Effect of the specific thromboxane receptor blocking drug AH23848 in patients with angina pectoris

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SUMMARY The effect of the specific thromboxane receptor blocking drug AH23848 was investigated in two double blind placebo controlled studies in male patients with exercise induced angina pectoris and angiographically verified coronary lesions. In the first study cardiac pacing was performed in twenty patients after coronary angiography. Patients were then randomised into two groups and received either AH23848 (70 mg orally) or placebo. One hour later cardiac pacing was repeated. Neither treatment had any significant effect upon time to angina or the rate-pressure product at the onset of chest pain in these patients. In the second study twenty male patients were randomised to seven days' treatment with AH23848 (70 mg three times a day) or placebo followed by a crossover to the other treatment for a further seven days. Clinical assessment was performed before treatment and at the end of each treatment period. There was no significant difference between the placebo and AH23848 treatment periods in exercise tolerance, the rate-pressure product at angina after exercise testing, the number of ischaemic attacks as determined from 24 hour ambulatory electrocardiograms, the number of attacks of pain, or the number of glyceryl trinitrate tablets consumed. This lack of a clinical effect with AH23848 was seen despite a profound inhibition of ex vivo platelet aggregation stimulated by the thromboxane A_2 -mimetic U-46619. Because in experimental animals in vivo AH23848 blocks vascular thromboxane receptors as well as platelet thromboxane receptors the lack of effect of AH23848 in cardiac pacing and exercise induced angina is unlikely to be the result of inadequate blockade of thromboxane receptors. The lack of effect of the drug is more likely to indicate that thromboxane A_2 is not a factor in the aetiology of the pain experienced by these patients during exercise or cardiac pacing.

Angina pectoris is the clinical manifestation of an imbalance between myocardial oxygen demand and the supply capabilities of the coronary arterial system. Most patients with angina have considerable fixed coronary obstruction by atheroma. But there has been much interest in the possibility that dynamic coronary obstruction produced by changes in tone of the coronary vessels or temporary obstruction by platelet thrombi may also play a part. Thromboxane A_2 is released from activated platelets and is a potent inducer of platelet aggregation^{1 2} and a powerful contractile agent in both animal and

human coronary arteries in vitro.³ This profile of activity led several workers to propose a role for thromboxane A_2 in coronary vasospasm leading to myocardial infarction, sudden cardiac death, and variant angina.^{4 5}

The evidence for a role of thromboxane A_2 in human angina is, however, equivocal. There have been several reports that concentrations of thromboxane B_2 , the stable degradation product of thromboxane A_2 , is raised in coronary sinus blood from patients with unstable angina⁶⁻⁸ or during cardiac pacing in patients with angina.^{9 10} Aspirin at doses that reduced serum or urinary concentrations of thromboxane B_2 by >75% was, however, without effect upon the frequency of ischaemic incidents in patients with variant angina.^{11 12} In contrast two studies have recently shown aspirin to be effective in

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reducing the frequency of myocardial infarction in patients with unstable angina.^{13 14} Equivocal results have also been reported with the thromboxane synthetase inhibitor, dazoxiben, which has been reported either to reduce^{15 16} or to leave unaltered^{17 18} the ischaemic response to atrial pacing or exercise in patients with coronary artery disease.

Evidence derived from drugs that interfere with synthesis of thromboxane A_2 is, however, difficult to interpret. If the inhibition of thromboxane A_2 is achieved by inhibition of fatty acid cyclo-oxygenase the formation of other biologically active prostanooids such as prostacyclin, prostaglandins D_2 and E_2 will also be inhibited, and if it is achieved by inhibition of thromboxane synthetase the production of the other products of the cyclo-oxygenase pathway may be enhanced.¹⁹ Thus in neither case it is possible to relate the end result solely to a deficiency of thromboxane A_2 . The ideal compound to determine the role of thromboxane A_2 in disease states is therefore one that specifically blocks the actions of thromboxane A_2 at the level of the receptor.

