Br. J. clin. Pharmac. (1983) **15**, 87S–95S

EFFECTS OF DAZOXIBEN ON ARRHYTHMIAS AND VENTRICULAR FIBRILLATION INDUCED BY CORONARY ARTERY OCCLUSION AND REPERFUSION IN ANAESTHETISED GREYHOUNDS

SUSAN J. COKER & J.R. PARRATT

Department of Physiology and Pharmacology, University of Strathclyde, 204 George Street, Glasgow, and Department of Surgery, University of Glasgow (Western Infirmary)

1 The effects of the thromboxane synthetase inhibitor dazoxiben (UK 37248) on haemodynamics, blood gases, thromboxane and prostacyclin release and on arrhythmias were examined in anaesthetised greyhounds subject to acute coronary artery occlusion and reperfusion.

2 Ten minutes after the administration of UK 37248 2 mg/kg intravenously, the plasma concentration of thromboxane B_2 in the coronary sinus was significantly reduced whereas the 6-keto-prostaglandin $F_{1\alpha}$ concentration was increased.

3 UK 37248 did not significantly alter the number of arrhythmias or the incidence of ventricular fibrillation resulting from coronary artery occlusion. There was evidence, however, that in some drug-treated animals there may have been incomplete inhibition of thromboxane synthesis during coronary artery occlusion.

4 A further dose of 1 mg/kg UK 37248 was administered intravenously 5 min before the release of the 40 min coronary artery occlusion. Seven out of eight control dogs died in ventricular fibrillation following reperfusion whereas only one out of eight drug-treated animals fibrillated.

5 This latter result suggests that thromboxane may be an important factor in reperfusion induced ventricular fibrillation and that dazoxiben may be a useful drug in clinically related situations.

Introduction

We have reported previously that thromboxane A_2 (TXA_2) is released from the acutely ischaemic myocardium in anaesthetised greyhounds and that this release is related to the occurrence of early cardiac arrhythmias (Coker *et al.*, 1981*a*). A low dose of aspirin suppressed this TXA_2 release and reduced both the early arrhythmias and ventricular fibrillation included by coronary artery ligation (Coker *et al.*, 1981*b*).

The aim of the present study was to investigate the effects of the selective thromboxane synthetase inhibitor UK 37248 (dazoxiben) on arrhythmias induced by coronary artery ligation in anaesthetized greyhounds. We have also extended our experiments to investigate whether thromboxane plays a role in the reperfusion arrhythmias that occur following the release of a coronary artery occlusion. These "reperfusion arrhythmias" are particularly severe and frequently fatal since they often progress to ventricular fibrillation. They also seem to be resistant to standard antiarrhythmic therapy (Naito, *et al.*, 1981), suggesting that their aetiology may vary from that of arrhythmias observed during myocardial ischaemia. Since thromboxane has been implicated in coronary vasospasm in patients with variant angina (Lewy *et al.*, 1979) it may also be involved in the reperfusion arrhythmias which can occur when spasm is reversed.

Methods

Anaesthesia was induced in greyhounds (19–35 kg) of either sex by the intravenous administration of sodium thiopentone 25 mg/kg. After endotracheal intubation, ventilation (with oxygen containing 1% halothane) was maintained using a Palmer respiration pump. The pump rate was 25 strokes/min and the volume was adjusted (between 350 and 500 ml depending on body weight) to give an arterial CO_2 tension of approximately 38 mmHg. Pancuronium bromide 0.15–0.20 mg/kg was administered intravenously to prevent reflex muscular movement. Catheters were inserted into the descending aorta and vena cava via the femoral vessels for pressure recording and blood sampling. After the insertion of these catheters, halothane was discontinued and chloralose 80–90 mg/kg was administered intravenously. Catheters were then positioned within the heart under fluoroscopic control using a Seimens image intensifier. A catheter was placed in the coronary sinus, via the jugular vein for blood sampling, a number seven Cournand catheter was inserted into the left ventricle, via the left carotid artery, for pressure recording, and a Swan-Ganz catheter was placed in the pulmonary artery via the jugular vein, for pressure recording, blood sampling and for the measurement of cardiac output by thermodilution using a Devices cardiac output monitor.

