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Effects of the myocardial-selective α_1-adrenoceptor antagonist UK-52046 and atenolol, alone and in combination, on experimental cardiac arrhythmias in dogs

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1 Adrenaline-induced arrhythmias in anaesthetized dogs respired with halothane were attenuated in 3 groups of 6 dogs by either UK-52046, $3.8 \pm 1.4\,\mu g\,kg^{-1}$ (mean ± s.e.mean), atenolol $14.6 \pm 2.1\,\mu g\,kg^{-1}$, or a combination containing equal amounts of the two drugs of $0.36 \pm 0.1\,\mu g\,kg^{-1}$. The pressor response to adrenaline was reduced ($P < 0.01$) by UK-52046 but not by atenolol or the combination of both drugs.

2 In a group of 6 dogs with multiventricular ectopic beats 24 h after coronary artery ligation (CAL), UK-52046, $32\,\mu g\,kg^{-1}$, increased the number of sinus beats in each 5 min period from 137 ± 47 to 662 ± 99 ($P < 0.01$); this was associated with a significant ($P < 0.01$) fall in blood pressure. Atenolol in doses of up to $800\,\mu g\,kg^{-1}$ had no effect.

3 UK-52046, $3.7 \pm 1.4\,\mu g\,kg^{-1}$, prevented adrenaline-induced arrhythmias 3–4 days after CAL in 6/6 conscious dogs; atenolol in doses of up to $100\,\mu g\,kg^{-1}$ produced an $84.4 \pm 7.4\%$ reduction in the number of ventricular ectopic beats. A combination containing $3.7 \pm 1.1\,\mu g\,kg^{-1}$ of each drug prevented the arrhythmia in 6/6 dogs. The pressor response to adrenaline was attenuated ($P < 0.05$) by UK-52046, but resting blood pressure was unaffected by the different treatments. An increase ($P < 0.01$) in heart rate was associated with both UK-52046 and the combination.

4 Neither UK-52046 (doses up to $64\,\mu g\,kg^{-1}$) nor atenolol (up to $800\,\mu g\,kg^{-1}$) had any effect upon ouabain-induced arrhythmias in 2 groups of 6 anaesthetized dogs.

5 In a study of the early (1a/1b) arrhythmias of acute myocardial ischaemia, the total number of ventricular ectopic beats occurring within 30 min of CAL was not reduced by $4\,\mu g\,kg^{-1}$ UK-52046 but fell ($P < 0.01$ compared with placebo) after $8\,\mu g\,kg^{-1}$ [median values with ranges for placebo, $4\,\mu g\,kg^{-1}$ and $8\,\mu g\,kg^{-1}$ respectively 190 (4-674), 246 (9-1204) and 12 (1-154)]. Both doses of UK-52046 were associated with significant falls in blood pressure.

6 The arrhythmias produced by programmed electrical stimulation were studied in 2 groups of 6 conscious dogs, 7–30 days after CAL. With placebo, 4/6 dogs remained unchanged and 2 died: UK-52046 prevented arrhythmias in 2/6, 2 remained unchanged and 2 died ($P = 0.29$). Compared with placebo, blood pressure fell with doses greater than $4\,\mu g\,kg^{-1}$.

7 These results indicate antiarrhythmic effects of UK-52046 in a number of experimental models and suggest an enhanced role of α-receptors in the genesis of ischaemia-related arrhythmias. In several of the models used, UK-52046 produced haemodynamic changes in keeping with peripheral α-adrenoceptor antagonism.

Introduction

Despite Govier's original description of myocardial α-adrenoceptors (Govier, 1967; 1968) and subsequent confirmation of their existence in man (Schumann *et al.*, 1978), investigations into the cardiac effects of adrenergic stimulation have continued to concentrate largely on the β-receptor, possibly because of uncertainty over the physiological effects of myocardial α-stimulation. It is known,

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however, that enhanced α-responsiveness is a feature of experimental myocardial ischaemia (Juhasz-Nagy & Aviado, 1976; Sheridan et al., 1980) and recent reports have correlated this with an increase in α-adrenoceptor concentration (Corr et al., 1981). Furthermore, it has been suggested that the malignant arrhythmias associated with myocardial ischaemia may be mediated primarily by α-adrenoceptors (Benfey, 1982; Sheridan & Culling, 1985). Studies in isolated preparations have demonstrated α-mediated changes in refractory periods (Govier, 1967), positive inotropy (Schumann et al., 1978) and prolongation of the action potential duration (APD) (Benfey, 1982). If α-adrenoceptor responsiveness is enhanced under ischaemic conditions, then α-mediated prolongation of APD in ischaemic areas may combine with β-mediated shortening of APD in non-ischaemia areas to produce the arrhythmogenic milieu suitable for the emergence of re-entrant pathways (Vaughan Williams, 1985). The cellular events mediating these changes remain unclear, as contractility appears to be augmented without increases in cyclic AMP (unlike β-stimulation) (Watanabe et al., 1977); nevertheless, it is thought that these α-mediated effects may involve modulation of intracellular calcium (Sharma et al., 1983). This has led to the suggestion that α-adrenoceptor antagonism may be antiarrhythmic by nature of effects on cytosolic calcium, perhaps by affecting the cyclic AMP-independent sodium/calcium exchange (Corr & Sharma, 1984).

The classification of α-adrenoceptors into α_1 and α_2 subtypes (Langer, 1977) enabled further exploitation of the antiarrhythmic potential of α_1-adrenoceptor antagonists without the attendant risks of increased myocardial noradrenaline concentrations seen with non-specific α-blockade. Nevertheless, studies with non-specific α-adrenoceptor antagonists have always been open to the argument that any antiarrhythmic activity demonstrated may be secondary to peripheral (including coronary artery) α-antagonism. UK-52046 [4-amino-6,7-dimethyhoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinol-2-yl)quinoline methanesulphonate] has been developed as an α_1-adrenoceptor antagonist with selective affinity for myocardial α-receptors. This selectivity was defined by UK-52046 abolishing or preventing arrhythmias in numerous experimental models with minimal effects on blood pressure in comparison to prazosin and doxazosin with equal antiarrhythmic action (dose ratio prazosin/UK52046: 12.5/1.0, blood pressure lowering effect; 2.04/1.0 halothane/adrenaline arrhythmia in rats, $n = 5$) (Pfizer Central Research, unpublished communication).