AH23848 is such a drug. It has no action on cyclo-oxygenase, thromboxane synthetase, prostacyclin synthetase, or cyclic adenosine monophosphate phosphodiesterase enzymes.²⁰ Over the same concentration range in vitro it inhibits platelet aggregation induced by thromboxane A_2 and its stable mimetic U-46619²¹ and contraction of vascular smooth muscle from various species.^{22 23} Most importantly, AH23848 is also equipotent in blocking platelet and vascular smooth muscle thromboxane receptors in animals in vivo²² and would thus be expected to block both the vascular and platelet effects of thromboxane A_2 in disease states. The compound is orally active and long acting in human volunteers^{24 25} and is active in certain animal models of occlusive vascular disease and ischaemia.^{20 26 27}

We have therefore studied the effects of orally administered AH23848 in patients with exercise induced angina pectoris and angiographically verified coronary lesions in an attempt to clarify the role of thromboxane A_2 in this disease state. We chose to study this group rather than patients with unstable or "vasospastic" angina because the latter are much more difficult to define as a homogeneous group and their symptoms are often capricious and hard to reproduce. The study was conducted in two parts: as a placebo controlled double blind trial of the effect of a single dose of AH23848 on pacing induced angina and as a double blind crossover trial of 70 mg AH23848 three times daily for one week against placebo with assessment by exercise testing, ambulatory electrocardiogram monitoring, patient

diaries, and glyceryl trinitrate tablet counts. In both groups of patients the magnitude of thromboxane receptor blockade produced by AH23848 was determined on platelets ex vivo so that any clinical effect of the drug could be correlated with its pharmacological effect.

Patients and methods

The studies were approved by the local advisory ethics committee. Consecutive male patients admitted for diagnostic coronary arteriography because of angina pectoris not adequately controlled by medical treatment were invited to enter the trials. Patients were excluded if they had left main coronary stenosis or had experienced a recent myocardial infarction. Their written informed consent was obtained.

PACING INDUCED ANGINA

Patients were studied at the time of coronary arteriography, which was performed by the Judkins technique²⁸ without heparinisation. Previous medication was discontinued at the time of hospital admission 24 hours before the study. After angiography a bipolar pacing catheter was inserted percutaneously via an arm or leg vein and positioned in the right atrial appendage. Before pacing, blood pressure was measured by sphygmomanometer cuff and auscultation. In the first study blood pressures were checked against intra-arterial blood pressures. Pacing was then started at 100 beats per minute and the rate was increased by 10 beats per minute every 20 seconds until either a rate of 140 beats per minute was reached or the maximum rate at which 1:1 atrio-ventricular conduction could be maintained was achieved. Pacing was continued until the patient experienced chest pain or for five minutes, whichever was the shorter. The duration of pacing, maximum pacing rate achieved, and the blood pressure at the onset of angina were recorded. The product of pacing rate and systolic blood pressure was then determined (rate-pressure product). The patient was then given 70 mg AH23848 or a placebo capsule with 100 ml water. One hour later blood pressure was measured and pacing was then repeated and the same variables were recorded as before. The pacing electrode was then removed. The placebo group was introduced to control for the possibility that the patient might "learn" the time to angina, or alternatively be more relaxed and have a higher angina threshold at the time of the second pacing study. The long duration of action of AH23848²⁴ precluded any acute crossover study.

EXERCISE INDUCED ANGINA

Patients admitted to this part of the trial all had a positive Bruce protocol exercise test²⁹ and had undergone diagnostic coronary arteriography. They included four patients who had taken part in the first study; but at least one month had elapsed between the two studies. Before starting the study patients were clinically examined and had a 12 lead electrocardiogram, a Bruce protocol exercise test, and a 24 hour ambulatory electrocardiogram recording with two-channel frequency modulated Tracker equipment.³⁰ Blood pressure was measured with a sphygmomanometer before and at one minute intervals during exercise testing. The electrocardiogram was monitored throughout exercise and the rate-pressure product at the time of onset of angina was calculated. Patients were issued with counted glyceryl trinitrate tablets and with diaries in which to record angina attacks and record the number of glyceryl trinitrate tablets taken. Previous antianginal treatment with β adrenoceptor antagonists, calcium channel blockers, or sustained release nitrates was not stopped nor was it altered during the trial. Patients were asked not to take aspirin or other non-steroidal anti-inflammatory agents during and for two weeks before the trial. Patients were allocated in random order to AH23848 70 mg three times daily one hour before meals or to identical placebo capsules. After six days of the seven day treatment period clinical examination and exercise testing were repeated. On the day of exercise testing the time of the morning treatment was adjusted so that the exercise test took place two hours after dosing. An ambulatory electrocardiogram was recorded for 24 hours on the seventh day of the treatment period. Diaries and unused glyceryl trinitrate tablets were collected and a fresh diary and supply of glyceryl trinitrate were issued. The patient then crossed over to the alternative treatment for a further week and the tests were repeated as before. As well as comments recorded in the diaries, subjective side effects were recorded on a standard questionnaire. Blood samples for routine laboratory investigations (urea, electrolytes, liver function tests, and full blood count) were taken before treatment and after each week's treatment.