A left thoracotomy was performed at the level of

0306-5251/83/15085-09 $01.00

the sixth rib which was reflected back to reveal the heart. The pericardium was incised and arranged to form a cradle in which the heart was suspended. A segment of the left anterior descending coronary artery was carefully dissected free from the surrounding tissue. At a site approximately 15–30 mm distal from the tip of the left atrial appendage, a ligature (Mersilk 4.0) was passed under this artery. A major coronary vein running alongside this artery and draining the area supplied by it was catheterized with a 6-inch Longdwel teflon catheter (size 20 G). After coronary artery ligation this catheter has been shown to drain blood predominantly from the ischaemic area (Marshall *et al.*, 1974). Arterial blood pressure, central venous pressure, pulmonary artery pressure and left ventricular pressure (LVP) were recorded via Elcomatic 751A transducers on a Siemens-Elema Mingograf 82 ink-jet recorder, along with the electrocardiogram (Lead II). LV dP/dt was recorded continuously using a Siemens-Elema differentiating circuit and LV end-diastolic pressure was measured from LVP at high gain. Mid-oesophageal temperature was recorded using a copper-constantan thermocouple (Ellab). Simultaneous anaerobic blood samples were taken at regular intervals from the aorta, coronary sinus, local coronary vein and pulmonary artery and analysed for O_2 and CO_2 tensions, pH and O_2 content (Ledingham *et al.*, 1970).

Blood samples were also taken at various times from the aorta, coronary sinus and local coronary vein and analysed for TXB_2 and 6-keto-$PGF_{1\alpha}$ (the stable breakdown products of TXA_2 and prostacyclin, respectively) using radioimmunoassay techniques (Coker *et al.*, 1982). Each blood sample (4 ml) was withdrawn using a sterile plastic syringe and transferred to a plastic centrifuge tube containing 40 µl indomethacin solution (1 mg/ml in ethanol) and 80 µl EDTA solution (70 mg/ml in normal saline). The samples were kept on ice until centrifugation, not more than 1 h later, at 2000 g for 10 minutes. The plasma was removed and stored at −20°C until assay. Aliquots of plasma (250 µl) were acidified and the prostanoids extracted with ethyl acetate. These extracts were then evaporated to dryness under reduced pressure at 37°C. The recovery of TXB_2 or 6-keto-$PGF_{1\alpha}$ was monitored in each sample using the appropriate tritiated internal standard. Sample extracts and standards were then redissolved in phosphate-buffered saline and tritiated TXB_2 or 6-keto-$PGF_{1\alpha}$ (NEN) was added followed by the appropriate specific antibody (Pasteur Institute). After overnight incubation at 4°C, the antibody-bound and free prostanoids were separated using dextran-coated charcoal. An aliquot of the antibody-bound fraction was placed in Biofluor scintillant and counted in a Packard Tri-Carb 460 liquid scintillation counter. With the above procedures the detection limits were 20–25 pg/ml for TXB_2 and 100 pg/ml for 6-keto-$PGF_{1\alpha}$.

Experimental protocol

After establishing stable control values for haemodynamics and blood gases, blood samples were taken from the aorta and coronary sinus for prostanoid measurement. UK 37248-01 (2 mg/kg, base) was then dissolved in 10 ml normal saline and administered intravenously. Ten minutes later haemodynamics were measured and blood samples were obtained for the measurement of blood gases and prostanoids. Fifteen minutes after the administration of UK 37248 the left anterior descending coronary artery was occluded. Blood samples for prostanoid measurement were taken from the coronary sinus and local coronary vein 2, 7, 15 and 30 min after occlusion, with blood gases also being assessed at 7, 15 and 30 min post-occlusion. The number of arrhythmias (ventricular ectopic beats) was counted in 1-min intervals during the first 30 min of coronary occlusion.

After 40 min of coronary artery occlusion the ligature was released, resulting in reperfusion of the formerly ischaemic myocardium. An additional dose of 1 mg/kg UK 37248 was given intravenously 5 min before reperfusion. Blood samples for prostanoid analysis were taken 1, 5 and 15 min after reperfusion, from the coronary sinus and the local coronary vein.

At the end of the experiment the heart was excised and a small volume of dye was injected slowly into the left anterior descending coronary artery distal to the point of ligation. The area outlined in this manner was then cut out and weighed; the "occluded zone" was expressed as a percentage of the free left ventricular wall.