The purpose of the present study was to study the antiarrhythmic effects of UK-52046 and compare it with another class II agent, the β_1-selective adrenoceptor antagonist atenolol, alone and in combination in four experimental models where arrhythmia production is dependent upon enhanced automaticity. It was of additional interest to evaluate the effects of UK-52046 alone in two re-entrant models, the arrhythmias of acute coronary ischaemia and the arrhythmias resulting from programmed electrical stimulation in a chronic canine model of myocardial infarction.

Methods

Ouabain-induced arrhythmias

Observations were made in adult greyhounds of either sex. The dogs were anaesthetized by the intravenous administration of sodium pentobarbitone ($30\,mg\,kg^{-1}$), intubated and ventilated with room air at a rate of $18\,min^{-1}$ and tidal volume of $13\,ml\,min^{-1}$ (Palmer Ideal Pump). Lead II of the electrocardiogram (ECG) and arterial pressure (recorded by means of a cannula in the femoral artery) were displayed simultaneously on an oscilloscope and recorded on a Lectromed LX216 2-channel recorder. A cannula in the femoral vein served for the administration of drugs. The right vagus nerve was exposed in the neck and divided between ligatures. A bipolar electrode was applied to the distal end of the nerve, which was stimulated for periods of 10 s with shocks of 1 ms duration at a frequency of 25 Hz and a voltage (0.2–3.5 V) sufficient to cause maximal slowing of the heart rate without loss of sinus dominance. Ventricular tachycardia was produced by the intravenous administration of ouabain $40\,\mu g\,kg^{-1}$, followed 15 min later by $20\,\mu g\,kg^{-1}$ and by 10 or $5\,\mu g\,kg^{-1}$ every 15 min until a ventricular arrhythmia was produced. Stimulation of the vagus nerve with the previously established voltage was repeated to confirm the ventricular origin of the arrhythmia. With the arrhythmia established for 10 min, increasing intravenous doses of UK-52046 or atenolol were administered until either the return of sinus rhythm or the death of the dog. A single drug was given to each dog.

Halothane-adrenaline arrhythmias

Adult greyhounds were anaesthetized by the intravenous administration of sodium pentobarbitone ($30\,mg\,kg^{-1}$). Ventilation, measurement of blood pressure and electrocardiographic recording were similar to the methods employed for the ouabain-induced arrhythmia. Following preparation, the dogs were respired with halothane at a concentration of 1% in room air. After 15 min, increasing doses of adrenaline starting with $0.4\,\mu g\,kg^{-1}$ and

using 0.4 $\mu g\,kg^{-1}$ increments were administered intravenously; these were continued at 10 min intervals until the production of ventricular tachycardia or multifocal ventricular ectopic beats. If ventricular fibrillation occurred, halothane administration was stopped and an external d.c. counter shock was applied (50–100 J: Pantridge Defibrillator type 280). Halothane was then reintroduced and the protocol continued with a lower dose of adrenaline after a 15 min recovery period. After determination of a test dose of adrenaline which would produce a similar severe arrhythmia on 2 successive occasions, increasing doses of UK-52046, atenolol or a combination of the two drugs were administered at 10 min intervals. Five min after each dose of the drug(s) under study, the dog was rechallenged with the test dose of adrenaline. The experiment continued until the test dose of adrenaline failed to produce any ectopic response.

Arrhythmias of acute coronary ischaemia

Adult greyhounds were anaesthetized by the intravenous administration of sodium methohexitone (10 $mg\,kg^{-1}$), intubated and ventilated as described above. Anaesthesia was maintained with a 1.5% concentration of halothane in room air. Lead II of the electrocardiogram and blood pressure were monitored continuously. Following thoracotomy, the fourth or fifth left rib was dissected free and removed and the heart exposed. The anterior descending branch of the left coronary artery (LAD) was then dissected free and a ligature passed loosely behind the artery. After a 5 min control period the dog was randomly allocated (investigator-blind) to receive intravenous placebo, UK-52046 4 $\mu g\,kg^{-1}$ or UK-52046 8 $\mu g\,kg^{-1}$. Five min later a critical stenosis of the artery was produced by tying the ligature tightly around the artery and a 21-gauge needle, which was then withdrawn. Attempts were made always to ligate below the second branch of the LAD in order to produce a uniform degree of ischaemia in all dogs. Ischaemia was confirmed by visually identifying an area of cyanosis and noting ST-segment changes on the electrocardiogram. Following ligation, the total number of ventricular ectopic beats was counted over a 30 min period.

Arrhythmias occurring 24 hours after coronary artery ligation

Adult greyhounds were prepared for surgery in a similar manner to that described above. In these dogs, no drug was given at any point after anaesthesia and 30 min after the production of the critical stenosis, a second ligature was tied tightly around the dissected coronary artery (Harris, 1950). The chest was subsequently closed in layers and the dog allowed to recover.

Further observations were made on the conscious dog 24 h after surgery. The dog was rested on its left side and lead II of the ECG and arterial pressure (recorded by means of a cannula in the femoral artery) were recorded throughout the duration of the experiment. Having ensured that at least 80% of beats were ventricular in origin, increasing doses of UK-52046 or atenolol were administered through a cannula in a foreleg vein at 5 min intervals until sinus rhythm was restored or side-effects became apparent.

