Evaluation of a conservative treatment with iloprost in severe peripheral occlusive arterial disease (POAD)

GISAP study

GISAP Group*, Italy

GISAP is a multicentre open study aimed to confirm the feasibility and safety of iloprost treatment in normal clinical practice and to identify subgroups of patients with severe POAD more likely to benefit from iloprost treatment than others. One hundred forty six patients were treated at the maximum tolerated dose of iloprost up to 2 ng/kg/min, 6 hours infusion per day, for a minimum of 3 weeks and a maximum of 8 weeks. Clinical efficacy was assessed by rest pain reduction, analgesic consumption, healing of trophic lesions, walking ability. A significant improvement of the efficacy parameters was recorded during and at the end of treatment: no difference between diabetics and non diabetics, stage III and IV patients was observed. After one year follow-up 10% major amputation and 6.8% death were recorded, these events were balanced between the diabetic and non diabetic patients. Overall 80% of the patients at risk of amputation at entry to the trial were alive with a viable limb after one year. Tolerability resulted quite acceptable. Even with the limitation of an open trial, it has been confirmed the therapeutic potential of iloprost in the treatment of POAD patients. [Int Angiol 1994;13:70-74].

Key words: Peripheral occlusive arterial disease - Iloprost.

The management of patients with severe peripheral occlusive disease remains clinically challenging: reconstructive procedures and angioplasty are the treatments of choice. Although such interventions are possible in about 60% of the patients, revascularization is not always successful and only 56% of these patients are alive with a viable limb one year after. For the patients who are unsuitable candidates for invasive procedures or when all the approaches fail, the only alternative is surgical amputation which is associated with high mortality rate and requires extensive psychological and social adjustment by the patient.

The role of primary conservative pharmacotherapy for POAD has been unproven and to date very limited, but the development of arachidonic acid derivatives has resulted in a new approach to the problem.

Intravenous preparations of prostaglandins E1 and I2 have been demonstrated to have therapeutic benefit in peripheral arterial disease. Iloprost is a chemically stable analogue of PGI2. Pharmacological studies have shown this drug can improve microcirculatory flow by a variety of mechanisms.

Iloprost's effectiveness in severe POAD has been assessed and demonstrated in several placebo controlled double-blind trials of patients selected by strict inclusion and exclusion criteria.

Given the reliable results obtained in the controlled studies it was considered of particular and crucial importance to assess the role of this new conservative therapeutic approach in the everyday clinical practice. Therefore the present open trial was designed to be performed in environments which reflect the conditions in daily clinical practice which influence the selection of patients and the duration of treatment in a disease such as severe POAD, where each patient's condition is different in terms of concurrent diseases, risk factors and duration of disease.


The aims of this current open multicentre study were to confirm the feasibility and safety of iloprost treatment in normal clinical practice and to identify whether particular subgroups of patients with severe POAD were more likely to benefit from this conservative treatment than others.

**Patients and methods**

Ethical approval was obtained for the centres who took part in the study. After giving their informed consent 146 patients affected by severe POAD were recruited from 17 angiology and vascular surgery centres.

Patients, diabetics and non diabetics, affected by POAD stage III and IV according to Fontaine's classification and patients with Buerger's syndrome were admitted, provided that, in the clinician's opinion, they required conservative treatment.

Patients in whom reconstructive surgery or angioplasty was indicated at the time of their entry into the study, patients with myocardial infarction or cerebral vascular accident within the previous four months, angina pectoris, cardiac failure (NYHA > II), Raynaud's disease, patients requiring dialysis, patients with bleeding diathesis or platelet counts $<80 \times 10^6$/ml or $>500 \times 10^6$/ml and patients unable to give informed consent were excluded.

The patients were treated at the maximum tolerated dose of iloprost up to 2 ng/kg/min as a six hour infusion per day. To allow clinicians a degree of flexibility patients could be treated for a minimum of three weeks and a maximum of eight weeks, depending on patient's clinical outcome.

Side effects experienced by the patient were recorded.

Safety of treatment was also monitored by measurement of blood pressure and heart rate during infusion, haematological and biochemical parameters before and at the end of treatment.

Other drugs for POAD were not allowed during the treatment. Therapies for concomitant diseases were documented.

Reduction of rest pain (by score: 1 absent, 2 slight or moderate, 3 intense, 4 constantly present excruciating pain), analgesic consumption, healing of trophic lesions (complete or clinically relevant), walking ability (by score: 1 absent, 2 $\leq 50$ m, 3 $>50$ m) were the chosen parameters of clinical efficacy recorded at the beginning of therapy, at fourteen day intervals during treatment and at the end of the infusion period. During the twelve month follow-up period the number of patients with minor and major amputation or who had died was also recorded.

