scale, 0–10), number of RP attacks per week and their mean duration. Information on the following laboratory tests was also collected before and after treatment: complete blood count, erythrocyte sedimentation rate, C-reactive protein, complement fraction (C3, C4), autoantibodies (antinuclear antibodies, anti-double-stranded DNA, extractable nuclear antigens) and rheumatoid factor.

Information on iloprost treatment included infusion rate (ng/kg/min), daily duration of each infusion (h), number of infusion days per cycle and number of cycles. Major and minor side-effects related to iloprost treatment were also recorded.

Descriptive statistics were used to report demographic and clinical characteristics, efficacy variables and adverse events. Data analysis included the χ^2 test, Student's *t* test and Fisher's exact test as appropriate.

Results

Demographics

The clinical characteristics of the patients are summarized in Table 1.

Fifteen patients (10 female, five male), all Caucasian, were treated one or more times with iloprost, with a total of 19 treatments. Six had juvenile SSc, five had SLE, three had MCTD and one had cutaneous PAN. The mean age at disease onset was 9.5 yr (range 1.5–16 yr) and the disease duration at the time of first iloprost treatment was 4.6 yr (range 1 month to14 yr).

All the patients were treated between June 1996 and December 2001.

Table 1. Clinical characteristics of the patients treated with iloprost

	No. (%)
No. of patients	15
Sex	
Female	10 (67)
Male	5 (33)
Disease	
Juvenile SSc	6 (40)
SLE	5 (33)
MCTD	3 (20)
Cutaneous PAN	1 (7)
Age at onset (yr)	
Mean	9.5
Range	1.5–16
Disease duration (yr)	
Mean	4.6
Range	0.1–14
Peripheral vascular involvement	
Ischaemic digits	15 (100)
Fingertip necrosis	11 (73)
Raynaud's phenomenon	14 (93)
Concomitant treatment	
Immunosuppressive	
Methotrexate	4
Azathioprine	2
Cyclosporin A	2
Cyclophosphamide	3
Symptomatic	
Corticosteroids	15
CCBs	13
Warfarin	4
Acetylsalicylic acid	2
Iloprost indications	
Resistance to CCB	13
Rapidly necrotizing digits	2

Clinical features

All the patients had ID (range 1–10). Most of them (73%) had involvement of more than two fingers. In 11 patients, ID were associated with FN in one or more fingers. RP was present in 14 patients.

Thirteen patients were treated with iloprost because they were resistant to CCB and two patients because they had acutely threatening ID as the presenting sign of the disease.

At the time of treatment three patients had fever, four had gastrointestinal involvement, seven respiratory involvement, six renal involvement, two cardiac involvement, three neurological involvement, seven muscular involvement and 11 articular involvement.

Before iloprost treatment, 11 patients had been treated with various immunosuppressive drugs: four with methotrexate, two with azathioprine, two with cyclosporin A and three with cyclophosphamide (Table 1). In all patients the vasculitic process was resistant to the usual symptomatic treatments: corticosteroids (15 patients), CCB (13), warfarin (four) and acetylsalicylic acid (two).

Iloprost infusion regimen

The infusion regimen is summarized in Table 2. Nineteen iloprost treatments were performed. Intravenous infusions were done at the mean rate of 2 ± 0.3 ng/kg/min (range 1–2.4) for 6 h/day for 10.7 ± 5.7 days for each cycle (range 5–28 days). Fourteen treatment courses included just one cycle, four included three cycles at 1-month intervals and one included six cycles. Whatever the treatment regimen, the number of days of infusion for each treatment course ranged from 6 to 30 days (mean 14.2 ± 6.1 days). Twelve patients were treated once, two patients (patients 1 and 15) twice (13 and 14 months after the first cycle) and one patient (patient 8) three times (after 35 and 26 months respectively) for relapse of vasculitis.

Treatment results

All patients treated with iloprost definitely improved in one or more parameters (Fig. 1).

The number of ID decreased significantly in each patient. In 14 treatments (74%) normal digital colour and temperature were achieved within 3–7 days. In five treatments (26%) the number of ID decreased from 5–10 to 1–5.