Adrenaline-induced arrhythmias 3–5 days after coronary artery ligation

Coronary artery ligation was performed in a similar manner to that already described. Further observations were made on the conscious dog, 3–5 days after surgery. Positioning, measurement of blood pressure and electrocardiographic recording was similar to that described for the arrhythmia 24 h after coronary artery ligation. After a 10 min control period, a dose of 10 $\mu g\,kg^{-1}$ of adrenaline was administered intravenously and the ectopic response noted. If ventricular tachycardia or multifocal ventricular ectopic beats did not result, adrenaline administration was repeated after 10 min at a dose of 20 $\mu g\,kg^{-1}$. Having demonstrated an adequate arrhythmia in response to adrenaline on 2 successive occasions, increasing doses of UK-52046, atenolol or a combination of the 2 drugs were administered at 10 min intervals. Five min after the dose of drug(s) under study, the animal was rechallenged with the test dose of adrenaline. The experiment continued until the test dose of adrenaline failed to produce any ectopic response or side effects occurred.

Arrhythmias induced by programmed electrical stimulation

Two-stage coronary artery ligation was performed in a similar manner to that already described. In these animals myocardial pacing leads (Medtronic 6400 temporary myocardial leads) were sutured into the myocardial wall after the second ligature was applied; one lead was placed in the centre of the infarcted area and a second in an area jointly supplied by an adjacent branch of the LAD. The leads were brought out through skin, the wound was closed in layers and the dog allowed to recover. Routine antibiotic prophylaxis (250 mg streptomycin and 300,000 iu procaine penicillin) was given intramuscularly for 3 days.

Starting at 7 days and at weekly intervals thereafter, the dog was returned to the laboratory for

electrophysiological testing in the conscious state. The protocol for programmed electrical stimulation employed in this laboratory has been described in detail previously (Uprichard et al., 1988). By use of unipolar pulses of 4 ms duration at twice diastolic threshold, up to three extrastimuli were introduced at a basic pacing rate of 170 min^{-1}. Arrhythmias considered suitable for the continuation of the study included non-sustained ventricular tachycardia (NS-VT, defined as a reproducible arrhythmia of 4 or more ventricular ectopic beats at any given extra-stimulus setting) and sustained ventricular tachycardia (S-VT, defined as a self-perpetuating tachyarrhythmia of at least 5 min duration). Dogs which developed these arrhythmias in response to stimulation were termed 'inducible'; dogs in which the pacing protocol was completed without meeting these criteria were termed 'non-inducible'.

Two groups of 6 inducible dogs were randomly allocated to receive increasing intravenous doses of UK-52046 or placebo. Drugs were administered at 5 min intervals until the arrhythmia was abolished, side effects became apparent or the dogs died (ventricular fibrillation (VF) in response to stimulation). Dogs with NS-VT were rechallenged every 5 min with the stimulus setting which had produced the arrhythmia. If stimulation failed to produce an arrhythmia after drug administration, the experiment was continued with further reductions in coupling intervals and only if the protocol was exhausted without the arrhythmia recurring was the dog deemed non-inducible. If a dog with S-VT reverted to sinus rhythm after drug, the protocol was continued as above. Any animal in an S-VT at the end of the experiment was converted to sinus rhythm by overdrive pacing.

PR intervals and QRS duration were calculated to the nearest 5 ms (paper speed 10 $cm\,s^{-1}$) before and after each treatment. QT intervals were measured and the QT_c calculated using the formula: $QT_c = QT\sqrt{RR}$ (Bazett, 1920). The effective refractory period (ERP) was taken as the shortest inter-stimulus interval (to the nearest 5 ms) that produced a ventricular response. The functional refractory period (FRP) was estimated from the shortest inter-response interval measured during the pacing protocol. Blood pressure was monitored continuously throughout the duration of the experiments and heart rate was recorded before and after each treatment.

With both the ouabain arrhythmia and the arrhythmia occurring 24 h after CAL, the ventricular rate was obtained by counting the number of sinus and ectopic beats in each successive 5 min period. For the 2 adrenaline-induced arrhythmia models, the ectopic response was determined by counting the total number of ventricular beats in the 5 min period following the test dose of adrenaline. In the acute ischaemic model, the total number of ventricular beats were counted for a 30 min period following the onset of ischaemia. In all cases, sinus beats were defined before the production of the arrhythmia. Beats with a distinct P wave preceding a mean frontal QRS vector of normal duration were defined as being of sinus origin; all others were denoted as ectopic.

Drugs

The following were used: halothane (May and Baker); (±)-adrenaline injection B.P. (Antigen Ltd); ouabain octahydrate (Sigma Ltd); UK-52046 [4-amino-6,7-dimethoxy-2-(6,7-dimethoxy-1,2,3,4-tetrahydroisiquinolin-2-yl)quinolin hydrochloride] was available as the methane sulphonate, mol. wt. 490 (Pfizer Laboratories Ltd); atenolol (Stuart Pharmaceuticals Ltd).

Statistics

All results for the ouabain-induced arrhythmias, the arrhythmia 24 h after CAL and the 2 adrenaline-induced models are expressed as mean ± s.e.mean. All statistical analyeses employed in these models used Student's *t* test for paired data.

Analysis of the arrhythmias of acute myocardial ischaemia were performed by comparing the total number of ectopic beats for each drug group with placebo using the non-parametric Mann-Whitney U test. Changes in blood pressure were studied by one-way analysis of variance with the method of contrasts used to compare each group with placebo. Results of the effects of UK-52046 on the arrhythmias produced by programmed electrical stimulation (PES) were ranked for abolition of arrhythmia, no change, or death, and compared by the Mann-Whitney U test. ECG parameters and changes in blood pressure and heart rate were compared by Student's *t* tests. In all cases, significance was determined at the 5% and 1% levels.

