HAEMODYNAMIC AND METABOLIC EFFECTS OF DAZOXIBEN AT REST AND DURING ATRIAL PACING

P.S. KIFF, G. BERGMAN, L. ATKINSON & D.E. JEWITT

Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

J. WESTWICK & V.V. KAKKAR

Thrombosis Research Unit, King's College Hospital, Denmark Hill, London SE5 9RS, UK

- 1 Thromboxane B₂ (TXB₂) levels were measured in three sites (coronary sinus, pulmonary artery, and femoral artery) at rest and during atrial pacing in 11 patients with stable angina pectoris.
- 2 There was a highly significant increase in arterial TXB₂ on pacing (by up to 820 pg/ml) but there was no change in the thromboxane levels at the other two sites.
- 3 Dazoxiben 200 mg orally abolished the increase in arterial TXB₂, but had no effect on systemic, pulmonary or coronary haemodynamics, no effect on myocardial metabolism and a variable effect on atrial pacing time to angina.

Introduction

ARACHIDONIC acid metabolites (Figure 1) have powerful but opposing actions on both platelets and the vessel wall (Vane & Bergstrom, 1979). It has been suggested that thromboxane A₂ (TXA₂), a powerful vasoconstrictor, may be released into the coronary circulation during atrial pacing (Lewy *et al.*, 1980). It remains controversial, however, whether thromboxane plays a causative role in the production of angina pectoris or is released merely as a secondary phenomenon.

Cyclo-oxygenase inhibitors have been shown not to be beneficial in stable angina pectoris (Friedman *et al.*, 1981). This may be explained by the fact that these compounds reduce the production of prostacyclin which we have previously shown to be beneficial in stable angina pectoris. (Bergman *et al.*, 1981).

In this study we wanted to reduce TXA₂ specifically, using dazoxiben (UK 37248), a selective inhibitor of thromboxane synthetase. Such a compound would not be expected to reduce prostacyclin production, but, by causing accumulation of cyclic endoperoxides, might result in the overflow of the endoperoxides to the beneficial prostacyclin pathway. Whether this can occur or not depends on a possible interaction between the platelets and vessel walls.

The source of the thromboxane released during pacing has previously been ascribed to the coronary circulation but the magnitude of the rise seen in arterial blood is larger than would be expected from the coronary sinus levels and estimated coronary blood flow. As part of the study, therefore, it was necessary to determine whether there was a second

Figure 1 Arachidonic acid metabolism.

source of thromboxane generation or whether it was released in much larger quantities prior to the onset of angina.

Methods

Eleven male patients (mean age 59.9 yr; range 48–65) were studied. All had stable exercise-induced angina pectoris with positive stress tests. None had significant concurrent disease particularly diabetes mellitus or hypertension. None had had previous myocardial infarction. All had had coronary angiography performed within the previous month, and six had been shown to have triple vessel disease (lesions of 70% or more affecting all three major vessels), two had two vessels affected, and three had single vessel disease.

The patients were then subjected to one of two atrial pacing protocols. Pulmonary pressures and samples, and cardiac output were obtained using a Swan Ganz thermodilution catheter positioned in the pulmonary artery. Coronary sinus samples and coronary blood flow estimations were made using a Wilton Webster catheter positioned under fluoroscopic control in the mid-coronary sinus. Arterial samples and pressures were obtained from a 19G needle positioned in the femoral artery. Intravascular pressures were monitored continuously on a Mingograph 82 recorder along with a continuous ECG record.

After insertion of the catheters the patients were allowed 30 min rest, then baseline measurements were made and the patients were atrially paced until they developed angina. At this point a further set of readings was made and the atrial pacing discontinued. Dazoxiben 200 mg was then given orally and the patients were allowed to rest for 1 hour. A further set of measurements was then made and an identical pacing protocol followed. Samples were taken at the same time as the previous end-point (if this was reached) and also at the new end-point of angina (if the pacing time was significantly prolonged). Pacing was discontinued if the atrial pacing time was doubled. Five patients were paced at a fixed heart rate (85% of their predicted maximum heart rate), whereas the six others were paced incrementally increasing their heart rate by 10 beats/min every 5 minutes. In this latter group samples and measurements were made at each stage of the incremental pacing.

Blood samples from all three sampling sites were withdrawn simultaneously and those for thromboxane B₂ (TXB₂) levels were transferred to an ice-cold mixture of indomethacin and EDTA within 10 s of withdrawal and plasma separated by rapid centrifugation (1500 g for 3 min at 4°C). The plasma

concentration of TXB₂ was assayed using a rabbit anti-TXB₂ antibody kindly provided by Dr J.B. Smith, Philadelphia, using a method previously described (Westwick *et al.*, 1982). Lactate, glucose, free fatty acids and oxygen saturations were measured as previously reported (Bergman *et al.*, 1980). Coronary thromboxane production was calculated as the difference between coronary sinus and femoral artery, multiplied by the coronary sinus blood flow, and pulmonary production was calculated as the same difference between femoral artery and pulmonary artery, multiplied by the cardiac output.