Results

Effects of acute administration of UK 37248

The administration of UK 37248 2 mg/kg had no effect on haemodynamics at the time of administration and after 10 min there was no significant changes in any of the measured parameters (Table 1). This drug did, however, cause some changes in basal prostanoid concentrations. Circulating TXB_2 concentrations in the aorta were unchanged, 45±13 pg/ml pre-drug, 50±10 pg/ml 10 min post-drug, but there was a significant decrease in coronary sinus TXB_2 concentrations from 77±21 pg/ml pre-drug to 52±12 pg post-drug ($P<0.05$, paired t test). Aortic 6-keto-$PGF_{1\alpha}$ concentrations tended to increase (354±48 pg/ml to 486±106 pg/ml) and coronary sinus concentrations were significantly increased from

Table 1 Haemodynamics in dogs receiving UK 37248 and subject to coronary artery occlusion and reperfusion

	Control (n=*10*)	*10 min post-UK 37248* (n=*10*)	*30 min post-ligation* (n=*8*)	*30 min post-reperfusion* (n=*7*)
Heart rate (beats/min)	134±6	131±6	146±11	143±12
Arterial blood pressure (mmHg)				
Systolic	145±11	140±12	138±14	128±16
Diastolic	107±10	102±11	98±11	86±12
Mean	120±10	115±11	111±12	101±13
Central venous pressure (mmHg)	4.1±0.3	4.2±0.3	4.1±0.3	4.1±0.3
Pulmonary artery pressure (mmHg)				
Systolic	20±1	21±1	21±1	21±1
Diastolic	12±1	13±1	12±1	13±1
Mean	16±1	17±1	16±1	16±1
Left ventricular end-diastolic pressure (mmHg)	7.9±1.2	6.7±1.0	7.4±0.9	6.6±1.2
Left ventricular d*P*/d*t* max (mmHg/s)	2320±260	2280±280	2260±340	1890±280
Cardiac output (ℓ/min)	2.42±0.23	2.27±0.18	1.73±0.16**	1.63±0.13

**$P<0.01$ compared with pre-ligation value (paired *t* test).

Table 2 Blood gases, *p*H and oxygen content in anaesthetized greyhounds which received UK 37248 2 mg/kg intravenously 15 min before coronary artery occlusion

	Control (n=*10*)	*10 min post-UK 37248* (n=*10*)	*7 min post-ligation* (n=*9*)	*15 min post-ligation* (n=*9*)	*30 min post-ligation* (n=*8*)
Arterial					
PO_2 (mmHg)	432±33	448±28			401±44
PCO_2 (mmHg)	39±1	39±1			37±1
*p*H (units)	7.38±0.01	7.38±0.01			7.37±0.01
O_2 content (ml/100ml)	24.3±1.0	24.9±1.0			25.4±1.2
Coronary sinus					
PO_2	32±1	32±1	29±1	28±1	26±1
PCO_2	57±2	58±1	58±2	60±1	59±1
*p*H	7.30±0.01	7.29±0.01	7.29±0.01	7.27±0.02	7.28±0.01
O_2 content	11.7±0.7	11.9±0.8	10.7±0.8	9.6±0.6	9.7±0.8
Coronary vein					
PO_2	30±1	31±2	26±1	26±1*	24±1*
PCO_2	57±2	58±2	66±3**	68±2***	64±2*
*p*H	7.30±0.01	7.30±0.01	7.21±0.01***	7.21±0.02**	7.23±0.02*
O_2 content	10.8±0.5	11.9±1.3	7.8±0.7*	7.9±0.5*	7.6±0.7*
Pulmonary artery					
PO_2	50±1	49±1			42±1
PCO_2	46±1	46±1			46±2
*p*H	7.34±0.01	7.33±0.01			7.32±0.01
O_2 content	18.8±1.0	18.9±1.0			17.3±0.8

*$P<0.05$; **$P<0.01$; ***$P<0.001$ compared with pre-ligation value (paired *t* test).