Results

Ouabain-induced arrhythmias

Observations were made in 2 groups of 6 dogs in which the intravenous administration of ouabain had produced a rapid multifocal ventricular tachycardia. The required doses of ouabain ($65.8 \pm 7.4\,\mu g\,kg^{-1}$ and $68.3 \pm 4.2\,\mu g\,kg^{-1}$ for the UK-52046 and atenolol groups respectively) were similar to those of a previous study which established that, with this protocol, arrhythmias persist for more than 2 h (Allen et al., 1971). After the

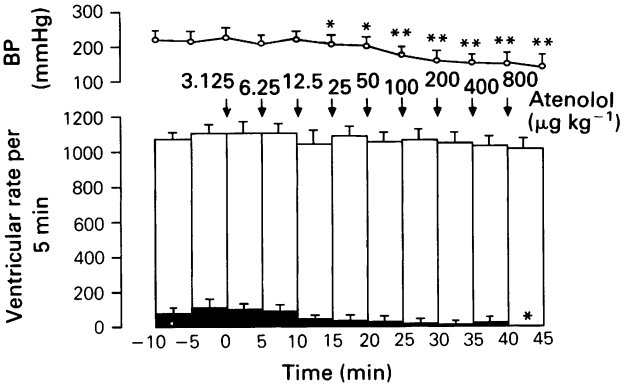

Figure 1 Effects of the intravenous administration of atenolol on the ouabain-induced arrhythmias in a group of 6 anaesthetized dogs. The histograms show the ventricular rate (open columns) and number of sinus beats (shaded) for each 5 min period. Values are expressed as mean with s.e.mean shown by vertical bars. BP, mean systolic blood pressure. * $P < 0.05$; ** $P < 0.01$.

arrhythmia had been established for 10 min, drugs were administered intravenously in increasing doses at intervals of 5 min.

The administration of up to 64 $\mu g\,kg^{-1}$ of UK-52046 had no effect upon the number of ectopic beats in each 5 min period. Mean systolic pressure fell from an initial 295.0 ± 27.0 to 198.0 ± 31.3 mmHg after 2.0 $\mu g\,kg^{-1}$ ($P < 0.05$) and after 32 $\mu g\,kg^{-1}$ of UK-52046 to 110.0 ± 9.1 mmHg ($P < 0.01$).

The effects of atenolol are summarised in Figure 1. It can be seen that the administration of up to 400 $\mu g\,kg^{-1}$ of drug had no effect upon the number of sinus beats in each 5 min period; after 800 $\mu g\,kg^{-1}$ the number of sinus beats fell ($P < 0.05$). Mean systolic pressure fell from an initial 220.0 ± 14.8 to 193.3 ± 18.7 mmHg after 12.5 $\mu g\,kg^{-1}$ of atenolol ($P < 0.05$) and after 800 $\mu g\,kg^{-1}$ to 140.0 ± 25.0 mmHg ($P < 0.01$).

Halothane-adrenaline arrhythmias

Observations were made in 3 groups of 6 anaesthetized dogs. The mean dose of adrenaline required to produce an arrhythmia in each group was 4.3 ± 0.7 $\mu g\,kg^{-1}$ (UK-52046), 4.0 ± 0.9 $\mu g\,kg^{-1}$ (atenolol) and 7.6 ± 0.7 $\mu g\,kg^{-1}$ (combination).

In the UK-52046 group, the mean number of ectopic beats after the test dose of adrenaline was 52.2 ± 6.6. After 0.25 $\mu g\,kg^{-1}$ of drug this had fallen to 28.8 ± 7.7 ($P < 0.05$). The arrhythmia was prevented by a mean dose of 3.8 ± 1.4 $\mu g\,kg^{-1}$ of UK-52046 (Figure 2).

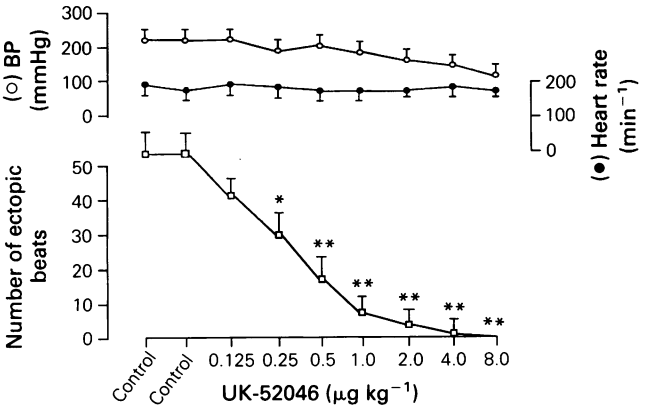

Figure 2 Effects of the intravenous administration of UK-52046 on the halothane-adrenaline arrhythmia in a group of 6 anaesthetized dogs. Dose of adrenaline required to produce the arrhythmia was 4.3 ± 0.7 $\mu g\,kg^{-1}$. All values expressed as mean with s.e.mean shown by vertical bars. BP, mean systolic blood pressure. * $P < 0.05$; ** $P < 0.01$.

Table 1 Arterial pressure and heart rate during the halothane-adrenaline arrhythmia recorded before the test dose of adrenaline, at peak response and at the onset of the arrhythmia

	Before adrenaline	*At peak response*	*At onset of arrhythmia*
Drug	*Mean systolic pressure* (mmHg)		
Control arrhythmia			
UK-52046	216.7 ± 29.2	**304.2 ± 34.9	**242.5 ± 30.2
Atenolol	211.7 ± 21.1	**288.3 ± 19.1	**255.8 ± 16.0
Combination	145.8 ± 18.0	**318.3 ± 24.1	**235.8 ± 29.4
Protected arrhythmia			
UK-52046	169.2 ± 28.1	177.5 ± 27.4	
Atenolol	157.5 ± 14.2	**200.0 ± 12.9	
Combination	135.0 ± 18.4	**245.0 ± 14.3	
	Heart rate (beats min^{-1})		
Control arrhythmia			
UK-52046	171.0 ± 9.2	178.7 ± 4.2	187.3 ± 6.4
Atenolol	168.8 ± 7.5	*183.0 ± 8.2	*183.0 ± 7.2
Combination	153.3 ± 6.8	*199.0 ± 5.5	*191.7 ± 5.2
Protected arrhythmia			
UK-52046	168.3 ± 10.0	172.0 ± 6.7	
Atenolol	145.0 ± 3.9	*154.0 ± 3.7	
Combination	150.3 ± 10.8	173.0 ± 8.4	

Values are mean ± s.e.mean.
Values are given for responses before the various treatments (control arrhythmia) and after preventative doses of drug(s).
* $P < 0.05$; ** $P < 0.01$ (compared with values before adrenaline).