Data were processed on Paradox 3.5 (Borland) and statistical analysis was performed by BMDP (BMDP Statistical Software Inc.).

Analysis of variance was used for repeated measurements of parametric data, Friedman's and Kruskal-Wallis' tests for non parametric data; frequencies were analysed by $\chi^2$ test. $p<0.05$ was considered significant.

**Results**

Baseline characteristics of the patient population are shown in Table I; 15% of the patients had previously undergone by-pass surgery and 10% amputation, whereas the majority of the patients (86%) had in the past received commonly used conservative agents.

Occlusive disease was confirmed by clinical and Doppler examinations in almost all the patients (98.6%) and by angiography (50.7%).

The incidence of risk factors and the generalised cardiovascular disease in the patient popu-
**TABLE II.—Risk factors and previous cardiovascular events (N. patients=146).**

<table>
<thead>
<tr>
<th>Factors</th>
<th>N.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>51</td>
<td>(34.9)</td>
</tr>
<tr>
<td>Ex smokers</td>
<td>52</td>
<td>(35.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57</td>
<td>(39.0)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>51</td>
<td>(34.9)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>35</td>
<td>(24.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>67</td>
<td>(45.9)</td>
</tr>
<tr>
<td>AMI</td>
<td>23</td>
<td>(15.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>(4.8)</td>
</tr>
</tbody>
</table>

**TABLE III.—Localization of arterial occlusion and >75% stenosis (% of patients).**

<table>
<thead>
<tr>
<th>Localization</th>
<th>Stage III (n=46)</th>
<th>Stage IV (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— right/left</td>
<td>4.3</td>
<td>9</td>
</tr>
<tr>
<td>— bilateral</td>
<td>17.4</td>
<td>11</td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— right/left</td>
<td>54.3</td>
<td>40</td>
</tr>
<tr>
<td>— bilateral</td>
<td>30.4</td>
<td>32</td>
</tr>
<tr>
<td>Tibial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— right/left</td>
<td>41.3</td>
<td>60</td>
</tr>
<tr>
<td>— bilateral</td>
<td>26.1</td>
<td>24</td>
</tr>
<tr>
<td>Popliteal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— right/left</td>
<td>6.5</td>
<td>3</td>
</tr>
<tr>
<td>— bilateral</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Upper limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— right</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>— bilateral</td>
<td>2.2</td>
<td>2</td>
</tr>
</tbody>
</table>

Arterial occlusion and stenosis were mostly located at femoral and tibial level and often were bilateral (Table III).

Sixty-six out of 146 (45%) patients were considered at risk of amputation when entering the study.

In 45 (30.8%) patients treatment was discontinued for reason other than efficacy: 19 (13%) because of side effects, mainly headache, flushing, nausea and vomiting and 6 of them (4.1%) for less common events such as hypertension, dyspnoea and angina.

Nineteen (13%) patients discontinued for deterioration of clinical symptoms, 5 (3.4%) of them were amputated (4 major and 1 minor amputation). Other 7 (4.8%) interrupted the treatment for personal reasons.

During and at the end of treatment a significant (p<0.01) reduction in analgesic relief of rest pain mean score was recorded (Fig. 1). Pain score decreased from 2.65±0.60 to 1.71±0.73 after 14 days and to 1.53±0.91 in stage III patients, from 2.72±0.74 to 1.67±0.82 and 1.67±0.93 respectively in stage IV patients.

Rest pain decreased over a period of two weeks also in diabetic patients, from 2.64±0.75 to 1.65±0.68, the effect persisting up to the end of treatment to 1.60±0.88. No difference was observed between the results achieved in diabetic and non diabetic patients.

A significant (p<0.01) reduction in analgesic
consumption was also observed with a pattern similar to that of pain relief. A reduction of opiate and of other commonly used analgesics consumption was recorded at the end on infusion period in all subgroups examined.

Walking ability mean score increased significantly (p<0.01) at the end of treatment both in stage III and IV patients, from 2.13±0.54 to 2.65±0.65 and from 1.83±0.59 to 2.30±0.78 respectively, as well as in diabetics from 1.90±0.62 to 2.31±0.76 (Fig. 2). No statistical difference was again observed between diabetics and non diabetics.

A complete or clinically relevant healing of trophic lesions was evident in 40 of 86 patients (46.5%) who initially had lesions: mean ulcer area decreased from 4.93±5.60 to 3.05±4.75 cm² at the end of treatment.

