EFFECTS OF DAZOXIBEN ON TRANSCARDIAC THROMBOXANE LEVELS AND HAEMODYNAMICS IN CORONARY HEART DISEASE

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- 1 Plasma thromboxane levels were obtained from both the coronary sinus and aorta in patients with stable angina pectoris paced to angina, and in unstable angina patients before and after dazoxiben 100 mg.
- 2 Although there was a wide range of values in the different groups, dazoxiben significantly reduced plasma thromboxane levels in all patients.
- 3 Dazoxiben had no adverse effect on coronary and systemic haemodynamics, and atrial pacing time to angina was increased from 245 ± 41 to 308 ± 48 s ($P < 0.01$).

Introduction

THERE has been recent interest in platelets and platelet products, β -thromboglobulin and thromboxane, in the pathogenesis of coronary artery disease and its manifestations of myocardial infarction and acute myocardial ischaemia. Platelet aggregates have been found in coronary sinus blood in patients with spontaneous rest pain (Robertson *et al.*, 1980; Dalal *et al.*, 1982). Elevated β -thromboglobulin levels in peripheral blood have been reported in patients with acute myocardial ischaemia (Smitherman *et al.*, 1981) and in coronary sinus blood in patients with coronary artery spasm (Rubenstein *et al.*, 1981). Thromboxane A_2 (TXA₂) is a potent vasoconstrictor released by platelets which induces further platelet aggregation. TXA₂ is unstable and spontaneously converts to the inactive metabolite thromboxane B₂ (TXB₂). TXB₂ levels have been found to be increased in patients with unstable angina pectoris at rest by Hirsh *et al.* (1981) and Tada *et al.* (1981) and after atrial pacing by Lewy *et al.* (1980).

Prostacyclin (PGI₂) found in vascular endothelium inhibits platelet aggregation and is a potent vasodilator. Both PGI₂ and TXA₂ are derived from the prostaglandin endoperoxides and are thought to regulate the normal coronary circulation (Moncada & Vane, 1979). Selective inhibition of thromboxane synthesis would reduce circulating levels of TXA₂ and in theory should increase formation of PGI₂ with its vasodilating and platelet-anti-aggregating properties. Dazoxiben is a new orally active thromboxane synthetase inhibitor which has been shown in human volunteers to inhibit TXB₂ production in a dose-related fashion and to increase PGI₂ levels (Tyler *et al.*, 1981; Vermeylen *et al.*, 1981). The purpose of this study was to evaluate the effects of dazoxiben on both transcatheter thromboxane levels and coronary and systemic haemodynamics in patients with stable and unstable angina pectoris.

Methods

Two groups of patients were studied: those with stable angina and a second group with unstable angina. Patients with platelet aggregation evidence of cyclooxygenase inhibition were excluded.

The first group consisted of 20 patients with stable angina who were being considered for coronary artery bypass surgery. The mean age of the group was 47 y (range 43–65 y). At coronary arteriography, all patients were demonstrated to have significant disease, defined as a 70% or more reduction in luminal diameter, in one or more major vessel. The second group was of nine patients with unstable angina. This was defined as chest pain at rest, with a documented abnormal electrocardiogram, despite maximal medical therapy with cardioselective β -blockers, nitrates and slow channel calcium blockers. This group had a mean age of 50 y (range 30–60 y). Seven of these patients were shown to have significant coronary disease but in two, coronary spasm was demonstrated. The most recent cardiac pain had occurred in the 24 h before the study.

Thirty minutes following routine left ventriculography and coronary angiography, haemodynamic measurements and samples were obtained. Continuous electrocardiographic monitoring allowed measurement of heart rate; and, via a femoral artery, a No. 7 pigtail catheter was positioned near the coronary artery for arterial sampling and measurement of intra-aortic blood pressure. A Swan Ganz catheter was inserted percutaneously into a peripheral vein for measurement of cardiac output, pulmonary pressure and pulmonary capillary wedge pressure. Cardiac output was measured in triplicate using the thermodilution technique (Instrumentation Laboratories 701). In six patients a 7F double thermistor catheter (Wilton-Webster) was introduced into a left median antecubital vein and advanced into the proximal 1–2 cm of the coronary sinus. The

catheter tip was undisturbed during the study and coronary sinus flow was measured using a thermodilution technique with a constant infusion of 0.9% saline solution at 60 ml/min for 30 s with a reproducibility of $3 \pm 2\%$. In the remaining patients a No. 8 Goodale-Lubin catheter was inserted in the coronary sinus and simultaneous blood samples obtained from aortic and coronary sinus and assayed for oxygen content using an Instrumentation Laboratories co-oximeter 282.

