EFFECTS OF DAZOXIBEN ON EXERCISE PERFORMANCE IN CHRONIC STABLE ANGINA

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- 1 We have performed a double-blind, randomized, 7-d cross-over study of the thromboxane synthetase inhibitor dazoxiben (UK 37248) in 20 patients with stable coronary heart disease.
- 2 All patients had a history of exertional angina of greater than two years duration and no patient had suffered a myocardial infarction in the preceding twelve months.
- 3 All patients had a positive exercise stress test for myocardial ischaemia and 15 had undergone coronary angiography. All these patients had a 50% narrowing in at least one vessel.
- 4 All patients were on conventional anti-anginal medication and the doses of their various therapies remained unchanged in the three months prior to and during the study period.
- 5 Therapy with dazoxiben 200 mg four times daily produced no alteration in the subjective or objective features of angina in these patients. There was no alteration in angina attack rate, glyceryl trinitrate consumption or duration of treadmill exercise.
- 6 Dazoxiben produced a highly significant reduction in both the resting and the post-exercise levels of serum thromboxane B₂ levels, although there was no significant difference between the pre-exercise and post-exercise values.
- 7 Dazoxiben is an effective inhibitor of the synthesis of thromboxane but it has no effect on the subjective or objective features of stable coronary disease. This would suggest that the production of thromboxane and the development of circulating platelet aggregates play no part in the mechanism of angina in patients with stable coronary heart disease.

Introduction

THERE has been considerable interest in the role of platelets in atherogenesis for many years. More recently, attention has turned to the role of platelet aggregation and thromboxane release in the mechanism of anginal pain in both stable and unstable coronary heart disease. Miller and his group (Kumpuris *et al.*, 1980) reported an increased production of platelet aggregates by dynamic exercise in patients with coronary heart disease. At the same time Lewy *et al.* (1980) demonstrated an excessive release of thromboxane into the coronary sinus of patients with coronary heart disease, during pacing-induced angina.

The formulation and development of a selective thromboxane synthetase inhibitor, dazoxiben (UK 37248) interested us to evaluate the role of thromboxane release and its blockade in patients with coronary heart disease and stable angina pectoris.

Methods

We performed a double-blind placebo-controlled, crossover study, of the effects of dazoxiben on exercise performance in 20 patients with stable angina pectoris. All patients had a history of exertional angina of greater than 2 years duration and no patient

had suffered a myocardial infarction in the preceding 12 months. Each patient had a positive exercise stress test for myocardial ischaemia, using a treadmill and the Bruce protocol and conventionally accepted criteria for exercise test positivity.

Fifteen patients had undergone coronary arteriography for consideration of coronary revascularization surgery. All these patients had a 50% narrowing in at least one vessel. Three patients had previously undergone coronary artery bypass graft surgery, but with resultant incomplete control of angina with continuation of a positive exercise stress test. A further four patients are still awaiting coronary artery surgery.

All patients were receiving conventional medication for angina in adequate doses and their therapy consists of the following possible combinations:

- (1) β -blocker+long acting nitrate+glyceryl trinitrate (GTN) in 4 patients.
- (2) β -blocker+nifedipine+long acting nitrate in 5.
- (3) Verapamil+GTN in 6.
- (4) Verapamil+long acting nitrate+GTN in 3.
- (5) Verapamil+perhexilene+GTN in 1.
- (6) Nifedipine+GTN in 1.

For 3 months before, and during the study period, conventional therapy remained unchanged. The only variable in therapeutic terms being GTN consump-

tion: the patients were instructed not to take any non-steroidal anti-inflammatory drug in 2 weeks before the study, nor to smoke during that period. The exercise tests were performed in the morning with the patients fasted and each test was performed at the same time of day. The ambient temperature of the exercise laboratory was constant throughout the study period and the treadmill was calibrated at frequent intervals. The end-point of the stress test was the development of angina and heart rate and blood pressure were monitored throughout the test and for the following twenty minutes. A full 12-lead electrocardiogram (ECG) was taken before the exercise test and during the test the precordial leads V2, V4 and V5 were monitored. At cessation of exercise, when the patients were returned to the supine position, the three standard leads, I, II, III and the precordial leads V2, V4 and V5 were monitored and strictly recorded at 2-min intervals for 20 minutes.

Blood was taken before the exercise test, after the patients had rested supine for at least half an hour. This was analysed for: (1) platelet aggregate ratios by the method of Wu & Hoak (1974); (2) measurements from a Helige thromboelastograph test; and (3) serum thromboxane B₂ (TXB₂) levels. These tests were repeated on cessation of the exercise test, as

soon as was practically possible, when the patient was returned to the supine position.