After one year follow-up the overall clinical events recorded in the patient population studied were: 15 major amputations (10.3%), 14 minor amputations (9.6%) and 10 deaths (6.8%) (Table IV).

Ten of the major amputations occurred early during treatment period and the first month of follow-up, whereas the others occurred later than five months after the end of treatment.

**Table IV.**—Clinical events after one year follow-up.

<table>
<thead>
<tr>
<th>Events</th>
<th>Diabetics</th>
<th>Non diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>(%)</td>
<td>N.</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>Patients entered</td>
<td>67 (45.9)</td>
<td>79 (54.1)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>6 (9.0)</td>
<td>9  (11.4)</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>9 (13.4)</td>
<td>5  (6.3)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (10.4)</td>
<td>3  (3.8)</td>
</tr>
</tbody>
</table>

Four deaths occurred following major and/or minor amputation and were equally distributed between the diabetic and non diabetic groups. The distribution of the events resulted well balanced between the diabetic and non diabetic patients but, not unexpectedly, more relevant in the subgroup of stage IV patients (13% major amputation, 13% minor amputation and 4% death) than in stage III patients (4.3% major amputation, 2.2% minor amputation and 8.7% death).

The outcome of the patients who were at risk of amputation at entry to the trial was the following: out of 33 non diabetic patients 24 (72.7%) of these and 21 (63.3%) out of 33 diabetics resulted alive without any kind of amputation.

Overall 80.3% (53/66) of the patients at risk on entry were alive with a viable limb (without any amputation below the ankle) after one year.

At the end of follow-up 44 patients (29 stage IV and 15 stage III) were still free of pain and 48 not requiring regular use of analgesics.

Common side-effects as headache, flushing and less commonly nausea and vomiting during the first two weeks of treatment were reported as mild in 65 (44.5%) patients, moderate/severe in 63 (43.1%) and 18 (12.3%) patients did not complain any side-effects. With the continuation of the infusion a reduction in the incidence and severity of side-effects was registered and 36.3% of the patients were completely free from them up to the end of treatment.

No direct effects of iloprost treatment on the monitored haematological or biochemical parameters were reported.

**Discussion**

This open clinical experience showed that iloprost treatment given to severe POAD patients...
in an administration regimen suggested as effective by controlled clinical trials, is feasible in every day clinical practice despite the lengthy intravenous therapy.

Previous controlled double-blind trials provided the evidence of a clinical benefit at the end of the infusion period on the resolution of primary management problems in severe POAD patients such as pain and ulceration: accordingly in this study a therapeutic usefulness of the drug in improving the clinical conditions of the patients was observed, but the role of the continuous medical care the patients received during the study period should be taken into account in evaluating such an improvement.

In this non selected patient population with severe POAD all subgroups examined shown, at the end of treatment, a similar response to iloprost. No differences were observed between diabetics and non-diabetics, as previously reported in controlled trials as well as between stage III and IV patients, confirming the therapeutic potential of this conservative treatment.

However the results at the end of the infusion period give information about the pharmacological usefulness of the drug but the real clinical efficacy needs to be evaluated in the longer term, even though the patients received an uncontrolled variety of treatment after their iloprost infusion.

In controlled trials a sustained long-term improvement and a postponement of amputation during six months to one year follow-up have been reported in the majority (60 to 90%) of the patients who responded to the treatment. The Second Consensus Document on Critical Limb Ischemia reports that after one year from the onset of critical ischaemia, irrespective of medical treatment, only 55% of the patients were alive with a viable limb, 25% underwent a major amputation and 20% will have died.

Even with the limitation of an open study this experience is the first evaluating the one year outcome of the patients and supports the role of iloprost in improving the long-term prognosis of the POAD patients as about 80% of the patients who were at risk of amputation on entry were alive with a viable limb after one year.

Patients in this clinical experience were variable in their ability to tolerate iloprost, the discomfort due to side-effects, which however can be easily reduced by individual dose titration, appears to be acceptable in view of the severity of the disease being treated and the potential benefit of iloprost treatment.

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References


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ERRATA CORRIGE

(Vol. 13, issue no. 1, pages 70-74).
“Evaluation of a conservative treatment with iloprost in severe peripheral occlusive arterial disease (POAD). Gisap study”.

Gisap Group, Italy.

Page 73:
“Overall 80.3% (53/66) of the patients at risk on entry were alive with a viable limb (without any amputation below the ankle) after one year”.

Should read as follows:
“Overall 80.3% (53/66) of the patients at risk on entry were alive with a viable limb (without any amputation above the ankle) after one year”.

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