Haemodynamic and haematological measurements and samples were obtained at rest in all patients. In those patients with stable angina, the myocardium was stressed by means of rapidly increasing the heart rate by atrial pacing until angina was induced. Haemodynamic measurements and samples were obtained during pacing-induced pain. Fifteen minutes later dazoxiben 100 mg was administered orally and all measurements and samples were repeated 1 h after ingestion. Atrial pacing to angina was repeated. A second coronary arteriogram was performed in all patients. Dazoxiben treatment was continued for 7 d in an oral dose of 100 or 200 mg three times daily in the nine patients with unstable angina. A peripheral venous sample was obtained on day 7 and platelet function studies were repeated.

Haematological methods

In each patient, initial platelet aggregation studies were performed to exclude ingestion of cyclo-oxygenase inhibitors within the previous 7 days.

Plasma thromboxane samples were collected into EDTA and indomethacin and kept on ice until centrifugation for 30 min at 1600 g. Plasma was removed and stored at -70°C . Serum thromboxane samples were collected into glass tubes incubated for 1 h at 37°C . Samples were centrifuged at 1600 g for 10 min and serum removed and stored at -70°C . TXB₂ was assayed using a radioimmunoassay technique (New England Nuclear). Plasma thromboxane results

were expressed as pg/ml with a normal range of less than 50 pg/ml and serum thromboxane as ng/10⁸ platelets, from the original sample, with a normal range of 34–160 ng/10⁸ platelets. Statistical analysis used was a non-parametric test, the Kruskal-Wallis procedure, for analysis of the thromboxane levels in the ascending aorta, coronary sinus and peripheral venous blood to assess intergroup differences between patients with stable angina and unstable angina. A paired Student's *t* test was used to analyse the effects of dazoxiben on haemodynamics and thromboxane levels.

Results

In the unstable angina patients the mean TXB₂ levels in coronary sinus and aorta were 116 ± 61 and 100 ± 44 pg/ml respectively, the coronary sinus/aorta ratio being 1.1 ± 0.5 (Table 1). There was no significant difference between the transcatheter thromboxane levels in the three groups of patients because of the wide range of values.

After dazoxiben treatment there was significant inhibition of thromboxane production both in the coronary sinus and aorta in all groups. In the patients with coronary heart disease who did not have angina, TXB₂ levels fell from 108 ± 66 to 55 ± 10 pg/ml ($P < 0.02$) and from 108 ± 70 to 60 ± 16 pg/ml ($P < 0.02$) in the paced to angina group from 204 ± 115 to 60 ± 22 pg/ml and from 180 ± 106 to 52 ± 10 pg/ml ($P < 0.02$). In the unstable angina group the TXB₂ levels fell from 116 ± 62 to 51 ± 30 pg/ml ($P < 0.05$) and from 100 ± 44 to 59 ± 23 pg/ml ($P < 0.02$). After 7 d of dazoxiben therapy the TXB₂ level in peripheral venous blood remained low at 51 ± 10 pg/ml.

The mean plasma TXB₂ level in patients paced to angina increased from 106 ± 61 to 180 ± 106 pg/ml in the aorta, 160 ± 99 to 204 ± 115 pg/ml in the coronary sinus, with ratios of 1.2 ± 0.6 and 1.0 ± 0.5 . These increases in thromboxane levels did not reach statistical significance.

Table 1 TXB₂ levels (pg/ml) (normal range 51 ± 10 pg/ml)

	CHD patients without angina (n=20)			CHD patients paced to angina (n=10)			CHD patients with unstable angina (n=9)		
	CS	Aorta	CS/ Aorta	CS	Aorta	CS/ Aorta	CS	Aorta	CS/ Aorta
Pre-dazoxiben	108 ± 66	108 ± 70	1.1 ± 0.7	204 ± 115	180 ± 106	1.0 ± 0.5	116 ± 61	100 ± 44	1.1 ± 0.5
Post-dazoxiben	$55 \pm 10^{**}$	$60 \pm 16^{**}$	1 ± 0.1	$60 \pm 22^{***}$	$52 \pm 10^{***}$	1 ± 0.1	$51 \pm 30^*$	$59 \pm 23^*$	1 ± 0.1

CHD, coronary heart disease; CS, coronary sinus.

Results are the mean $\pm$ s.d.

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.005$.