Table 3 Haemodynamic effects of acute coronary artery ligation in anaesthetized greyhounds

	Control (n=9)	*15 min post-vehicle* (n=9)	*30 min post-ligation* (n=8)	*30 min post-reperfusion* (n=1)
Heart rate (beats/min)	144±5	145±6	153±5	160
Arterial blood pressure (mmHg)				
Systolic	163±15	158±15	161±15	185
Diastolic	117±10	114±11	119±12	145
Mean	133±11	130±13	133±12	155
Central venous pressure (mmHg)	4.9±0.3	4.6±0.2	4.8±0.3	4
Pulmonary artery pressure (mmHg)				
Systolic	23±1	23±1	23±1	24
Diastolic	14±1	14±1	14±1	17
Mean	18±1	18±1	18±1	21
Left ventricular end-diastolic pressure (mmHg)	7.7±1.0	7.9±1.0	8.6±1.0	17
Left ventricular d*P*/d*t* max (mmHg/s)	2080±200	2070±200	2030±120	2300
Cardiac output (ℓ/min)	2.38±0.22	2.28±0.22	2.00±0.16*	

*$P<0.05$ compared with pre-ligation values (paired *t* test).

Table 4 Blood gases, *p*H and O_2 content in anaesthetized greyhounds subject to acute coronary artery ligation

	Control (n=9)	*15 min post-vehicle* (n=9)	*7 min post-ligation* (n=9)	*15 min post-ligation* (n=8)	*30 min post-ligation* (n=8)
Arterial					
PO_2 (mmHg)	528±30	542±16			534±27
PCO_2 (mmHg)	42±1	40±1			39±1
*p*H (units)	7.39±0.01	7.38±0.01			7.39±0.01
O_2 content (ml/100ml)	25.3±0.7	26.2±0.8			26.7±0.9
Coronary sinus					
PO_2	35±1	33±1	31±1	30±1	30±1
PCO_2	62±2	61±2	62±2	64±2	60±2
*p*H	7.30±0.02	7.30±0.01	7.29±0.01	7.28±0.01	7.30±0.01
O_2 content	12.9±0.5	12.2±0.6	11.1±.0.6	10.4±0.7	11.2±0.59
Coronary vein					
PO_2	33±1	31±1	27±1*	26±1**	27±1**
PCO_2	62±3	60±3	72±3***	74±3**	68±3*
*p*H	7.30±0.01	7.29±0.01	7.20±0.03**	7.18±0.03**	7.22±0.02
O_2 content	12.0±0.6	10.9±0.7	8.2±0.8**	7.6±0.7**	8.4±0.8*
Pulmonary artery					
PO_2	54±3	52±3			47±2
PCO_2	50±2	48±2			46±1
*p*H	7.34±0.01	7.34±0.01			7.34±0.01
O_2 content	19.3±0.7	19.6±1.0			18.8±0.9

*$P<0.05$; **$P<0.01$; ***$P<0.001$ compared with pre-ligation value (paired *t* test).

397±75 pg/ml to 542±101 pg/ml after the drug ($P<0.05$). Blood gases, oxygen content and pH were not altered by UK 37248 (Table 2). Thus, the only significant effects of this drug were a decrease in thromboxane concentration and an increase in prostacyclin concentration in coronary sinus blood.

Effects of UK 37248 on the changes induced by coronary artery occlusion

Coronary artery ligation in anaesthetized greyhounds results in characteristic electrocardiographic, haemodynamic and metabolic changes which have been described previously (Marshall *et al.*, 1974; Coker *et al.*, 1981*a*; Coker *et al.*, 1981*c*). The haemodynamic changes in the current control group are detailed in Table 3. The only significant effect of coronary artery ligation is a decrease in cardiac output. This effect was also observed in the group of dogs which had been pretreated with UK 37248 (Table 1), although the magnitude of the fall in cardiac output seemed to be greater.

The changes in blood gases during coronary artery occlusion in the control and drug-treated groups are detailed in Tables 4 and 2 respectively. Coronary artery occlusion caused an increase in CO_2 tension and decreases in O_2 tension, O_2 content and pH in local coronary venous blood. These alterations were confined to blood draining from the acutely ischaemic region of the myocardium; no changes were observed in coronary sinus blood draining from the essentially normal region of the left ventricle. Similar alterations in blood gases were observed in both the control group and in the group which received UK 37248, although the magnitude of the increase in CO_2 tension seemed to be less in the drug-treated group. The increases in mean local coronary venous PCO_2 were 12, 14 and 8 mmHg at 7, 15 and 30 min post-occlusion in the controls and 8, 10 and 6 mmHg at the same times in the dogs which received UK 37248.