The test dose of adrenaline produced a significant increase in blood pressure before the onset of the arrhythmia, with the peak occurring shortly after the start of the arrhythmia. With doses of UK-52046 which prevented the arrhythmia, the pressor response to adrenaline was significantly reduced when compared with the control arrhythmia (Table 1). Initial blood pressure (before the administration of adrenaline) was reduced compared with control values (169.2 ± 28.1 and 216.7 ± 29.2 mmHg respectively), but the difference did not reach statistical significance. No change in heart rate was observed as the result of UK-52046 in doses up to 8 $\mu g\,kg^{-1}$ (Figure 2).

In the atenolol group the mean number of ectopic beats after the test dose of adrenaline was 32.0 ± 5.2. This fell ($P < 0.01$) after 6.25 $\mu g\,kg^{-1}$ of drug and arrhythmia was prevented by a mean dose of 14.6 ± 2.1 $\mu g\,kg^{-1}$ of atenolol. Doses of atenolol that prevented the arrhythmia were associated with a fall in blood pressure, but this was not significant and the pressor response to adrenaline was maintained (Table 1). Atenolol at doses of 12.5 $\mu g\,kg^{-1}$ and 25 $\mu g\,kg^{-1}$ produced significant reductions in heart rate compared with placebo (147.0 ± 4.1, 142.0 ± 3.7 and 168.8 ± 7.5 per min respectively), but the adrenaline-induced increase in heart rate seen in the control arrhythmia was maintained in the protected arrhythmia (Table 1).

In the group which was given a combination containing equal amounts of UK-52046 and atenolol the mean number of ectopic beats in the control arrhythmia was 97.8 ± 17.1. This fell ($P < 0.05$) after 0.25 $\mu g\,kg^{-1}$ of each drug and was prevented after a mean dose of 0.36 ± 0.1 $\mu g\,kg^{-1}$ of each (Figure 3). The pressor response to adrenaline was maintained at doses which prevented the arrhythmia. The combination in doses of up to 1.0 $\mu g\,kg^{-1}$ of each drug had no effect on heart rate but the adrenaline-induced increase in heart rate was attenuated in the protected arrhythmia (Table 1).

Arrhythmia occurring 24 h after coronary artery ligation

Observations were made in 2 groups of 6 conscious dogs, 24 h after experimental coronary artery ligation. The number of sinus beats varied among dogs during the control period but was never greater than 20%.

The effects of UK-52046 are summarised in Figure 4. After 16 and 32 $\mu g\,kg^{-1}$ of drug the number of sinus beats in each 5 min period had increased from a control value of 137.7 ± 47.0 to 586.0 ± 128.9 and 662.3 ± 99.1 respectively ($P < 0.01$). These 2 doses of UK-52046 were also associated with a fall ($P < 0.05$) in the total ventricular rate. Blood pressure fell ($P < 0.05$) with doses of 8 $\mu g\,kg^{-1}$ and above.

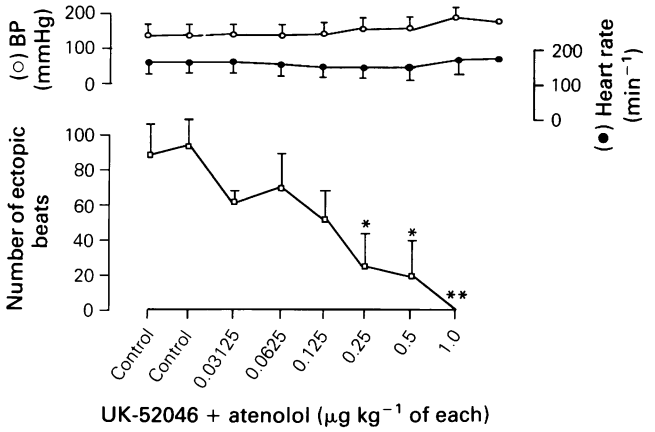

Figure 3 Effects of the intravenous administration of a combination of equal parts of UK-52046 and atenolol on the halothane-adrenaline arrhythmia in a group of 6 anaesthetized dogs. Mean dose of adrenaline required to produce the arrhythmia was $7.7 \pm 0.7\,\mu g\,kg^{-1}$. BP, mean systolic blood pressure. * $P < 0.05$; ** $P < 0.01$.

Atenolol in doses of up to $800\,\mu g\,kg^{-1}$ had no effect upon the same arrhythmia in a second group of 6 conscious dogs. Blood pressure did not vary during the course of the experiment.

Adrenaline-induced arrhythmias 3–5 days after coronary artery ligation

Observations were made in 3 groups of 6 conscious dogs. The dogs were studied 72 h after coronary artery ligation but only included if an initial 15 min ECG recording showed no evidence of arrhythmia. If any ectopy was observed the experiment was delayed a further 24 h. Any dog not in total sinus rhythm at 120 h was excluded from the study. The mean dose of adrenaline required to produce an arrhythmia in each group was $15.0 \pm 2.2\,\mu g\,kg^{-1}$ (UK-52046), $15.0 \pm 2.2\,\mu g\,kg^{-1}$ (atenolol) and $18.3 \pm 4.0\,\mu g\,kg^{-1}$ (combination). In the UK-52046 group the mean number of ectopics after the test dose of adrenaline was 267.5 ± 33.4; a significant reduction was apparent after $0.25\,\mu g\,kg^{-1}$ of UK-52046 (128.0 ± 24.5, $P < 0.01$) and the arrhythmia was prevented in 6/6 dogs with a mean dose of $3.7 \pm 1.4\,\mu g\,kg^{-1}$ (Figure 5). There was no significant change in blood pressure although the pressor response to adrenaline was reduced from 153.7 ± 26.5 mmHg in the control arrhythmia to 58.7 ± 4.3 mmHg in the protected state ($P < 0.05$). Compared with the control period, heart rate increased ($P < 0.01$) after $1\,\mu g\,kg^{-1}$ of drug (117.7 ± 10.4 and 138.3 ± 10.6 beats per min respectively). After $8\,\mu g\,kg^{-1}$ this had further increased to 157.0 ± 7.0 per min.