Statistical analysis was performed using Student's paired *t* test, where appropriate a one-way analysis of variance, and for the incrementally paced patients a standard repeated measures analysis (Winer, 1971).

Results

At rest (Figure 2a) the level of arterial thromboxane was 112 ± 19.5 pg/ml (mean $\pm$ s.e.m.). The level of pulmonary arterial thromboxane was 126.1 ± 24.6 pg/ml and the mean level of coronary sinus thromboxane was 132 ± 67.4 pg/ml.

By contrast, at the onset of angina (Figure 2b), arterial thromboxane increased to 310.5 ± 86.9 pg/ml, statistically significant at $P < 0.001$. The simultaneous pulmonary arterial and coronary sinus levels were not significantly different from the rest values. Thus, at rest, there was a net pulmonary thromboxane consumption of 243 ng/min which was converted to a net pulmonary production of 419 ± 39 ng/min at the onset of angina. It can also be calculated that there is a

Figure 2 Thromboxane levels at rest and during pacing, plus or minus dazoxiben.

Figure 3 Thromboxane levels during and after atrial pacing plus or minus dazoxiben. *a*, control; *b*, dazoxiben.

small amount of thromboxane production within the coronary circulation at rest (2.05 ± 0.9 ng/min), while at the onset of angina there is actually binding of the arterial thromboxane within the coronary bed (45.4 ± 25.3 ng/min). Figure 3*a* demonstrates the change in thromboxane level at the three sites, in the seven patients in whom thromboxane was measured during atrial pacing.

When dazoxiben 200 mg was given orally to ten of these patients, the resting plasma thromboxane level was little changed (Figure 2*c*), but there was a small increase in the arterial level and a small decrease in coronary sinus and pulmonary arterial levels. However, at the onset of angina, the arterial increase previously noted was totally abolished (Figure 2*d*) and the increase during pacing was approximately one-third of that before dazoxiben (Figure 3*b*).

Despite this consistent reduction in thromboxane levels, dazoxiben had a variable effect on atrial pacing time to angina. Five patients significantly prolonged their pacing time, two showed no change,

and three reduced their pacing time. The mean pacing time to angina was increased from 10.1 to 12.8 min but this failed to reach statistical significance. As there was no correlation between reduction in TXB₂ levels and prolongation of atrial pacing time, it was not possible to identify those patients likely to respond on the basis of their thromboxane release.

There were no significant haemodynamic or cardiac metabolic differences at rest (Table 1) or at the onset of angina (Table 2) in the presence of the drug. Neither was there any correlation of thromboxane levels and change in any of these parameters. There were no reported side-effects from the compound.

Discussion

Platelet aggregation has been demonstrated in unstable and vasospastic angina by several groups of workers (Robertson *et al.*, 1980, 1981; Sobel *et al.*, 1981), but in the case of stable exercise-induced angina

Table 1 Haemodynamic and metabolic parameters at rest

	Control	Dazoxiben	
Heart rate	69.2 $\pm$ 3.8	73.3 $\pm$ 5	beats/min
Mean blood pressure	120.0 $\pm$ 4.5	111.0 $\pm$ 6.7	mmHg
Mean pulmonary arterial pressure	16.6 $\pm$ 2.1	14.1 $\pm$ 4.1	mmHg
Coronary sinus flow	117.7 $\pm$ 8.4	125.8 $\pm$ 13.4	ml/min
Cardiac output	4.92 $\pm$.22	5.35 $\pm$.22	l/min
Systemic vascular resistance	19.9 $\pm$.78	17.8 $\pm$.87	units
Pulmonary vascular resistance	1.0 $\pm$.1	.97 $\pm$.1	units
Lactate extraction ratio	27.7 $\pm$ 4.1	20.4 $\pm$ 4.0	%
Oxygen % uptake	13.5 $\pm$ 1.1	14.4 $\pm$ 1.7	ml/min

Table 2 Haemodynamic and metabolic parameters at the onset of angina

	Control	Dazoxiben	
Heart rate	123.8±4.8	125.2±4.8	beats/min
Mean blood pressure	120.0±4.5	111.5±6.7	mmHg
Mean pulmonary arterial pressure	21.6±2.2	17.5±2.0	mmHg
Coronary sinus flow	190.4±22.0	220.1±43.5	ml/min
Cardiac output	5.63±.33	5.47±.22	l/min
Systemic vascular resistance	21.5±1.8	20.3±1.5	units
Pulmonary vascular resistance	.73±.1	.76±.07	units
Lactate extraction ratio	1.4±9.5	3.0±6.4	%
Oxygen % uptake	20.1±1.9	22.1±3.2	ml/min

the role of platelets is much less clear. Similarly, whether the ratio of the prostaglandins, TXA₂ and prostacyclin is important is equally controversial. At least two pathogenetic roles for thromboxane have been suggested. First, excess thromboxane might result in aggregation of platelets at the site of a coronary stenosis; and second, thromboxane released from the platelet-vessel wall interaction at the site of such a stenosis might result in distal vasoconstriction.