Haemodynamic changes

During rapid atrial pacing the majority of the patients developed ST segment changes on the ECG at a time when they complained of their typical anginal pain. After dazoxiben treatment the mean atrial pacing time to angina increased from 245 ± 41 to 308 ± 48 s ($P < 0.01$). There were no changes in systemic haemodynamics (heart rate, blood pressure and cardiac output) nor in coronary haemodynamics (coronary sinus blood flow and myocardial oxygen consumption) (Table 2).

In the unstable angina group of patients there were fewer documented episodes of angina, and daily 24 h tape analysis of the ECG over the 7 d period of the study revealed fewer asymptomatic significant ST segment changes when the patients received dazoxiben in addition to their standard anti-anginal therapy, which included cardioselective β -adrenoreceptor-blocking drugs, slow channel calcium blockers and long-acting nitrates.

Discussion

Some of the discrepancies in the reported studies related to thromboxane levels could well be methodological differences between different laboratories. In this study careful attention was paid to sampling of blood by the use of wide bore catheters with both end and side-hole apertures. In addition platelet factor 4 measurement was used as a means of detecting artefactual release of TXB_2 (Kaplan, 1981). These precautions were confirmed by comparing different catheters and sampling techniques with

straight venepunctures from patients before commencement of the study.

The range of TXB_2 values found in the coronary heart disease patient population was large, and although some of the unstable angina patients had quite marked elevations of coronary sinus TXB_2 , there were no significant differences between the three groups of patients either in absolute values or when the coronary sinus and aortic results were expressed as a ratio. It must be emphasized that although the unstable patients had had an episode of cardiac pain in the previous 24 h none of them had cardiac pain at the time of the study either spontaneously or by provocation. The hypothesis still remains that in patients with angina at rest or acute myocardial infarction, the reduction in coronary blood flow could be due to coronary arterial spasm or platelet aggregation with release of vasoactive compounds such as thromboxane. This concept is supported experimentally by Folts (1976) who has demonstrated that platelet aggregation is induced by constriction of a coronary artery with consequent endothelial damage.

Selective thromboxane inhibition in theory would seem to be an appropriate strategy in patients with unstable angina, or developing myocardial infarction. In this study dazoxiben was well tolerated and significantly reduced TXB_2 levels in patients with coronary heart disease. PGI_2 and its metabolite 6-keto- $\text{PGF}_{1\alpha}$ were not measured, but Veyrmen (1981) has demonstrated increased 6-keto- $\text{PGF}_{1\alpha}$ in normal volunteers when dazoxiben was administered.

No adverse haemodynamic effects were observed either in the systemic or coronary circulations; specif-

Table 2 Coronary and systemic haemodynamic effects of dazoxiben

	Control	Dazoxiben
Heart rate (beats/min)	70 ± 4	67 ± 3
Systolic blood pressure (mmHg)	128 ± 3	125 ± 4
Diastolic blood pressure (mmHg)	84 ± 2	81 ± 2
Mean blood pressure (mmHg)	100 ± 2	96 ± 2
Pulmonary capillary wedge pressure (mmHg)	8 ± 1	5 ± 1
Cardiac output (l/min)	5.8 ± 0.4	5.6 ± 0.5
Coronary sinus flow (ml/min)	133 ± 10	124 ± 4
Myocardial oxygen consumption (ml/min)	17.8 ± 2	15.6 ± 1

Results are mean $\pm$ s.e. in six patients.

ically there was no evidence of peripheral vasodilatation such as is found with PGI₂ infusion (Bergman, 1981). Adequate perfusion of coronary arteries is critical in patients with coronary artery obstruction, and hypotension in the patient with unstable angina could well lead to complete occlusion of the coronary artery with subsequent myocardial infarction.

Despite lack of haemodynamic effect the atrial pacing time to angina significantly increased suggesting reduced myocardial ischaemia after the drug was administered. Similar results have been reported by Fox (1981) with ticlopidine, a drug which inhibits platelet aggregation and does not reduce myocardial oxygen consumption by altering haemodynamics.

In the unstable group of patients treatment for 7 d with dazoxiben was well tolerated, and there was a sustained inhibition of thromboxane production. Although this was an open study and the patients were receiving different forms of anti-anginal therapy, after dazoxiben therapy was instituted there were fewer documented episodes of angina and fewer asymptomatic ST segment changes on the electrocardiogram, which was monitored continuously.

In conclusion dazoxiben would seem to be a selective inhibitor of thromboxane synthesis and is devoid of adverse haemodynamic effects. Preliminary results particularly in patients with unstable angina are sufficiently encouraging to warrant further clinical evaluation of this group of compounds.

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