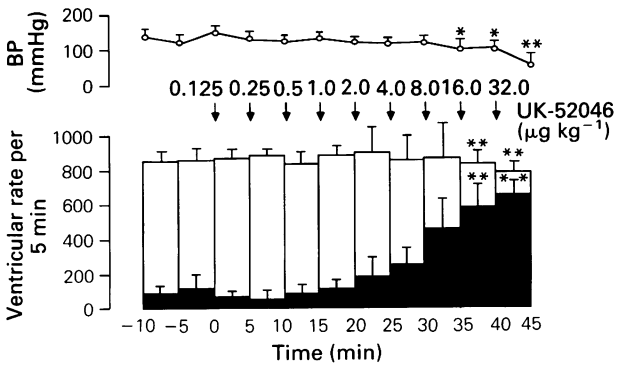

Figure 4 Effects of the intravenous administration of UK-52046 upon the ventricular arrhythmia occurring 24 h after experimental coronary artery ligation. The histograms show the ventricular rate (open columns) and number of sinus beats (shaded) for each 5 min period. Values expressed as mean with s.e.mean shown by vertical bars. BP, mean systolic blood pressure. * $P < 0.05$; ** $P < 0.001$.

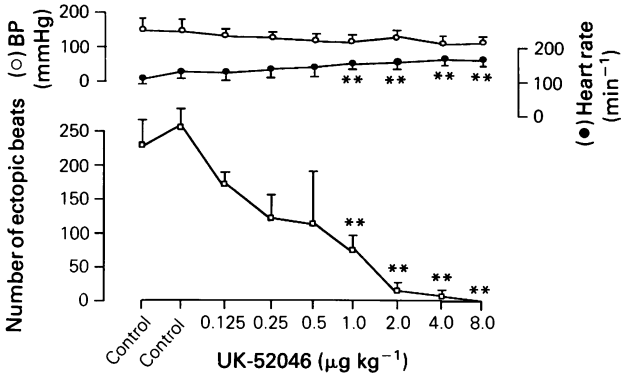

Figure 5 Effects of the intravenous administration of UK-52046 upon the adrenaline-induced arrhythmia in a group of 6 dogs, 3–5 days after coronary artery ligation. Required dose of adrenaline was $15.0 \pm 2.2\,\mu g\,kg^{-1}$. Values expressed as mean with s.e.mean shown by vertical bars. BP, mean systolic blood pressure. ** $P < 0.01$.

The results for the atenolol group are summarised in Figure 6. The mean number of ectopic beats after adrenaline was 277.5 ± 91.2; after $100\,\mu g\,kg^{-1}$ of atenolol this had fallen to 31.3 ± 17.2, representing an 84.4% reduction ($P < 0.01$). Further increases in doses of atenolol were prevented by agitation that occurred in all dogs under study. There was no change in blood pressure and the pressor response to adrenaline, although attenuated compared with control values, was still significant (140 ± 11.9 mmHg and 173 ± 133.5 mmHg respectively).

In the group studied with a combination of UK-52046 and atenolol, the mean number of ectopic beats after adrenaline was 140.5 ± 31.5. The arrhythmia was prevented in 6/6 dogs with a mean dose of $3.7 \pm 1.1\,\mu g\,kg^{-1}$ of each drug. With the arrhythmia protected, the pressor response to adrenaline was not significantly reduced and overall blood pressure did not change. However, as with the UK-52046 group, heart rate increased ($P < 0.01$) after $2\,\mu g\,kg^{-1}$ reaching a maximum of 146.3 ± 6.8 beats min^{-1} after the final dose ($P < 0.01$ compared with control value of 104.8 ± 8.7 per min).

Arrhythmias of acute coronary ischaemia

A total of 24 dogs were studied. The median number of ventricular ectopic beats for 12 dogs which received placebo was 190 (range 4-674), with peaks at 5–10 min and 25–30 min (Table 2). The corresponding value for the group that received UK-

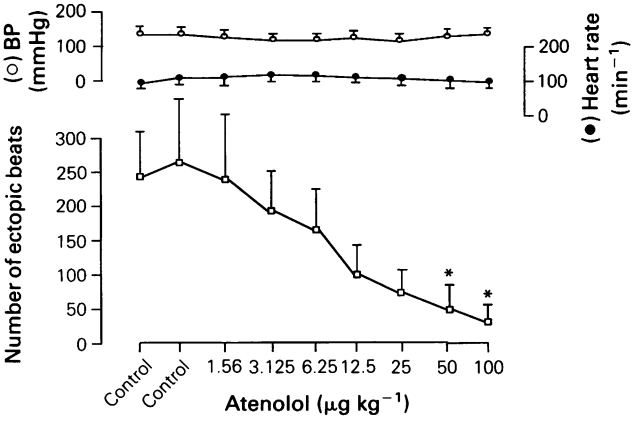

Figure 6 Effects of the intravenous administration of atenolol upon the adrenaline-induced arrhythmia in a group of 6 dogs, 3–5 days after coronary artery ligation. Required dose of adrenaline was $15.0 \pm 2.2\,\mu g\,kg^{-1}$. Values expressed as mean with s.e.mean shown by vertical bars. BP, mean systolic blood pressure. * $P < 0.05$.