Acute ligation of the left anterior descending coronary artery of anaesthetized greyhounds results in bursts of arrhythmias varying from single premature beats, usually ventricular in origin, to ventricular tachycardia and in some cases ventricular fibrillation and death. One of the nine controls and two of the ten drug-treated animals died in ventricular fibrillation during coronary artery occlusion. Although the mean number of ectopic beats during the first 30 min of occlusion for the drug-

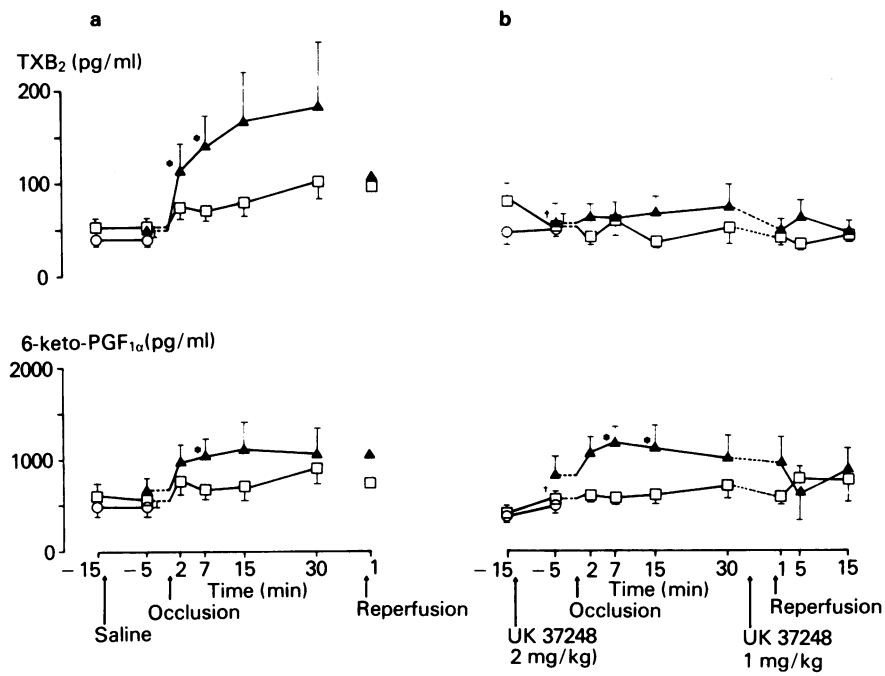

Figure 1 Plasma prostanoid concentrations in the aorta (o), coronary sinus (□) and local coronary vein (▲) in control dogs (*a*; n=8-9) and in dogs receiving UK 37248 (*b*; n=7-10). Each value is the mean±s.e. mean, except at 1 min post-reperfusion in the controls where the values are the mean of the four dogs from which samples were obtained. *Statistically significant different from pre-occlusion value; †statistically significant difference from the pre-drug value; $P<0.05$ (paired t test).

treated group (511±141) seemed to be lower than the mean for the controls (875±264), this was not statistically significant. The size of the occluded zone was similar in both the control and drug-treated groups, 35.3±1.1% and 35.6±0.9% of the free left ventricular wall respectively.

When the mean values of TXB_2 measured during coronary artery occlusion are plotted out (Figure 1*b*) it seems that thromboxane synthesis has been prevented by UK 37248; there were no significant differences between any of the values in either coronary sinus or local coronary venous blood throughout the period of occlusion. This is in marked contrast to the results obtained in the control group (Figure 1*a*). In this group there was a rapid local release of thromboxane into blood draining from the acutely ischaemic region of the myocardium.