STATISTICAL ANALYSIS

Results were analysed by appropriate non-parametric statistics. For the second study we used Koch's method of applying these to a two period crossover trial.³¹ In addition we used methods based on Wilcoxon's rank sum statistic to compare AH23848 and placebo groups and to derive confidence intervals for each data set.³² Data for each of the measured variables were analysed separately.

PLATELET AGGREGATION

Blood was obtained from patients by venepuncture from an antecubital vein and anticoagulated with trisodium citrate. Platelet aggregation in response to the stable thromboxane A₂ mimetic U-46619 and adenosine diphosphate was monitored by a previously reported technique.³³ Briefly, the number of single platelets in a 0.5 ml volume of whole blood were counted electronically before and at intervals after addition of an aggregating agent. The peak fall in platelet count was recorded and expressed as a percentage of the control count for that volume. By adding a different concentration of aggregating agent to separate volumes of blood, aggregation concentration-effect curves were constructed (see legend to fig 1 for further experimental details).

Concentration ratios were calculated where possible on the parallel parts of the aggregation concentration-effect curves. The concentration of aggregating agent required to give 50% aggregation (EC₅₀) after treatment was divided by the mean EC₅₀ taken from the duplicate pre-treatment control curves (see below).

Pacing-induced angina

Duplicate blood samples for control platelet aggregation studies were taken fifteen minutes apart and before angiography. A third blood sample was taken immediately after the first pacing period and a further sample one hour after treatment but before pacing. Finally, a further sample was taken immediately after the second pacing period.

Exercise-induced angina

During the pre-treatment examination of patients, but before exercise testing, duplicate blood samples for ex vivo platelet aggregation studies were taken approximately 30 minutes apart. A further sample was taken immediately after the exercise test. On the subsequent two visits single blood samples were taken before and immediately after the exercise test.

DRUGS USED

Glaxo Group Research Ltd supplied white opaque unmarked hard gelatin capsules each containing the equivalent of 35 mg AH23848 acid as the calcium salt or placebo. Trisodium citrate (BDH) was prepared as a 0.129 mol/l solution in distilled water. Acetylsalicylic acid (aspirin, BDH) was dissolved in TRIS hydrochloride (HCl) buffer (100 mmol/l, pH 8.5) to give a stock solution of 10 mg/ml. Adenosine diphosphate (Sigma) was dissolved in Tris HCl buffer (100 mmol/l, pH 6.5) to give a solution strength of 1.0×10^{-2} mol/l, dilutions were prepared in 0.9% wt/vol sodium chloride solution (saline). U-46619 (Glaxo Group Research) was pre-

Table 1 Effect of AH23848 (70 mg) or placebo upon the time to angina and the rate-pressure product in patients with coronary artery disease undergoing cardiac pacing

Case No	Pre-treatment		Post-treatment		Ratio of post: pretreatment RPP
	Time to angina (min)	RPP	Time to angina (min)	RPP	
AH23848:					
01	5.0	19800	3.5	20400	1.03
03	5.0	13800	5.0	14950	1.08
06	5.0	12350	5.0	12610	1.02
07	1.5	14300	1.5	15950	1.12
10	5.0	12100	5.0	13200	1.09
12	3.0	15600	5.0	21450	1.38
13	5.0	14400	5.0	13200	0.92
14	5.0	14300	5.0	18200	1.27
19	3.5	14375	5.0	13750	0.96
20	1.5	15600	2.5	13200	0.85
Placebo:					
02	5.0	13800	5.0	8970	0.65
04	5.0	14300	5.0	11050	0.77
05	5.0	11760	5.0	11400	0.97
08	5.5*	9900	5.0	11500	1.17
09	5.0	10925	5.0	11270	1.03
11	5.0	18900	5.0	16200	0.86
15	5.0	14175	5.0	15120	1.07
16	3.5	11700	3.0	14300	1.22
17	3.0	14300	4.5	17550	1.23
18	1.5	20000	4.5	13750	0.69

RPP, rate-pressure product.