Table 2 Number of ventricular ectopic beats and mean systolic blood pressures in response to acute coronary ischaemia in 3 groups of anaesthetized dogs

Number of ectopic beats

Drug	n	*Time following coronary artery ligation* (min) 0–5	5–10	10–15	15–20	20–25	25–30	*Median No.* (range)
Placebo	12	14.7 ± 8.8	47.2 ± 31.5	12.1 ± 8.3	25.7 ± 18.8	101.2 ± 37.7	56.2 ± 13.9	190 (4–674)
UK-52046 4 $\mu g\,kg^{-1}$	6	3.1 ± 1.9	41.3 ± 38.9	5.5 ± 5.1	1.8 ± 1.8	244.6 ± 131.2	123.2 ± 59.8	246 (9–1204)
UK-52046 8 $\mu g\,kg^{-1}$	6	5.8 ± 5.8	6.3 ± 5.2	7.6 ± 5.7	9.6 ± 7.2	7.5 ± 6.3	4.8 ± 3.0	12 (1–154)

Systolic blood pressure

Drug	n	*Before drug*	*Time following coronary artery ligation* (min) 0	5	10	15	20	25	30
Placebo	12	75.9 ± 8.3	82.1 ± 7.7	90.0 ± 7.9	91.7 ± 6.6	90.4 ± 6.2	91.8 ± 5.4	90.0 ± 4.9	88.8 ± 4.9
UK-52046 4 $\mu g\,kg^{-1}$	6	74.2 ± 12.2	65.8 ± 6.6	64.2 ± 6.4*	65.0 ± 7.4*	67.5 ± 7.4*	65.8 ± 6.5*	64.0 ± 8.0*	69.1 ± 8.3
UK-52046 8 $\mu g\,kg^{-1}$	6	80.0 ± 6.8	54.2 ± 7.5*	52.5 ± 6.7**	50.0 ± 5.0**	57.5 ± 12.7**	58.5 ± 12.1*	65.0 ± 10.7*	64.0 ± 10.4*

Coronary artery ligation was performed 5 min after administration of placebo ($n = 12$), UK-52046 4 $\mu g\,kg^{-1}$ ($n = 6$) or UK-52046 8 $\mu g\,kg^{-1}$ ($n = 6$).
* $P < 0.05$; ** $P < 0.01$.

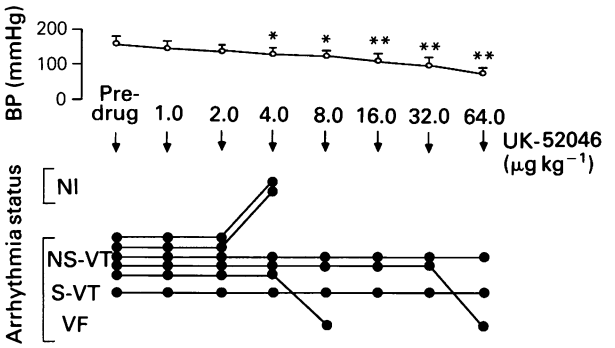

Figure 7 Effects of UK-52046 upon the arrhythmias produced by programmed electrical stimulation in 6 conscious dogs, 7–30 days after experimental coronary artery ligation. NI, non-inducible; NS-VT, non-sustained ventricular tachycardia; S-VT, sustained ventricular tachycardia; VF, ventricular fibrillation. * $P < 0.05$; ** $P < 0.01$.

52046, 4 $\mu g\,kg^{-1}$, was 246 (9–1204), again with a biphasic distribution (Table 2). In the group that received UK-52046, 8 $\mu g\,kg^{-1}$, the number of ectopic beats was significantly reduced with a median of 12 (1–154). Mean initial systolic for the 3 groups were respectively 75.9 ± 8.3 mmHg (placebo), 74.2 ± 12.2 (UK-52046, 4 $\mu g\,kg^{-1}$) and 80.8 ± 6.7 mmHg (UK-52046, 8 $\mu g\,kg^{-1}$) (difference not statistically significant). However, both 4 $\mu g\,kg^{-1}$ and 8 $\mu g\,kg^{-1}$ of drug produced significant falls in systolic pressure which persisted throughout the duration of the experiments (Table 2).

Arrhythmias induced by programmed electrical stimulation

For the 6 dogs in the placebo group, programmed stimulation resulted in a reproducible NS-VT in 5 dogs and a sustained VT in one dog prior to treatment. Of the dogs with NS-VT, 3 remained inducible when stimulated after each of the 7 doses of placebo. The other 2 developed VF when stimulated 5 min after the first dose of placebo. The dog with S-VT remained in this arrhythmia throughout the duration of the experiment.

The effects of UK-52046 are summarised in Figure 7. In this group 5/6 dogs had a NS-VT and one was in an S-VT prior to treatment. Of the 5 with NS-VT, 2 became non-inducible after 4.0 $\mu g\,kg^{-1}$ of drug, one remained unchanged and 2 died when stimulated after 8 $\mu g\,kg^{-1}$ and 64 $\mu g\,kg^{-1}$ respectively. The dog with S-VT remained in this arrhythmia throughout. Statistical analysis indicated that, when compared with placebo, UK-52046 did not exhibit significant antiarrhythmic activity ($P = 0.29$). Mean initial systolic pressure for the dogs receiving UK-52046 was 171 ± 5.6 mmHg. After 4 $\mu g\,kg^{-1}$, this had fallen to 136 ± 13.6 mmHg ($P < 0.05$ compared with pretreatment and placebo); further falls were apparent with increasing doses of drug (Figure 7). Heart rate rose from an initial 95.8 ± 7.5 per min to 116.7 ± 5.9 per min (difference not statistically significant).

