INITIAL IMPRESSIONS OF DAZOXIBEN IN THE TREATMENT OF THE ISCHAEMIC LIMB

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- 1 Dazoxiben, a selective thromboxane synthetase inhibitor, which is active after oral administration, has been used to treat eight patients with severe peripheral vascular disease associated with ischaemic rest pain.
- 2 Patients were selected for treatment on the basis that amputation was the only alternative procedure.
- 3 Three of eight patients are well and pain-free 1, 7 and 11 months after initially receiving the drug and have not required amputation.
- 4 Dazoxiben may prove useful in the treatment of peripheral vascular disease.

Introduction

THE pharmacological treatment of advanced peripheral vascular disease with vasodilators has been of little, if any, value. Prostaglandins have been used in the treatment of advanced peripheral vascular disease with some success. It has been reported that intra-arterial (Carlson & Eriksson, 1973) or intravenous infusions (Carlson & Olsson, 1976) of prostaglandin E₁ (PGE₁) will alleviate rest pain and gangrene. Szczeklik *et al.* (1979) treated patients with advanced arteriosclerosis obliterans of the lower extremities with an intra-arterial infusion of prostacyclin (PGI₂) and demonstrated relief of rest pain, regression of necrosis and healing of ischaemic ulceration.

The main disadvantage of this form of treatment is that the drug has to be administered intravenously or intra-arterially and requires hospitalization. More recently Tyler *et al.* (1981) have reported early work with a selective thromboxane synthetase inhibitor, dazoxiben (UK 37248-01), which is absorbed following oral administration and inhibits the production of thromboxane A₂ (measured as TXB₂). This drug has the theoretical advantage that by inhibition of thromboxane synthetase, it may make more endoperoxides available for conversion to vasodilatory PGI₂ or PGE₂; in other words it may function as an "oral prostacyclin".

In view of the possible advantages of this drug it was decided to treat a limited number of patients with it. Patients were selected for treatment on the basis that amputation was the only alternative procedure.

Methods

Eight patients with severe peripheral vascular disease were treated with dazoxiben. All patients gave informed consent to treatment. The details of the patients and the disease processes are shown in Table 1. Their

mean age was 72 yr (range 42-84). Patients were considered for treatment only if they: (1) had ischaemic rest pain; (2) were unsuitable for reconstructive arterial surgery; (3) had previously had a failed attempt at reconstructive arterial surgery; and (4) had had a failed lumbar sympathectomy. Patients were excluded from the trial if there was: (1) no rest pain; (2) wet gangrene involving more than the toes; (3) treatment with peripheral vasodilators in the previous 2 weeks; and (4) treatment with an antiplatelet agent within the preceding 2 weeks.

The treatment schedule was dazoxiben 100 mg three times daily initially for 1 month, the initial 7 d treatment period being carried out in hospital. The following investigations were carried out during the course of treatment: full blood count, platelet count, urea and creatinine on alternate days for 7 d while the patient was in hospital and weekly thereafter. Blood pressure and heart rate were measured every 4 h while the patients were in hospital.

Assessment of progress was subjective, in that the patients were asked whether their pain was better or not, and the ultimate objective assessment was whether they required amputation or not.

Results

The results are summarized in Table 1. There was an initial subjective improvement in six patients as far as pain relief was concerned. However, in this group two patients died (2, 7), one relapsed (5), and at the present time three remain well (1, 4, 8). Two patients showed no improvement whatever. One died within a month of starting treatment and the other had an above-knee amputation. Of the three patients still showing sustained improvement, the patient with Buerger's disease is working, has no rest pain and no ulceration or gangrene. The 65-y-old patient with

Table 1 Details of patients: duration and results of treatment

Patient	Sex	Age (yr)	Disease	Duration of treatment	Results of treatment	
					Initial	Final
1	M	42	Buerger's disease	20 weeks	Pain relief	Well. Healed ulcers. No rest pain.
2	M	79	Arteriosclerotic peripheral vascular disease	10 weeks	Pain relief	Continued improvement. Died. Chronic bronchitis and emphysema.
3	M	75	Arteriosclerotic peripheral vascular disease	10 d	No improvement	Above knee amputation
4	M	65	Arteriosclerotic peripheral vascular disease	8 weeks	Pain relief	No rest pain. Healed ulcers. Ambulant
5	M	72	Arteriosclerotic peripheral vascular disease. Congestive cardiac failure. Left hemiplegia	4 weeks	Some improvement	Pain recurred on treatment. Persistent severe rest pain and ischaemic ulcers.
6	F	84	Diabetic. Small vessel disease.	4 weeks	No improvement	Died. Bilateral infected gangrene.
7	F	75	Diabetic. Arteriosclerotic peripheral vascular disease. Small vessel disease.	5 d	Some improvement	Died. Myocardial infarction.
8	F	82	Diabetic. Small vessel disease.	4 weeks	Pain relief	No rest pain. Dry gangrene of toes. Separating.

peripheral vascular disease is well, has no rest pain, his ischaemic ulcer has healed, and his gangrenous toes have separated and healed. The third patient, an 82-yr-old lady, is well with no rest pain and with dry gangrene of the toes which are separating.

Of the three patients who died on treatment, one died of chronic bronchitis and emphysema, one died of bilateral gangrene, and the other had a myocardial infarction, proven at post-mortem. None of the deaths was attributed to dazoxiben.

Of the observations and investigations carried out while the patients were on the treatment, no change was noted in routine blood count, platelet count, urea and creatinine. There was no change in heart rate or blood pressure. No side-effects were reported.

At the present time three of the eight patients are well and pain-free 1, 7 and 11 months after initially receiving the drug and have not required amputation.

Discussion

This limited study has resulted in an encouraging level of clinical response in a small group of patients with very severe peripheral vascular disease. Four of the eight patients became pain-free and avoided am-

putation after treatment with dazoxiben, a selective inhibitor of thromboxane synthetase. Three of these remain well, the fourth having died after 10 weeks. It is difficult to draw any firm conclusions in an uncontrolled study such as this. It is not clear what effect the drug has had; whether it is primarily its antiplatelet effect or whether it acts via a vasodilator effect possibly by enhancing PGI₂ or PGE₂ production.

The absence of side-effects suggests that if PGI₂ synthesis was increased, the amount was insufficient to show any of the side-effects which may occur when PGI₂ is infused (Moncada & Vane, 1978). If PGI₂ is to be useful in the treatment of vascular disease, analogues must be developed because PGI₂ itself has a short half-life, is chemically unstable, and has to be infused intravenously or intra-arterially, and also has significant side-effects.

Certainly dazoxiben has theoretical advantages. It is absorbed after oral administration, it reduces pro-aggregatory thromboxane A₂ and it increases production of anti-aggregatory PGI₂ (Vermeylen *et al.*, 1981). In the dose used in this study it seems to be without side-effects.

Although no firm conclusions may be drawn from this small open study, the drug may prove useful in

the treatment of peripheral vascular disease. These encouraging results suggest the need for further evaluation of dazoxiben in controlled trials.

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