*Pacing continued for 5.5 minutes in this patient.

pared as a 1.0×10^{-2} mol/l solution in 1% wt/vol sodium bicarbonate in saline; dilutions were prepared in saline. All drug solutions were stored on ice during use. All concentrations of drugs refer to whole blood.

Results

PACING-INDUCED ANGINA

Twenty male patients with stable angina were entered into this study. Of these patients 13 had three vessel disease, four had two vessel disease, and three had single vessel disease. Fourteen patients subsequently went on to have coronary artery bypass graft surgery. The age distributions were similar for the two groups of patients, the median and range being 54 (40–59) years for placebo and 56 (41–65) years for AH23848. There was no significant difference between the groups in pre-catheter exercise tolerance, coronary artery score, or subsequent requirement for coronary surgery.

In both groups of patients treatment had no effect on the time to angina, the mean (range) in minutes before and after placebo being 4.4 (1.5–5.5) and 4.7 (3.0–5.0) respectively compared with 4.0 (1.5–5.0) and 4.3 (1.5–5.0) before and after AH23848. The rate-pressure product was similarly unaffected by either treatment (table 1). Diastolic blood pressure at the onset of angina was significantly higher in

patients receiving AH23848 than in patients receiving placebo (median difference (95% confidence interval) 13 (5, 30) mm Hg). In contrast, diastolic pressure was not higher in the AH23848 group before pacing nor was such a difference seen at angina during the pre-treatment pacing. In addition, no such difference in systolic blood pressure was seen between the two groups of patients either before pacing or at angina. The reason for the slightly higher diastolic blood pressure at angina after AH23848 treatment is not known.

Despite the apparent lack of effect of AH23848 upon the variables assessed during pacing, this agent did have a profound effect upon U-46619-induced ex vivo platelet aggregation in blood samples taken one hour after drug treatment. In all of the patients given AH23848 a profound rightward displacement of the U-46619 concentration effect curve was seen. In only one patient was a U-46619 concentration ratio of <50 obtained (range 19–251); in contrast platelet aggregation induced by adenosine diphosphate was not affected by AH23848 treatment. Placebo treatment was also without effect upon aggregation in response to both aggregating agents. Figure 1 shows the mean aggregation concentration-effect curves for the two groups.

During this study blood samples were taken immediately after the end of cardiac pacing. These were taken to determine whether pacing per se pro-

Fig 1 The effect (mean (SE)) of a single oral dose of either AH23848 (70 mg) (upper panel) or placebo (lower panel) upon platelet aggregation induced by U-46619 and adenosine diphosphate (ADP) *ex vivo* in whole blood from patients with angina pectoris undergoing cardiac pacing. Blood samples (4.5 ml) were obtained by venepuncture and anticoagulated with trisodium citrate (final concentration 12.9 mmol/l). Volumes of whole blood were then incubated at 37°C in a shaking water bath while aggregation studies were performed. Aspirin (2.0 mmol/l) was added to blood volumes to prevent the formation of endogenous prostaglandins during the aggregation process. Aggregation studies were started as rapidly as possible, usually 10–15 minutes after venepuncture. Platelet counts were determined before and 10, 20, and occasionally 30 minutes after addition of U-46619, the peak fall in platelet count usually occurring at 10 minutes in control and placebo blood samples but up to 30 minutes after AH23848 treatment. Platelet counts were determined before and one minute after addition of adenosine diphosphate (ADP); this has previously been shown to represent the time of peak aggregation.³³ The control curves represent the second of the two preliminary U-46619 and adenosine diphosphate curves.

duced any change in platelet sensitivity and whether treatment with a thromboxane receptor blocking drug would modify any such change. Comparison of the EC₅₀ values of the control concentration effect curves in response to both U-46619 and adenosine diphosphate with those from curves obtained after the first pacing period from the twenty patients showed no consistent change in platelet sensitivity

that could be attributed to pacing.