However, close examination of the individual TXB_2 concentrations in the drug-treated group (Table 5) reveals some discrepancies. Although the mean values of the whole group did not alter significantly some individual animals did in fact show thromboxane release during coronary artery occlusion, for example, dog numbers 42, 43, 50 and 51 all had elevated thromboxane concentrations in local coronary venous blood after coronary artery occlusion, and in two cases (50 and 51) there were also elevated levels in the coronary sinus. These alterations in TXB_2 concentrations are greater than any fluctuations that could be expected as a result of variation with the assay. The mean intra-assay coefficient of variation for TXB_2 is 8.5% (range 5–13%). This suggests that the dose of 2 mg/kg UK 37248 did not provide satisfactory inhibition of thromboxane synthesis in all the dogs in this group. In four animals the TXB_2 concentrations remained below the detection limit of the assay after the administration of UK 37248 whereas in others the concentrations of TXB_2 varied considerably. In one or two animals the TXB_2 concentrations appeared to decrease with time suggesting that lack of inhibition of thromboxane synthesis may have been due to a slow onset of action. Another problem may be a short duration of action; concentrations rising at 30 min post-occlusion, that is, 45 min post-drug and then decreasing again after the second dose of UK 37248 before reperfusion. The fluctuations in TXB_2 concentration suggest that this dosage schedule provided inadequate inhibition of the thromboxane synthetase enzyme during occlusion of the coronary artery.

Table 5 Individual values of TXB_2 in plasma from the aorta, coronary sinus and local coronary vein in greyhounds which received UK 37248 2 mg/kg intravenously 15 min before coronary artery ligation with a further 1 mg/kg intravenously 5 min before reperfusion

Time	*Site*	*TXB_2 (pg/ml) Dog No.*										*Mean±s.e.m.*
		8140	*8141*	*8142*	*8143*	*8144*	*8149*	*8150*	*8151*	*8153*	*8160*	
5 min pre-drug	Aorta	28	<25	118	24	<20	<25	77	108	<25	<25	45±13
5 min pre-drug	Sinus	39	<25	89	70	201	31	64	191	<25	34	77±21
5 min pre-ligation	Aorta	<20	<25	92	33	85	35	55	103	<25	<25	50±10
5 min pre-ligation	Sinus	25	<25	54	34	133	32	65	101	<25	<25	52±12
2 min post-ligation	Sinus	<20	<25	34	17	115	<25	49	73	<25	<25	41±10
7 min post-ligation	Sinus	<20	<25	41		83	<25	120	160	<25	<25	58±16
15 min post-ligation	Sinus	<20	<25	43		38	<25	62	25	<25	<25	36±6
30 min post-ligation	Sinus	<20	<25	36		32		179	52	<25	<25	50±19
1 min post-reperfusion	Sinus	<20		23		31		83	74	<25	<25	39±9
5 min post-reperfusion	Sinus	<20		43		24		26	63	<25	<25	32±5
15 min post-reperfusion	Sinus	<20		51				69	74	<25	<25	42<8
5 min pre-ligation	Vein	<20	<25	65	24	214	<25	50	106	<25	<25	58<19
2 min post-ligation	Vein	<20	<25	110	51	150	32	71	113	<25	<25	62±15
7 min post-ligation	Vein	<20	<25	57		152	<25	85	134	<25	<25	61±18
15 min post-ligation	Vein	<20	<25	41		130		128	123	<25	<25	65±18
30 min post-ligation	Vein	<20	<25	35		150		112	185	<25	<25	73±23
1 min post-perfusion	Vein	<20		40		98		66	82	<25	<25	48±10
5 min post-perfusion	Vein	<20		125		124		46	100	<25	<25	62±16
15 min post-reperfusion	Vein	<20		43				34	125	<25	<25	48±14

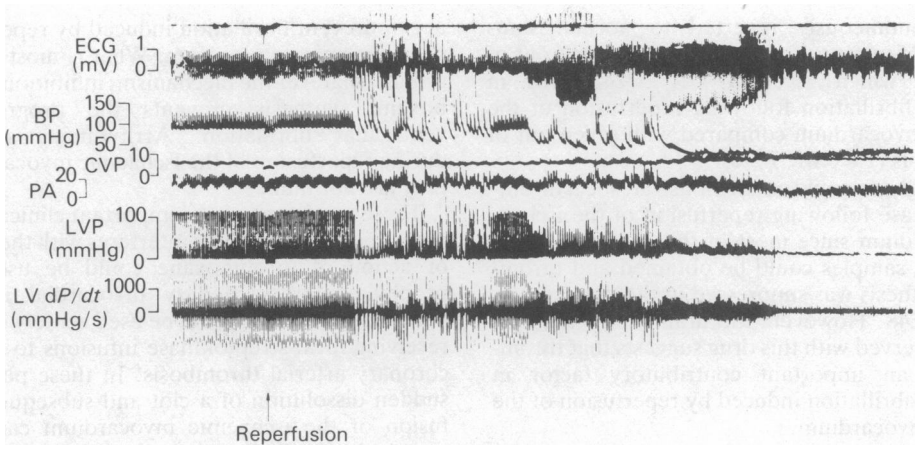

Figure 2 Effects of reperfusion of the formerly ischaemic myocardium on the lead II electrocardiogram (ECG), arterial blood pressure (BP), central venous pressure (CVP), pulmonary artery pressure (PA), left ventricular pressure (LVP) and its first derivative with time (LV d*P*/d*t*). The time marker at the top is in seconds.