Previous atrial pacing studies (Lewy *et al.*, 1980; Hirsh *et al.*, 1981; Kuzaya *et al.*, 1980) have shown elevated coronary sinus levels of thromboxane which have been interpreted as demonstrating thromboxane release from the coronary circulation. An increase in arterial levels has also been noted but previously explained on the basis of release from the coronary circulation. Although exact values for cardiac output and coronary blood flow are not given in these studies, by assuming average values it can be calculated that TXB₂ appearing in arterial blood is approximately 20 times the quantity released from the coronary circulation. By showing no increase in coronary sinus or pulmonary arterial levels at any stage of atrial pacing, while arterial levels increased dramatically, we have demonstrated that thromboxane release is occurring within the pulmonary circulation. This has been suggested by Tada *et al.* (1981) to be characteristic of vasospastic angina, but in our series all patients had atherosclerotic coronary artery disease. We have not investigated patients with spasm, but it is possible that such patients might have an exaggerated pulmonary response.

The influence of dazoxiben in this study was to abolish the increase in arterial thromboxane seen on atrial pacing. This reduction in thromboxane release was associated with no demonstrable effect on systemic, pulmonary or coronary haemodynamics; nor on myocardial metabolism. We were therefore unable to find any physiological or pathological role for thromboxane in these patients. We would speculate that under certain circumstances, for example, vasospastic or cold-induced angina, pulmonary throm-

boxane release might produce undesirable coronary (or even systemic) vasoconstriction, and this might be prevented by pretreatment with dazoxiben.

This study has demonstrated high arterial levels of thromboxane without major release into the coronary circulation. This is likely to be due to prostaglandin release from lung, a tissue known to be rich in such compounds. Dazoxiben causes a major reduction in this release, and although theoretically of value we could find no overall benefit from the compound.

References

- BERGMAN, G., ATKINSON, L., METCALFE, J., JACKSON, N. & JEWITT, D. (1980). Beneficial effect of enhanced myocardial carbohydrate utilisation after oxfenicine (UK25842) in angina pectoris. *Eur. Heart J.*, **1**, 247–253.
- BERGMAN, G., DALY, K., ATKINSON, L., ROTHMAN, M., RICHARDSON, P.J., JACKSON, G. & JEWITT, D.E. (1981). Prostacyclin: haemodynamic and metabolic effects in patients with coronary artery disease. *Lancet*, **i**, 569–572.
- FRIEDMAN, P.L., BROWN, E.J., GUNTHER, S., ALEXANDER, R.W., BARRY, W.H., MUDGE, G.H., & GROSSMAN, W. (1981). Coronary vasoconstrictor effect of indomethacin in patients with coronary artery disease. *New Engl. J. Med.*, **305**, (20), 1171–1175.
- HIRSH, P.D., HILLIS, L.D., CAMPBELL, W.B., FIRTH, B.G. & WILLERSON, J.I. (1981). Release of transcardiac prostaglandins and thromboxane into the coronary circulation in patients with ischaemic heart disease. *New Engl. J. Med.*, **304**, 685–691.
- KUZAYA, T., TADA, M., INOUE, M., KODAMA, K., FURUSHIMA, M. & ABE, H. (1980). Increased levels of thromboxane A₂ in peripheral and coronary circulations in patients with angina pectoris. *Am. J. Cardiol.*, **45**, 454.
- LEWY, R.I., WIENER, L., WALINSKY, P., LEFER, A.M., SILVER, M.J. & SMITH, J.B. (1980). Thromboxane release during pacing induced angina pectoris. *Circulation*, **61**, 1165–1171.

- ROBERTSON, R.M., ROBERTSON, D., ROBERTS, L.J., MAAS, R.L., FITZGERALD, G.A., FRIESINGER, G.G. & OATES, J.A. (1981). Thromboxane in vasotonic angina. *New Engl. J. Med.*, **304**, 998–1003.
- ROBERTSON, R.M., ROBERTSON, D., FREISINGER, G.C., TIMMONS, S. & HAWIGER, J. (1980). Platelet aggregates in peripheral and coronary sinus blood in patients with spontaneous coronary artery spasm. *Lancet*, **ii**, 829–831.
- SOBEL, M., SALZMAN, E.W., DAVIS, G.C., HANDIN, R.I., SWEENEY, J., PLOETZ, J. & KURLAND, G. (1981). Circulating platelet products in unstable angina. *Circulation*, **63**, 300–306.
- TADA, M., KUZUYA, T., INOUE, M., KODAMA, K., MISHIMA, M., YUMADA, M., INUI, M. & ABE, H. (1981). Elevation of thromboxane B₂ levels in patients with classic and variant angina pectoris. *Circulation*, **64**, 1107–1115.
- VANE, J.R. & BERGSTROM, S. (eds). (1979). *Prostacyclin*. New York: Raven Press.
- WESTWICK, J., WATSON-WILLIAMS, E.G., KRISHNAMURTHI, S., MARK, G., ELLIS, V., SCULLY, M.F., WHITE, J. & KAKKAR, V.V. (1982). Platelet activation during steady state sickle cell disease. *Am. J. Med.* (in press).
- WINER, B. (1971). *Statistical Principles in Experimental Design*. New York: McGraw-Hill.