Few side effects were noted in this study. One patient became dizzy and hypotensive after taking placebo, one experienced nausea 30 minutes after taking AH23848, and a third patient experienced chest pain not typical of angina one hour after taking AH23848 but before the second pacing.

EXERCISE-INDUCED ANGINA

Twenty male patients including four who had taken part in the pacing-induced angina study, entered the study. Of these patients 13 had three vessel disease, four had two vessel disease, and two had single vessel disease (the remaining patient was withdrawn, see below). Eleven patients subsequently went on to have coronary artery bypass graft surgery. Two patients did not complete the study: patient 3 was called in for coronary artery surgery after completing only one week of the study and patient 10 was withdrawn before receiving active treatment because of a sudden deterioration in exercise tolerance. Patient 1 inadvertently took only half the dose of AH23848 and was therefore excluded from the analysis. Of the remaining 17 patients platelet aggregation studies indicated non-compliance in three patients (numbers 11, 13, and 17, see below) and in patient 8 aggregation studies were incomplete. Results were therefore analysed twice, both including these patients (n = 17) and excluding them (n = 13). Both analyses gave the same result.

Table 2 summarises the results. There was no significant difference in exercise tolerance, number of ischaemic attacks (defined as a depression of the J junction by at least 1 mV followed by an ST segment depression sloping downwards detected by ambulatory electrocardiogram monitoring), number of attacks of pain, or number of glyceryl trinitrate tablets consumed between the placebo and AH23848 treatment periods. In addition we found no significant difference between the two treatments in the rate-pressure product at angina after exercise testing nor any effect on blood pressure.

As in the first study, patients receiving AH23848 for six days generally showed a large rightward displacement in the U-46619 aggregation concentration-effect curve. We saw no effect upon adenosine diphosphate induced aggregation. Figure 2 summarises the data for all patients. Patients who received AH23848 as the first treatment showed no residual blocking effect of the drug on day 6 of the subsequent placebo treatment. Patients 11, 13, and 17 unexpectedly displayed low U-46619 concentration ratios after AH23848 (1.7, 0.7, and 5.2 respectively) and were deemed to be non-compliant. This apparent lack of effect after AH23848 treatment was also seen in the blood samples from these

Table 2 Effect of AH23848 or placebo for seven days upon various indices of ischaemia in patients with angina pectoris undergoing exercise stress testing

Case No	Duration of exercise test (min)		No of ischaemic attacks		No of attacks of pain		No of GTN tablets	
	Placebo	AH23848	Placebo	AH23848	Placebo	AH23848	Placebo	AH23848
<i>Placebo followed by AH23848</i>								
02	4.75	4.5	0	4	—	—	24	18
04	1.75	2.75	6	4	53	35	30	20
05	7.5	7.5	0	0	6	3	1	3
06	6.25	5.0	0	0	9	3	9	3
08†	—	—	2	3	5	7	9	13
11†	5.5	6.5	0	0	1	1	2	3
12	5.0	6.0	1	0	3	2	3	2
13†	5.75	6.0	2	7	19	28	82	90
15	10.0	11.0	0	0	2	0	0	0
18	1.7	2.25	0	1	2	2	0	1
<i>AH23848 followed by placebo</i>								
01*	5.0	5.5	0	0	—	—	4	11
03†	—	4.5	—	1	—	—	—	—
07	3.5	3.5	0	0	44	22	90	44
09	3.0	3.0	5	0	22	12	27	25
10*	—	—	—	—	—	—	—	—
14	4.5	4.0	1	0	5	8	8	10
16	3.0	2.7	0	5	18	26	17	19
17†	8.0	7.0	3	4	—	—	—	—
19	2.0	2.0	—	—	28	24	28	25
20	7.5	6.5	—	—	1	6	0	6

*Patients excluded from analysis (see text).

†Analyses performed with and without these patients (see text).