Effects of UK 37248 on reperfusion arrhythmias and ventricular fibrillation

When the ligature around the coronary artery was released after a 40 min occlusion period arrhythmias were observed as soon as direct perfusion of the formerly ischaemic area was restored. The arrhythmias were multifocal in origin and caused marked reductions in systemic arterial blood pressure. In seven out of eight control animals these arrhythmias rapidly progressed to ventricular fibrillation; five of these dogs fibrillated within one minute of reperfusion (for example Figure 2). A different pattern was observed in the drug-treated animals. The initial arrhythmias appeared to be similar but instead of progressing to fibrillation they normally settled into a steady ventricular rhythm. Although ventricular in origin (there were no *P*-waves) the rate was usually only 5–10 beats/min faster than normal sinus rhythm and arterial blood pressure was fairly well maintained (see Figure 3). This ventricular rhythm persisted for anything from 2–15 min, the majority of animals

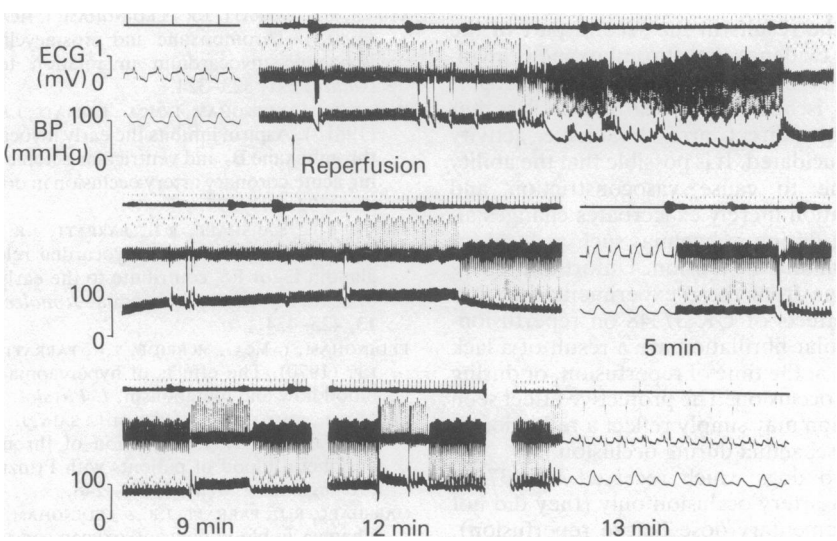

Figure 3 Effects of reperfusion on the electrocardiogram (ECG) and arterial blood pressure (BP) in a dog which had been pre-treated with UK 37248. The time marker at the top of each panel is in seconds.

having spontaneously reverted to normal sinus rhythm by 15 min post-reperfusion. Only one out of eight dogs which received UK 37248 died in ventricular fibrillation following reperfusion of the ischaemic myocardium compared with seven out of eight controls ($P<0.01$, χ^2 test).

In this study we could not demonstrate local thromboxane release following reperfusion of the ischaemic myocardium since most of the control animals died before samples could be obtained and thromboxane synthesis was suppressed in the dogs receiving UK 37248. However, the dramatic increase in survival observed with this drug suggests that thromboxane is an important contributory factor in ventricular fibrillation induced by reperfusion of the ischaemic myocardium.

Discussion

Unfortunately no clear conclusions can be drawn from the first part of this study. Although UK 37248 did not significantly reduce arrhythmias occurring during myocardial ischaemia, we cannot conclude that thromboxane is not involved. The results indicate that a single bolus dose of 2 mg/kg intravenously of UK 37248 15 min before coronary artery occlusion did not adequately suppress thromboxane synthesis throughout the period of occlusion in all the dogs. These experiments would need to be repeated using a more suitable dosage schedule such as an initial bolus dose followed by a continuous infusion. Another alternative would be to use a different compound with a longer duration of action.

