Correspondence

Prostacyclin Analogues

Sir,

We read with interest the recent reports by Thomson et al.\(^1\) and Sayers et al.\(^2\) concerning the effects of the prostacyclin analogue iloprost on leukocyte adhesion and smooth muscle cells of vein grafts. Prostacyclin may have a role in the regulation of cell growth in the vascular wall,\(^3\) and reduced prostacyclin production from damaged vein graft endothelium is thought to contribute to smooth muscle cell proliferation, the principal cause of late graft failure.\(^4\) These data have been extrapolated to suggest that prostacyclin analogues might be useful in minimising intimal hyperplasia in vein grafts.

We tested this hypothesis in an established organ culture model of human saphenous vein\(^5\) using Cicaprost (Schering Health Care Ltd, U.K.), a stable prostacyclin analogue. Segments of freshly isolated saphenous vein harvested from eight patients undergoing elective coronary artery bypass surgery were obtained. Vein was transferred to the laboratory at room temperature in Hepes buffered RPMI 1640 culture medium supplemented with penicillin (100 μg/ml), streptomycin (100 units/ml), amphotericin (2.5 μg/ml), gentamycin (2.5 μg/ml), glutamine (2mM). Each vein segment was then split into three equal sections (one for control and two to test) and cultured as previously described.\(^6\)

Briefly, excess fat and adventitial tissue were dissected from the vessel which was then opened out along its upper aspect and pinned, intimal surface uppermost, onto a polyester gauze support resting on sylgard resin set in the base of a glass Petri dish. Vein segments were washed several times with medium and then cultured in RPMI 1640 culture medium containing sodium bicarbonate (2.0 g/l) and 30% foetal calf serum (Northumbria Biologicals, Northumberland, U.K.). Cultures were maintained for 14 days in a humidified atmosphere with 5% (v/v) CO\(_2\) in air. The culture medium was replaced every 2-3 days. Parallel cultures were set up with the addition of Cicaprost at two concentrations (10\(^{-8}\) M and 10\(^{-9}\) M). Cultures were pulse labelled with [\(^3\)H] thymidine (Amersham Int., U.K.) for the last 24 h of the 14 day culture period.

Tissue viability as defined by adenosine triphosphate (ATP) concentration was measured in perchloric acid extracts of vein using HPLC.\(^5\) Intimal thickening was assessed in 5 μm histological transverse paraffin sections stained with Alcian Blue/Millers Elastic/Van Gieson at 20 equidistant points along the section length using an image analyser (SeeScan, Cambridge, U.K.). Cell proliferation was quantified by [\(^3\)H] thymidine incorporation and autoradiography.

ATP concentration (nmol/g wet weight) was maintained throughout the culture period in the freshly isolated veins and in the presence of Cicaprost. There were no significant differences in the degree of intimal thickening or cell proliferation in veins cultured with either concentration of Cicaprost when compared to controls using paired data in a Student t-test (Table 1). Autoradiography also showed no significant difference in the number of [\(^3\)H] thymidine labelled cells/mm section length in the neointima. These data show that Cicaprost does not inhibit smooth muscle cell proliferation and neointimal formation in the human saphenous vein organ culture when used at concentrations of 10\(^{-8}\) M and 10\(^{-9}\) M.

Table 1. Data expressed as mean ± SE (n=8)

<table>
<thead>
<tr>
<th></th>
<th>ATP concentration (nmol/g wet weight)</th>
<th>Intimal thickness (μm)</th>
<th>[(^3)H] thymidine uptake (DPM/μg DNA)</th>
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<tbody>
<tr>
<td>Freshly isolated vein</td>
<td>320±135</td>
<td>0</td>
<td>0</td>
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<td>(day 0)</td>
<td></td>
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<tr>
<td>Freshly isolated vein</td>
<td>310±78</td>
<td>34.2±10.1</td>
<td>752±168</td>
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<tr>
<td>(day 14)</td>
<td></td>
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<td></td>
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<tr>
<td>Freshly isolated vein+</td>
<td>296±41</td>
<td>38.9±1.6</td>
<td>605±68</td>
</tr>
<tr>
<td>Cicaprost [10(^{-8}) M]</td>
<td></td>
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<tr>
<td>(day 14)</td>
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<td></td>
</tr>
<tr>
<td>Freshly isolated vein+</td>
<td>356±125</td>
<td>29.6±7.1</td>
<td>585±98</td>
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<tr>
<td>Cicaprost [10(^{-9}) M]</td>
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There is ample evidence that, during surgical preparation, the loss of endothelial cells in the saphenous vein and impairment of their ability to produce prostacyclin and endothelium-derived relaxing factor promote platelet and leukocyte adhesion, and result in an early occlusion of 8-18% of grafts in the first month following surgery. The recently reported improvement in vein graft patency at 1 month in man, with the topical application of prostacyclin analogues, is likely to be due to its ability to counteract these effects by inhibiting platelet and leukocyte activation, aggregation and adhesion, and also improving graft flow, all of which have been well documented.

Vein grafts that remain patent following this initial period experience a predictable and progressive intimal hyperplasia, long after the restoration of a morphologically intact endothelium and the termination of platelet and leukocyte adhesion. This intimal thickening is caused by the proliferation and migration of vascular smooth muscle cells from the media, and results in late occlusions of saphenous vein grafts. In this study, we were not able to show any effect of Cicaprost on smooth muscle proliferation or intimal hyperplasia, we therefore conclude that it may not have any benefit in preventing late saphenous vein graft failure.

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References

Femoral Osteochondroma

Sir,
I have read with interest the case reported by Fox et al.1 about femoral artery occlusion secondary to a benign osteochondroma of the femur. Certainly, intermittent claudication in young patients is extremely uncommon and unlikely to be atherosclerotic in origin. Thorough investigation is warranted although I am not sure MRI added much information to the case described.

Apart from arterial problems these patients may present with venous thrombosis—I have described a similar case of a 44-year-old man with a femoral metaphysis osteochondroma presenting with a spontaneous DVT 3 years prior to the onset of occlusive arterial symptoms.2 Plain radiography and colour flow Duplex were sufficient to diagnose the problem. Arteriography was necessary to determine the state of the distal vasculature—all 3 vessels were occluded secondary to microemboli. The case described by Fox et al. was fortunate in being diagnosed early, before distal microemboli caused further problems.

In summary, as stated by Fox et al. any young person presenting with symptoms and signs of arterial disease or spontaneous DVT warrants full investigation. I would suggest plain radiography, colour flow Duplex and arteriography.

References