—Measurement not carried out.

patients after the exercise testing, thus ruling out an erroneous platelet aggregation determination. A ratio of 10 was chosen as the limit below which patient non-compliance was assumed. This value was based upon those obtained from patients given AH23848 in the first study and our experience in healthy volunteers taking this dosage regimen.^{24 25}

Placebo did not have a pronounced effect on aggregation in response to U-46619 or adenosine diphosphate, except in patient 17 in whom platelet aggregation in response to the thromboxane A₂ mimetic appeared to be antagonised more by placebo treatment than by AH23848. This was one of the patients deemed to be non-compliant.

The effect of exercise per se upon platelet aggregation was also studied. In blood samples taken immediately after the pre-treatment exercise test there was no consistent change in platelet sensitivity to either U-46619 or adenosine diphosphate.

In the second study two patients experienced malaise and one patient described diffuse muscle aches while taking placebo; one patient had heartburn, nausea, and vomiting while taking AH23848 and one patient reported feeling very tired while taking the active drug. No clinically significant changes in laboratory values were noted.

Discussion

The present study was designed to test the hypothesis that thromboxane A₂ has a role in angina induced by cardiac pacing and exercise in patients with angiographically confirmed coronary artery disease and therefore whether a thromboxane A₂ receptor blocking drug would be therapeutically useful in this condition.

Evidence for an involvement of thromboxane A₂ in various forms of angina has been largely circumstantial. Thus for example raised concentrations of thromboxane B₂ have been measured in coronary sinus blood during pacing in angina patients.^{9 10 17} However, sampling procedures themselves, especially withdrawal of blood through long indwelling catheters, may induce platelet activation and thromboxane A₂ release.³⁴ If platelets are more reactive after cardiac pacing than before pacing, different degrees of activation and hence thromboxane A₂ release may occur with sampling. These raised concentrations would not then necessarily imply a pathophysiological role for thromboxane A₂ per se.

Evidence from drug studies is also difficult to interpret. Negative studies with cyclo-oxygenase

Fig 2 Effect of AH23848 and placebo upon platelet aggregation *ex vivo* in angina patients undergoing exercise tolerance testing. Histograms represent concentration ratios for U-46619 and adenosine diphosphate after treatment with either AH23848 or placebo. Columns designated > represent minimum estimates of U-46619 concentration ratio values when 50% aggregation to U-46619 was not achieved in the post-AH23848 blood samples. In these instances the U-46619 EC_{50} value during treatment was assigned a value of $>1.0 \times 10^{-5}$ mol/l, the highest concentration of aggregating agent used. In patients 11 and 13 there was no antagonism of U-46619-induced aggregation after AH23848 treatment and in patient 17 placebo treatment appeared to be more effective than drug treatment. This profile was not expected from previous experience with the drug. NT, not tested.

inhibitors such as aspirin in pacing-induced angina¹⁶ may be a consequence of the reduction in prostacyclin and platelet-derived prostaglandin D_2 concentrations rather than reduction in thromboxane A_2 itself. The balance between prostacyclin and thromboxane A_2 has been shown to be important in animal models of cardiac ischaemia.³⁵ In contrast, positive findings with the thromboxane synthetase inhibitor dazoxiben^{15 16} could equally well reflect the beneficial diversion of endogenous prostaglandin endoperoxides to prostacyclin rather than to a reduction in thromboxane A_2 concentrations.

As has been pointed out previously²⁰ definitive evidence for the action of thromboxane A_2 in a disease state depends upon the use of a highly specific thromboxane A_2 receptor blocking drug. Such a drug would only block the actions of thromboxane A_2 and leave untouched the production of thromboxane A_2 and prostacyclin. AH23848 is a specific and potent thromboxane A_2 receptor blocking drug

that has no effect upon cyclo-oxygenase, thromboxane synthetase, or prostacyclin synthetase.²⁰ In addition it is non-selective, being approximately equipotent in blocking thromboxane A_2 receptors present on both the platelet and vascular smooth muscle. This profile has been observed both in isolated tissues and *in vivo* in laboratory animals.²² AH23848 would therefore be expected to block local vasoconstriction as well as platelet aggregation induced by thromboxane A_2 *in vivo*.