In contrast, the results in the second part of the study give clear evidence that thromboxane is involved in ventricular fibrillation resulting from reperfusion of the ischaemic myocardium. Whether thromboxane has direct arrhythmogenic activity remains to be elucidated. It is possible that the ability of thromboxane to cause vasoconstriction and platelet aggregation merely exacerbates changes already occurring during ischaemia, such as local increases in carbon dioxide tension. Unfortunately we cannot determine from these experiments whether the beneficial effects of UK 37248 on reperfusion-induced ventricular fibrillation are a result of a lack of thromboxane at the time of reperfusion, or during coronary artery occlusion. The protective effect seen during reperfusion may simply reflect a reduction in the severity of ischaemia during occlusion.

However, two dogs which received UK 37248 before coronary artery occlusion only (they did not receive a supplementary dose before reperfusion), died in ventricular fibrillation approximately 20 min after reperfusion. This suggests that the continued inhibition of thromboxane synthesis may be necessary to prevent fibrillation induced by reperfusion of the ischaemic myocardium. What is most intriguing is that, whatever the mechanism, inhibition of thromboxane synthesis prevents the progression to ventricular fibrillation. Arrhythmias still occur during reperfusion of the ischaemic myocardium but they are not fatal.

These results may have important clinical implications. First, a drug which interferes with the synthesis or action of thromboxane could be used in the prophylaxis of secondary myocardial infarction. Second, such a drug could be used acutely in patients receiving local streptokinase infusions to dissolve a coronary arterial thrombosis. In these patients the sudden dissolution of a clot and subsequent reperfusion of the ischaemic myocardium can lead to ventricular fibrillation, an occurrence which would presumably be prevented by a drug such as UK 37248.

We thank Professor I. McA. Ledingham for the continued use of facilities at the Western Infirmary and Ian Douglas, Dick Thomson, Alan Fleming and Margaret Macdonald for excellent technical assistance. Financial support was provided by the Scottish Hospital Endowments Research Trust and by Pfizer.

References

COKER, S.J., CLARKE, B. & ZEITLIN, I.J. (1982). Radioimmunoassay techniques for the determination of the local release of prostaglandins and thromboxanes. *J. Pharmac. Meth.* **7**, 207–217.

COKER, S.J., PARRATT, J.R., LEDINGHAM, I. MCA. & ZEITLIN, I.J. (1981*a*). Thromboxane and prostacyclin release from ischaemic myocardium in relation to arrhythmias. *Nature*, **291**, 323–324.

COKER, S.J., LEDINGHAM, I. MCA., PARRATT, J.R. & ZEITLIN, I.J. (1981*b*). Aspirin inhibits the early myocardial release of thromboxane B_2 and ventricular ectopic activity following acute coronary artery occlusion in dogs. *Br. J. Pharmac.*, **72**, 593–595.

COKER, S.J., MARSHALL, R.J., PARRATT, J.R. & ZEITLIN, I.J. (1981*c*). Does the local myocardial release of prostaglandin E_2 or $F_{2\alpha}$ contribute to the early consequences of acute myocardial ischaemia? *J. molec. cell. Cardiol.*, **13**, 425–434.

LEDINGHAM, I. MCA., MCBRIDE, T.I., PARRATT, J.R. & VANCE, J.P. (1970). The effects of hypercapnia on myocardial blood flow and metabolism. *J. Physiol.*, **210**, 87–105.

LEWY, R.I., SMITH, J.B., SILVER, M.J., SAIA, J., WALINSKY, P. & WEINER, L. (1979). Detection of thromboxane B_2 in peripheral blood of patients with Prinzmetal's angina. *Prostaglandins Med.*, **2**, 243–248.

MARSHALL, R.J., PARRATT, J.R. & LEDINGHAM, I. MCA. (1974). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **8**, 204–215.

NAITO, M., MICHELSON, E.L., KMETZO, J.J., KAPLINSKY, E. & DREIFUS, L.S. (1981). Failure of antiarrhythmic drugs to prevent experimental reperfusion ventricular fibrillation. *Circulation*, **63**, 70–79.