FN was present at the start of 14 treatments. Complete healing was observed following seven treatments (50%) and clinical improvement was noted in one. There was no response to treatment in six (three with gangrene). Among these six failures, four were in patients at their first treatment and two were in the same patient, who failed twice to respond to iloprost.

In 17 treatments the degree of pain was measured before and after infusion by VAS (Fig. 1). Significant improvement was recorded in all of them. Complete pain relief was observed after 10 treatments (59%) within 2–5 days from the first infusion and pain was significantly reduced (from a VAS score of 7–10 to 1–4) following the remaining seven treatments. This result was sustained and persistent during the follow-up period, which ranged from 12 to 72 months (mean 33 ± 22 months).

RP was present in 14 patients (17 treatments). However, complete data on the number and duration of attacks were obtained in 11 patients (13 treatments). After iloprost infusion, all but one showed significant improvement. In two patients there

Table 2. Iloprost infusion regimen for 19 treatment courses in 15 patients

Patient no.	Sex	Disease	Iloprost infusion regimen		Days	Cycles	General treatment	
			Dose (ng/kg/min)	Infusion (h)			Before	After
1	F	cPAN	2.0	6	14	1	CS, IVIG, ASA	CPM, CS, CCB
1		cPAN	2.0	6	10	1	CS, CCB	CPM, CS, CCB
2	F	JSSc	2.0	6	6	3	CS	CS, CCB
3	F	JSSc	2.0	6	5	3	CS, MTX, CCB	CS, MTX, CCB
4	F	SLE	2.0	6	6	1	CS, AZA, CCB	CS, AZA, CCB
5	F	JSSc	2.0	6	8	1	CS, CCB	CS, CCB
6	M	SLE	2.0	6	12	1	CS, CCB	CS, CCB
7	M	JSSc	2.0	6	5	3	CS, CTX, MTX, CCB	CS, CTX, MTX, CCB
8	M	MCTD	2.4	6	11	1	CS, AZA, CCB, WA	CS, AZA, CCB, WA
8		MCTD	2.4	6	10	1	CS, CYA, CCB, WA	CS, CYA, CCB, WA
8		MCTD	2.4	6	15	1	CS, CYA, CCB, WA	CS, CYA, CCB, WA
9	F	JSSc	2.0	6	15	1	CS, CCB	CS, CCB
10	M	SLE	2.0	6	14	1	CS, CCB	CS, CCB
11	F	SLE	2.3	6	28	1	CS, PE, CTX, WA	CS, CTX, CCB
12	F	MCTD	2.4	6	14	1	CS, ASA	CS, AZA, ASA, CCB
13	F	JSSC	2.0	6	14	1	CS, CCB	CS, CCB
14	F	SLE	1.0	6	6	1	CS, AZA, CCB	CS, AZA, CCB
15	M	MCTD	1.7	6	5	6	MTX, CCB, ACEI	MTX, ACEI, CCB
15		MCTD	2.0	6	5	3	MTX, CCB, ACEI	MTX, CCB, ACEI

cPAN, cutaneous polyarteritis nodosa; JSSc, juvenile SSc; CS, corticosteroids; MTX, methotrexate; CTX, cyclophosphamide; CYA, cyclosporin A; ACEI, angiotensin converting enzyme inhibitor; IVIG, intravenous immunoglobulins; PE, plasma exchange; ASA, acetylsalicylic acid; AZA, azathioprine; WA, warfarin.

were no attacks of RP during the following 24 months. Eight experienced a significant decrease both in the number of attacks per week (from 3–30 to 0–15) and in the duration of each attack (from 15–60 to 0–30 min).

No significant changes in the laboratory parameters were observed during iloprost treatment. No difference in response rate was observed among the different underlying diseases.

No major side-effects leading to discontinuation of iloprost infusion were reported (Table 3). Minor, reversible side-effects consisted of mild headache in seven patients (37%), hypotension in three (16%), dizziness/irritability in three (16%), nausea in two (10.5%) and vomiting or injection-site reaction in one (5.2%). The overall rate of side-effects in our series was significantly lower than in similar studies in adults, particularly for events such as headache, nausea and vomiting. Indeed, while almost all the adults (91%) in the previous studies presented one or more side-effects during infusion, in our series seven patients (37%) reported no side-effects at all (Table 3).