In the present study AH23848 did not have any clinically beneficial effect on angina pectoris after pacing or exercise in patients with angiographically confirmed coronary artery disease. Platelet aggregation in response to the thromboxane A_2 mimetic U-46619, however, was substantially inhibited by AH23848 at the time of pacing or exercise. Sufficient thromboxane receptor blockade was achieved to produce an approximately 100-fold rightward displacement of the U-46619 platelet aggregation concentration-effect curves. In contrast with the

effect upon U-46619, adenosine diphosphate induced aggregation, which occurs independently of thromboxane A₂ under the conditions of this study, was unaffected. This profile of action would be expected of a specifically acting receptor blocking drug such as AH23848. Thus in the patients studied a very large level of platelet thromboxane A₂ receptor blockade was apparent yet no effect on time to pain was seen in either study. As mentioned above, in experimental studies AH23848 also produces a similar degree of blockade of vascular thromboxane receptors to that produced on the platelet thromboxane receptor. While the pharmacodynamic profile of the actions of this drug upon vascular thromboxane receptor in man has not been studied, both pacing and exercise testing were performed within 1–2 hours of AH23848 administration. Thus it is presumed that a large degree of blockade of the vascular thromboxane receptor was also achieved in these patients. These results are therefore strong evidence for the lack of effect of thromboxane A₂ in angina, at least in the patients we studied and under the circumstances of this study.

In the exercise study several patients were excluded from analysis because there was no antagonism of the U-46619 induced aggregation responses after AH23848. We believed this action to be justified because our experience with the drug in volunteers and patients^{24 25 36} had never shown such a lack of effect. Two analyses performed after inclusion or exclusion of the "non-compliant" patients were both negative.

We believe that the measurement of antagonism of the aggregatory action of U-46619 by AH23848 was essential in the present study so that we could reach valid conclusions about the actions of thromboxane A₂ in these patients. Does this level of thromboxane receptor blockade have any clinical relevance, however? Other studies suggest that it does. Thus in patients with mature aorto-bifemoral arterial Dacron grafts AH23848 appeared to reduce deposition of platelets onto the grafts.³⁶ In the deposition study AH23848 was administered to patients for a similar period (nine days) to that used in the present exercise study and produced a similar level of antagonism of U-46619 induced platelet aggregation. Thus the lack of effect of AH23848 in the present study is unlikely to be caused by an inadequate level of thromboxane receptor blockade.

It could, however, also be argued that since several patients in our study were taking β adrenoceptor antagonists, calcium channel blockers, or nitrates any minor antianginal effect of AH23848 might be overshadowed. Our ethical advisory committee was unhappy about stopping all medication in patients with known severe angina for the trial of

an agent of unproven efficacy. It might be expected that an antianginal agent with a completely different mode of action may have an additive or synergistic effect, however, as has been demonstrated for β adrenoceptor antagonists and calcium channel blockers. The present study does not necessarily contradict observations of increased thromboxane A₂ production in angina, but suggests this is a secondary rather than a primary phenomenon. Nor does it exclude a long term role for platelet activation in extending or perpetuating coronary arterial damage.

Finally, we chose to study patients with exercise induced rather than unstable or vasospastic angina, for the reasons stated in the Introduction and also because we wished to become more familiar with the clinical properties of AH23848 before using it in patients in an unstable state. A priori, vasospastic angina might be more likely to respond to a thromboxane receptor blocking drug. In fact the recent studies with aspirin^{13 14} have provided evidence for the involvement of thromboxane A₂ in this condition. Specific thromboxane receptor blocking drugs like AH23848, by sparing vascular prostacyclin and platelet derived prostaglandin D₂, may prove to be more effective than aspirin.

In conclusion, AH23848 was well tolerated but was without effect upon the indices of ischaemia in patients with pacing and exercise induced angina pectoris despite producing a considerable blockade of the platelet thromboxane A₂ receptor. The results of the present study strongly suggest, therefore, that thromboxane A₂ is not important in severe angina pectoris. AH23848 is a valuable drug, and drugs like it, in addition to resolving the controversy about the involvement of thromboxane A₂ in various diseases, may also prove to be valuable therapeutic agents.

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