The Effect of Iloprost in Patients with Rest Pain

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Thirty-four patients with ischaemic rest pain in 42 limbs and ankle pressure equal to or less than 50 mmHg have been treated with intravenous infusion of synthetic prostacyclin (iloprost) for eight days. Leg blood flow was measured with air plethysmography before treatment, on day 4 and day 8 of treatment. Total relief of pain for at least 6 weeks occurred in 91% of patients with leg blood flow >40 ml/min, in 18% with leg flow 30–39 ml/min and in 11% with leg flow <30 ml/min. Complete relief of pain for at least 6 weeks occurred in 92% of patients in whose limbs the blood flow on day 8 was greater than 50 ml/min but only in 6% with blood flow less than 50 ml/min. These results indicate that iloprost increases leg blood flow and that patients likely to respond can be identified from the baseline air plethysmographic measurement of leg blood flow.

Key Words: Lower limb ischaemia; Iloprost; Air plethysmography

Introduction

Clinically used prostanoids, prostaglandin E1 (PGE1) and prostacyclin (PGI2) are believed to act beneficially on activated platelets, activated leucocytes, leucocyte-vessel interaction, and damaged endothelium improving microvascular perfusion. Despite the promising results of early trials, the chemical instability of PGI2 has limited its clinical use. The development of the stable PGI analogue (iloprost) in 1981 which maintained its ability to inhibit activated platelets and vasodilate the microcirculation has stimulated further attempts to determine its clinical value.

Controlled studies have demonstrated an increased rate in the healing of ischaemic ulcers and relief of ischaemic rest pain not only in patients with peripheral occlusive atherosclerotic disease but also in patients with thromboangiitis obliterans. The aim of our study was to test the hypothesis that in patients with ischaemic rest pain as a result of lower limb atherosclerotic disease, treatment with intravenous infusion of iloprost is associated with an increased leg blood flow; also to determine the relationship between changes in leg blood flow and relief of symptoms.

Material and Methods

Patients and plan of study

Thirty-four patients with stable ischaemic rest pain present for at least 4 weeks in 42 limbs and with ankle pressure equal to or less than 50 mmHg were admitted. Patients with gangrenous or pregangrenous changes in the foot or any toe were excluded. Five patients (7 limbs) were non-insulin diabetics. The remaining had atherosclerotic disease. All patients had angiography in order to establish the presence and extent of the arterial disease since they were potential candidates for vascular reconstruction. Patients with moderate to severe aortoiliac disease who were candidates for aortoiliac reconstruction were also excluded from the study. Leg blood flow was measured using air plethysmography before the commencement of iloprost therapy and then every 2 days during therapy up to day 8 when iloprost therapy was discontinued.

Leg blood flow

Leg blood flow was measured with venous occlusion plethysmography using a commercially available air plethysmograph (APG®-1000, ACI Medical, 9249 Glenoaks B1, Sun Valley, Ca 91352). Its calibration has
been described in detail previously. Briefly, the air plethysmograph (APG) consists of a 35 cm long polyurethane air-chamber (5 l capacity) which surrounds the whole leg and applies a pressure of 6 mmHg, connected to a pressure transducer, amplifier and recorder (Fig. 1). The patient was placed in the supine position with the knee of the examined leg slightly flexed and the heel on a support, 15 cm in height. This pressure was selected because it is the lowest pressure that ensures good contact between the air chamber and the limb with minimum compression of the veins. Calibration was performed by depressing the plunger of the syringe (Fig. 1), reducing the volume of the air in the APG (air-chamber and tubing) by 100 ml and then observing the corresponding pressure change. After the calibration the plunger was pulled back to its original position when the pressure in the air-chamber returns to 6 mmHg. An 11 cm wide pneumatic tourniquet, with a bladder 40 cm in length was placed just above the knee and connected to a manometer. Ten min after the air chamber was inflated, when a stable leg/air-chamber/room temperature gradient was achieved, and resting arterial inflow in the leg ensured, the tourniquet was inflated rapidly to 50 mmHg. An increase in leg volume was recorded for 20 sec and then the tourniquet was deflated. This increase represents the arterial inflow to the limb. The latter can be calculated from the slope of the volume recording in ml/min (Fig. 2). Reproducibility studies previously reported have demonstrated a coefficient of variation in the range 3.2 to 7.6%.

**Iloprost therapy**

One ml of iloprost was diluted in 500 ml of normal saline. IV infusion of iloprost was started at a rate of 0.5 ng/kg per min and gradually increased during the first 2 days in steps of 0.25 ng/kg to a maximum tolerated dose or up to 2.0 ng/kg per min, whichever was reached first. The duration of the infusion was 8 h per day. The maximum dose used on day 2 was used on days 3–8.