Discussion

Clinical manifestations of systemic vasculitis syndromes include RP and digital ischaemia, which are caused by inflammation of the vessel wall and abnormal regulation of regional blood flow.

General principles of the treatment of these manifestations include the avoidance of a cold environment, the use of vasodilators (such as CCB and platelet antiaggregants) and immunosuppressive treatment [1, 2]. Some prostanoids are additional drugs that can be used in patients resistant to previous conventional treatment or in threatening conditions. They are potent vasodilators, inhibit platelet aggregation and fibrosis and act as anti-inflammatory agents by leucocyte inhibition and decreasing the production of tumour necrosis factor [11, 13].

Iloprost, a stable analogue of the natural prostacyclin PGI_2, mimics its pharmacodynamic properties and has been used successfully in adults for the treatment of severe RP [6–8, 14, 15], ischaemic ulcers secondary to SSc and other necrotizing vasculopathies [7, 9, 10, 16].

In the present study we have shown that iloprost is also effective in the paediatric age group.

Complete healing of fingertip ulcers were noted in the majority of patients. Normal digital blood flow was observed as early as 24 h after the first iloprost infusion, and efficacy was prolonged. In patients with severe RP resistant to CCB, iloprost induced a substantial reduction in both the number and the duration of attacks in most patients (78.6%) and led to complete remission in two. Furthermore, significant relief from pain was observed in all treated patients.

When fingertip necrosis and gangrene, the final manifestations of the ischaemic process, were already present, iloprost was only partially effective. FN disappeared after seven treatments (50%), but in the remaining (treatments) only mild improvement was detected. In three patients in whom dry gangrene had already set in, the treatment did not prevent the eventual amputation of the affected phalanges. The lack of response was not correlated with the disease duration but with either the duration or the severity of each ischaemic event before iloprost treatment. This observation underlines the importance of starting iloprost treatment as soon as the patient becomes unresponsive to CCB, and before the development of an extensive irreversible necrotic process.

Previous experience in adults has shown that iloprost promotes healing of ischaemic lesions in patients with severe RP secondary to SSc or after vasculitic processes.

In a prospective trial, Wigley *et al.* [7] reported complete healing of cutaneous lesions in 6/7 patients treated with iloprost compared with none of the four patients in the placebo group. Improvement in ischaemic digital tip ulcers was noted in four patients on iloprost, compared with none of four patients in the placebo group.

Similar results were obtained in two other studies in adults. In one, which included 12 patients with SSc, iloprost stopped imminent gangrene in two, induced complete healing of ischaemic ulcers in six and was ineffective in one [14]. In the second study, iloprost proved to be effective in cases refractory to alprostadil, a synthetic PGE_2 analogue, but was less well tolerated [14].

Reports on the use of iloprost for the treatment of RP show controversial results. While some authors have reported good efficacy in reducing both frequency and duration of RP attacks [8, 14, 15], others have not confirmed these results [7, 15].

Reports on the use of iloprost in paediatric patients are very few and are mainly restricted to the treatment of both primary and