In the post-exercise period ST depression was measured in the three standard leads and the three precordial monitoring leads, at 2-min intervals and a cumulative value calculated for the 20 min post-exercise period.

After completion of the pre-trial measurements, the patients were randomized either to dazoxiben 200 mg four times daily or an equivalent placebo for 7 days. The patients returned on the final day after therapy for the complete protocol to be repeated before crossing over to the alternative treatment.

Results

Table 1 shows that therapy with dazoxiben produced no alteration in treadmill exercise time (control 301 ± 149 s; dazoxiben 327 ± 143 s, placebo 321 ± 141 s). Table 1 also shows that there is no alteration in the amount of cumulative ST depression (control 15.8 ± 10.5 mm; dazoxiben 14.0 ± 8.9 mm; placebo 13.0 ± 6.8 mm). Dazoxiben produced no changes in the resting blood pressure and heart rate nor on their responses to exercise and so the pressure-

Table 1

<i>Treadmill exercise time (s)</i>		
<i>Control</i>	<i>Placebo</i>	<i>Dazoxiben</i>
301	321	327
± 149	± 141	± 143
<i>Cumulative ST segment depression (mm)</i>		
<i>Control</i>	<i>Placebo</i>	<i>Dazoxiben</i>
15.8	13.0	14.0
± 10.5	± 6.8	± 8.9

Numbers are group mean values ($n=20$) $\pm$ s.d.

Table 2

<i>Angina attack rate (number per week)</i>		
<i>Control</i>	<i>Placebo</i>	<i>Dazoxiben</i>
11	8	10
± 10	± 10	± 11
<i>GTN consumption (number per week)</i>		
<i>Control</i>	<i>Placebo</i>	<i>Dazoxiben</i>
7	5	6
± 9	± 9	± 10

Numbers are group mean values ($n=20$) $\pm$ s.d.

Table 3

Platelet aggregate ratios					
Control		Placebo		Dazoxiben	
Pre-exercise	Post-exercise	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
1.04	1.05	1.00	0.92	1.05	1.01
±0.35	±0.30	±0.17	±0.19	±0.23	±0.23
Thromboelastograph values (ITP)					
Control		Placebo		Dazoxiben	
Pre-exercise	Post-exercise	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
8.51	9.19	10.55	11.09	9.19	10.01
±2.90	±3.45	±4.85	±4.83	±3.85	±4.54

Numbers are group mean values ($n=20$)±s.d.

Table 4

Serum TXB ₂ production (ng/ml)					
Control		Placebo		Dazoxiben	
Pre-exercise	Post-exercise	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
105.2	83.8	57.9	44.7	19.8	12.4
±57.1	±48.4	±41.2	±34.5	±23.9	±18.6

rate product was not altered.

Table 2 summarizes the patients' subjective response in terms of angina attack rate and GTN consumption. It can be seen that there is no significant alteration in either of these two variables which are the group mean values with standard deviation.

Platelet function tests determined from measurements of platelet aggregate ratios and the thromboelastograph (expressed as ITP) showed considerable inter- and intra-patient variation (Table 3). Table 3 also gives the group mean values with standard deviations. Therapy with dazoxiben has produced no change in these measurements nor has exercise produced a trend.

Table 4 gives the group mean values for serum TXB₂ levels with standard deviations. Once again there was considerable inter- and intra-patient variations. The group mean values are much lower than observed in other studies but the explanation for this observation remains elusive. It is highly improbable that the whole group of patients were taking aspirin-containing medication. It is also unlikely that their conventional anti-anginal medication interfered with the resting and post-exercise levels. There is no obvious explanation for the significant reduction in the placebo values when compared to the control values before starting either the placebo or active drug treatment phase. Table 4 also shows that exercise did not

have any significant effect on the level of serum TXB₂. But therapy with dazoxiben did, however, produce significant pre-exercise reductions in this measurement, which was also much lower in the post-exercise period, but not significantly different from the pre-exercise value.

Discussion

The results of this study have confirmed that dazoxiben is highly effective in inhibiting the synthesis of TXB₂ and although the duration of active drug therapy was only 7 d, it had no effect whatsoever on the clinical features of chronic stable angina nor on the exercise performance of patients with this disease. These data strongly suggest that the release of TXB₂ into the coronary sinus and the formation of circulating platelet aggregates, play no part in the mechanism of angina in patients with obstructive coronary disease who have typical exercise and emotion-induced angina as opposed to "vasospastic" angina.

We are grateful to Mrs Kay Mansfield for typing the manuscript and to the Research Laboratories of Pfizer Limited for measurement of serum TXB₂.

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