**Assessment of pain relief**

At the end of the treatment each patient was classified into the following three groups: having complete pain relief; improvement with pain only when the leg was elevated or at night, without requirements for analgesia during the day; little or no change, with pain persisting even when the leg was dependent.

**Results**

At the end of iloprost therapy 23 limbs became free of pain, seven improved, having pain only when the limb was elevated or at night, and 12 did not notice any improvement. Limbs were classified into 3 groups according to the initial baseline leg blood flow before therapy started: (A) initial flow >40 ml/min; (B) initial flow <40 with increase on therapy; (C) initial flow <40 without increase on therapy. The median and 90% confidence levels (90% range) of the leg blood flow in the three groups are shown in Fig. 3. The median increase in flow was 15 ml/min (range 5–33) in group A, 14 ml/min (range 4–45) in group B and 15 ml/min (range 0–25) in group C. The outcome
of iloprost therapy (total relief of pain, improvement or no change) in relation to the initial flow measurement is shown in Table 1. Total relief of pain occurred in 91% of patients in Group A, 18% in Group B and 11% in Group C (p < 0.001, χ² test).

Table 1. Results in relation to initial leg blood flow

<table>
<thead>
<tr>
<th>Leg blood flow (total before therapy)</th>
<th>No rest pain</th>
<th>Improved</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 ml/min</td>
<td>20 (91%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-39 ml/min</td>
<td>2 (18%)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>1 (11%)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>

The complete relief of rest pain at the end of therapy was associated with leg blood flow on day 8 that was greater than 50 ml/min (Table 2) (p < 0.001; χ² test).

Table 2. Results in relation to final leg blood flow

<table>
<thead>
<tr>
<th>Leg blood flow (total on day 8)</th>
<th>No rest pain</th>
<th>Improved</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 ml/min</td>
<td>24 (92%)</td>
<td>2 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>&lt;50 ml/min</td>
<td>1 (6%)</td>
<td>7 (44%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

The angiographic runoff was three vessels in five limbs, two vessels in 11 limbs, one vessel in 21 limbs and zero in four limbs. The initial and final (day 8) flow in relation to the number of vessel runoff is shown in Fig. 4. The median increase in flow as a result of iloprost therapy was 7% in patients with zero runoff but this is not significant because it is within the experimental error of the method. It was 32, 46 and 54% for 1, 2 and 3 vessel runoff. Thus, with the exception of the 4 limbs with zero runoff that had a low initial flow (<30 ml/min) and a very poor response to iloprost (15 ml/min increase in one and nil in the other three), there was no correlation between the angiographic runoff and the initial flow, increased inflow and final flow on day 8.

The natural history of the patients studied 1 year after therapy is as follows. Of the 19 patients (22 legs with rest pain) in group A, six patients developed recurrence of pain and three of these required vascular reconstruction which failed in two resulting in amputation. The other three had a second course of iloprost and were free of pain at 1 year. Thus, a total of 16 (84%) of the 19 patients in Group A remained free of pain without any surgery or amputation. Of the seven patients (11 legs with rest pain) in Group B, three became free of pain after iloprost. Two of these developed recurrence, and had a second course of iloprost therapy. All were free of pain at 1 year. Of the remaining four, two had amputation and two had vascular reconstruction. Of the eight patients in Group C, only one patient became free of pain and remained so for 1 year. Of the remaining seven, six required amputations and one vascular reconstruction.

Treatment was well tolerated in all patients without severe side-effects with the exception of one patient, in whom it was stopped on the third day because of severe headache.

Discussion

Several studies have demonstrated a beneficial effect
of iloprost in patients with severe lower limb ischaemia by relieving rest pain and healing of ischaemic ulcers. However, the mechanism of action of iloprost is not clear. Measurements of blood flow using technetium-labelled red cells in patients with intermittent claudication have failed to show any changes following a 3-day intravenous infusion at maximum dose of 2 ng per kg per min.\textsuperscript{20} Another study also in patients with intermittent claudication investigated with venous occlusion strain-gauge plethysmography did not demonstrate any significant change of limb blood flow after the intravenous infusion of iloprost up to a mean maximum dose of 2.8 mg per kg per min.\textsuperscript{21} A third study using intravenous iloprost at an average dose of 2.6 mg per kg per min for 6 per day, for 15 to 30 days in 11 patients demonstrated a variable change in blood flow during infusion of iloprost using computerised strain-gauge plethysmography. Blood flow doubled in the asymptomatic limbs of all patients. It increased in five of the 11 and no significant changes in the remaining six.\textsuperscript{4} Patients who had shown an increase in blood flow during the acute infusion of iloprost were more likely to demonstrate a clinical improvement at the end of the treatment period than those who did not demonstrate an increase in blood flow. In the latter, the clinical symptoms either remained unchanged or deteriorated after a longer treatment period.