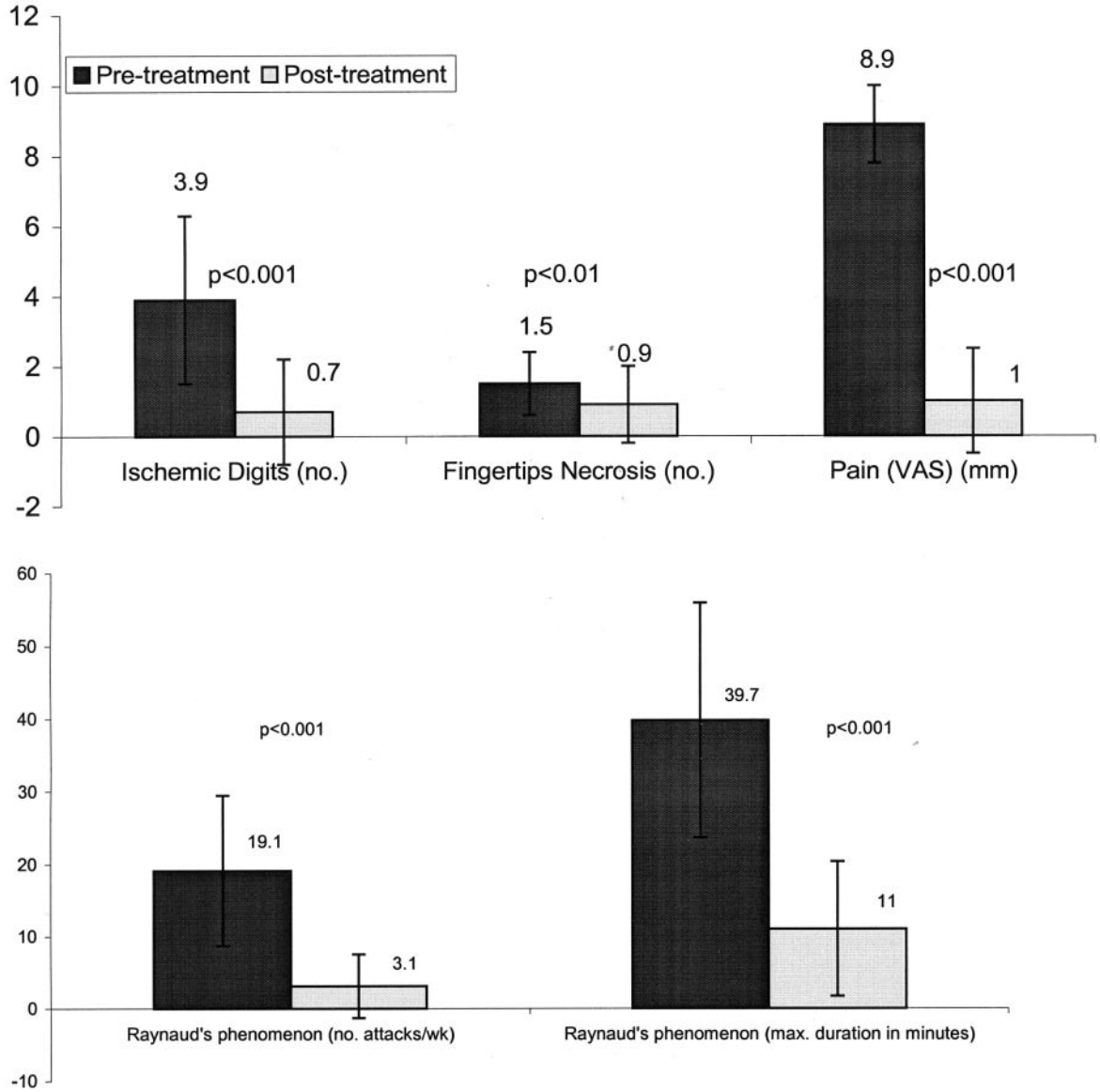

FIG. 1. Efficacy of iloprost in paediatric CTD.

TABLE 3. Adverse reactions during iloprost infusion: comparison with previous series of adult patients

	Children in present series (total = 19) *n* (%)	Adults (references 7–9, 14–16) (total = 82) *n* (%)	*P*
None	7 (37)	7 (9)	< 0.005
Headache	7 (37)	65 (79)	< 0.001
Hypotension/vasodilatation	3 (16)	16 (20)	n.s.
Nausea	2 (11)	53 (65)	< 0.0001
Vomiting	1 (5)	36 (44)	< 0.005
Diarrhea	0	16 (20)	< 0.05
Myalgia	0	12 (15)	n.s.

n.s., not significant.

secondary pulmonary hypertension [17, 18]. The only report on the use of iloprost for the treatment of necrotizing vasculopathy was in a 3-yr-old girl with cutaneous PAN. She was treated successfully with iloprost and immunosuppressive drugs, and there was rapid disappearance of ischaemia in all the fingers involved and arrest of progression of necrosis [19].

The regimen of iloprost treatment in our series was comparable to that reported in adults in infusion velocity and the number of hours of infusion per day. On the contrary, the average number of days of infusion per treatment course was higher than that reported in adults (10.7 *vs* 4–5 days). It ranged from 5 to 15 days in 14 patients, and in one SLE patient with recalcitrant drug-resistant

RP it lasted as long as 28 days. Two hypotheses could explain this difference: (i) the vasculitic process could be more aggressive in some children with CTD in comparison with adults; and (ii) the lack of significant side-effects related to iloprost could have led to prolongation of treatment in some patients to improve its efficacy, particularly for FN and RP.