The method of air plethysmography used in our study has been recently developed. The use of an air-chamber that surrounds the whole leg from ankle to knee and its method of calibration provides volume changes (ml) and flow in ml/min. The coefficient of variation for volume changes is 3.2–7.6\%.\textsuperscript{19} This is in contrast to strain-gauge plethysmography which has a coefficient of variation of 7.4–14.2\%.\textsuperscript{22} It has been argued that air plethysmography is more likely to show small changes in blood flow than strain-gauge plethysmography and was the method of choice for our study. The range of leg blood flow in 20 limbs of 20 healthy volunteers has been in the range of 58 to 120 ml/min.

Our results demonstrate that intravenous infusion of iloprost increases arterial inflow in all patients except those with zero runoff. This increase is 32, 46 and 54\% for limbs with 1, 2 or 3 vessel runoff respectively. The flow on day 9 is related to the initial flow prior to therapy. The initial blood flow was a good predictor of relief of symptoms. Twenty of 22 limbs with initial flow less than 40 ml/min became asymptomatic; also final flow greater than 50 ml/min was associated with complete relief of symptoms in 24 (92\%) of 26 limbs, in contrast only one out of 16 limbs with final flow of less than 50 ml/min.

Although this study was not designed to study the long-term effect of iloprost therapy and no measurements of leg blood flow were made after day 8, the preliminary results and natural history suggest that a randomised, placebo controlled double blind study is warranted with blood flow measurements not only during the period of therapy but also long-term. Confirmation of the findings in such a controlled study with information on the relationship between blood flow and the long-term clinical results (continued relief or recurrence of symptoms) is needed.

Air plethysmography has the potential not only of assessing objectively the effect of therapy, but also determining the optimum duration. The aim of our study was to demonstrate whether there was a change in blood flow after 8 days of therapy. Future studies should determine how many days of infusion are required to achieve maximum blood flow and for how long this increase is maintained.

References

13 NORGREN L, ANGQVIST KA, BERGQVIST D, et al. A stable prosta-
cyclin analogue (iloprost) in the treatment of ischaemic ulcers
14 HOSMANN V, AUEL H, SCHROK K. Plazebokontrollierte cross-
over studie uber die Wirkung von iloprost (ZK 36374) auf fort-
geschrattete Stadien der arteriellen Verschlusskrankheit. In:
TRUBESTEIN G, ed, "Konservative Therapie arterieller Durchblutungs-
15 PESSI T, LAUKINEN S, YLITALO P, REINIKAINEN P, VAPAATALO H.
Iloprost, a prostacyclin analogue in the treatment of advanced
double blind study with PGE1 (α-cyclodextrin clathrate) in
patients with ischaemic ulcer of the extremities. VASA 1978; 7:
263–267.
17 NIZANKOWSKI R, KROLIKOWSKI W, BEILATOWICZ J, SZCZEKLIK A.
Prostacyclin for ischaemic ulcers in peripheral arterial disease.
A random-assignment, placebo-controlled study. Thromb Res
18 FIESINGER SN, SCHAPER M. Trial of iloprost verus aspirin treat-
ment for critical limb ischaemia of thromboangiitis obliterans.
19 CHRISTOPOULOS D, NICOLAIIDES AN, SZENDRO G, IRVINE AT, BULL
M, EASTCOTT HHG. Air-plethysmography and the effect of elastic
compression on venous haemodynamics of the leg. J Vasc
20 WILKINSON D, VOWDEN P, McNULTY A, PARKIN, KOSTER RC. A
placebo-controlled trial using iloprost in intermittent claudi-
21 ROBERTS K, LINGE DH, NIXON DP, GRATERS PT, MCLoughlin
GA, BRECKENRIDGE AM. The effects of iloprost on calf blood
flow in patients with stable intermittent claudication. Br J Phar-
22 ROBERTS DH, TSAO Y, BRECKENRIDGE AM. The reproducibility of
limb blood flow measurements in human volunteers at rest and
after exercise by using mercury-in-elastic strain gauge plethys-
ography under standardised conditions. Clin Sci 1986; 70:
635–638.

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