Our experience in children shows iloprost to have an acceptable safety profile compared with experience in adults [7–9, 14–16]. There were no major untoward reactions during infusion. Mild and transient headache was the most frequent side-effect reported during one-third of the treatments (Table 3). Possible explanations for this difference could be the better reactivity of the circulatory system in children, the lack of concomitant environmental factors (smoke, obesity, stress) and, perhaps, variation in the pharmacokinetics of the drug.

In conclusion, iloprost appears to be safe and effective for the treatment of ischaemic digits and recalcitrant RP in children with CTD. As in adults, when used in conjunction with conventional immunosuppressive drugs, iloprost may help prevent irreversible complications such as digital gangrene, and even amputation. Prospective multicentre studies are needed to confirm these preliminary observations.

Conflict of interest

The authors have declared no conflicts of interest.

References

1. Athreya BH. Vasculitis in children. Pediatr Clin North Am 1995;42:1239–61.
2. Cassidy JT, Petty RE. Systemic vasculitis. In: Cassidy JT, Petty RE, eds. Textbook of Pediatric Rheumatology, 4th edn. W.B. Saunders, 2001:564–604.
3. Dormandy JA. Use of prostacyclin analogue iloprost in the treatment of critical leg ischemia. Therapie 1991;46:319–22.
4. Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischemia for thromboangiitis obliterans. Lancet 1990;335:555–7.
5. Oberender H, Krais TH, Schäfer M, Belcher G. Clinical benefits of iloprost, a stable prostacyclin (PGI_2) analog in severe peripheral arterial disease (PAD). Adv Prost Thromb Leukot Res 1989;19:311–6.
6. Watson HR, Belcher G. Retrospective comparison of iloprost with other treatments for secondary Raynaud's phenomenon. Ann Rheum Dis 1991;50:359–61.
7. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous Iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol 1992;19:1407–14.
8. Scorza R, Caronni M, Mascagni B *et al*. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomized, controlled study. Clin Exp Rheumatol 2001;19:503–8.
9. Veale DJ, Muir AH, Morley KD, Belch JJF. Treatment of vasculitic leg ulcers in connective tissue disease with Iloprost. Clin Rheumatol 1995;14:187–91.
10. Zahavi J, Charach G, Schafer R, Toeg A, Zahavi M. Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost. Lancet 1993;342:862.
11. Grant SM, Goa KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic property and therapeutical potential in peripheral vascular disease, myocardial ischemia and extracorporeal circulation procedures. Drugs 1992;43:889–924.
12. Belch JJF, Sanibadi A, Dickson R, Sturrock RD, Forbes CD. Effects of Iloprost on white cell behavior. In: Gryglewski RJ, Stock G, eds. Prostacyclin and its stable analogue Iloprost. Berlin: Springer Verlag, 1986:97–102.
13. Stratton R, Shiwen X, Martini G *et al*. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. J Clin Invest 2001;108: 241–50.
14. Lamprecht P, Schnabel A, Gross WL. Efficacy of Alprostadil and Iloprost in digital necrosis due to secondary Raynaud's phenomenon. Br J Rheumatol 1998;37:703–4.
15. Kyle MV, Belcher G, Hazleman BL. Placebo controlled study showing therapeutic benefit of Iloprost in the treatment of Raynaud's phenomenon. J Rheumatol 1992;19:1403–6.
16. Zachariae H, Halkier-Sørensen L, Bjerring P, Heickendorff L. Treatment of ischaemic digital ulcers and prevention of gangrene with intravenous Iloprost in systemic sclerosis. Acta Dermatol Venereol 1996;76:236–8.
17. Machherndl S, Kneussl M, Baumgartner H *et al*. Long-term treatment of pulmonary hypertension with aerosolized iloprost. Eur Respir J 2001;17:8–13.
18. Rimensberger PC, Spahr-Schopfer I, Berner M *et al*. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation 2001;103: 544–8.
19. Zulian F, Costantini C, Montesco MC, Schiavon F, Zacchello F. Successful treatment of gangrene in systemic necrotizing vasculitis with iloprost. Br J Rheumatol 1998;37:228–30.