Electrophysiological measurements

The effects of placebo and UK-52046 upon the PR interval, QRS duration, QT_c and refractory periods are summarised in Table 3. Mean PR for the 6 dogs before placebo was 0.11 s; after placebo this had increased to 0.115 s, but the change was not statistically significant. Similarly, no differences

Table 3 Effects of placebo and UK-52046 on the corrected QT interval (QT_c), QRS duration (QRS), PR interval (PR) and effective (ERP) and functional (FRP) refractory periods in 2 groups of 6 dogs

Placebo *Parameter*	*Before drug*	*After drug*
QT_c	0.30 ± 0.01	0.31 ± 0.02
QRS	0.08 ± 0.005	0.085 ± 0.005
PR	0.011 ± 0.005	0.115 ± 0.005
ERP	0.105 ± 0.005	0.11 ± 0.005
FRP	0.105 ± 0.005	0.11 ± 0.01
UK-52046 *Parameter*	*Before drug*	*After drug*
QT_c	0.26 ± 0.02	0.295 ± 0.01
QRS	0.07 ± 0.005	0.075 ± 0.005
PR	0.011 ± 0.005	0.10 ± 0.005
ERP	0.125 ± 0.005	0.12 ± 0.005
FRP	0.18 ± 0.005	0.175 ± 0.01

All results in seconds (mean ± s.e.mean).

occurred for the mean QRS (0.08–0.085 s), mean QT_c (0.30–0.31 s), mean ERP (0.105–0.11 s) or mean FRP (0.165–0.17 s) after administration of placebo. The pretreatment figures for the placebo group were not statistically different from the corresponding values for the 6 dogs, receiving UK-52046, nor was any change observed as the result of drug therapy (Table 3).

Discussion

Ouabain increases ventricular automaticity and this appears to be the mechanism for the arrhythmia seen after toxic doses of the drug (Vassalle *et al.*, 1963; Rosen *et al.*, 1973). The pacemaker site is usually located in a left bundle branch or the Purkinje fibre network (Damato *et al.*, 1971). It has been suggested that the arrhythmia may be due in part to catecholamine release (Roberts *et al.*, 1963), but although early studies with pronethalol had demonstrated antiarrhythmic efficacy in the ouabain model (Vaughan Williams & Sekiya, 1963), subsequent work by Lucchesi (1965) indicated that this antiarrhythmic effect was not related to pronethalol's β-blocking properties. Pronethalol in conjunction with the class 1 antiarrhythmic agents has significant membrane-stabilizing properties and it is this action that accounts for its antiarrhythmic activity in the ouabain model (Somani & Lum, 1965). Indeed more recent studies with β-adrenoceptor antagonists devoid of class 1 activity have shown an exacerbation of the ouabain arrhythmia (Alkondon *et al.*, 1984). Our results with atenolol (β_1-adrenoceptor antagonist with no membrane-stabilizing properties) confirm these findings. Results in the present study would also indicate a lack of significant class 1 activity for UK-52046.

It is well established that adrenaline increases the rate of spontaneous depolarization in normal tissues and that this effect may be potentiated by prior exposure of the tissue to anaesthetic agents (Davis *et al.*, 1969). The mechanisms by which these agents, and halothane in particular, sensitize the heart remain unclear; *in vitro* experiments have demonstrated a direct effect on myocardial cells (Miletich *et al.*, 1983) but others have suggested that sensitization may be related to an initial slowing of the sinus rate by halothane (Hashimoto & Hashimoto, 1972). Adrenaline exerts its effects by binding to postsynaptic adrenoceptors on the myocardial cells. Since most of these receptors are β in nature, it was for many years assumed that it was this receptor type that accounted for the arrhythmogenicity of adrenaline. However, in a recent study investigating the effects of prazosin and metoprolol in this model, it was discovered that β_1-blockade by metoprolol was significantly less effective than α_1-blockade afforded by prazosin (Maze & Smith, 1983), nor was the effect of prazosin related to haemodynamic changes as sodium nitroprusside was found to be ineffective in abolishing the arrhythmia despite producing a similar fall in blood pressure. The present study demonstrated significant antiarrhythmic effects with both UK-52046 ($3.8 \pm 1.4\,\mu g\,kg^{-1}$) and atenolol ($14.6 \pm 2.1\,\mu g\,kg^{-1}$) in this model. Furthermore, when used in combination the two drugs appear synergistic (dose of each $0.36 \pm 0.1\,\mu g\,kg^{-1}$), supporting previous studies, showing potentiation of antiarrhythmic activity with combined α- and β-adrenoceptor antagonists in the halothane-adrenaline model (Maze & Smith, 1983).

Two-stage coronary artery ligation produces a high incidence of ventricular arrhythmias which reach a peak after 22–24 h (Harris, 1950). The arrhythmias are generally thought to subside after 48 h, but our experience in the present studies is that ectopic activity may last for up to 4 days. The focus of these arrhythmias is thought to arise in surviving Purkinje fibres on the endocardial surface of the infarct (Friedman *et al.*, 1973). Effectiveness of drugs in abolishing this arrhythmia has been thought to depend on class 1 antiarrhythmic activity (Allen & Shanks, 1974) and explains the ineffectiveness of atenolol in the present study. Early studies with nonspecific α-adrenoceptor antagonists showed little effect on this particular arrhythmia (Maling *et al.*, 1959), but more recent investigations with prazosin on isolated papillary muscle and Purkinje fibre preparations have shown a depression in the maximal upstroke velocity and a dose-dependent prolongation of action potential duration (Dukes & Vaughan Williams, 1984). Although we do not have any supporting microelectrode data for UK-52046, it is possible that the drug may share some of these electrophysiological effects and possess sufficient class 1 activity to suppress the '24 hour' arrhythmia while at the same time being unable to influence the ouabain-induced arrhythmia.

Although there is no evidence that sympathetic factors play a role in the ventricular arrhythmias 24 h after coronary artery ligation, the infarcted heart is more sensitive to the arrhythmogenic effects of adrenaline for several days after ligation (Maling & Moran, 1957). This is the basis for the adrenaline-induced arrhythmia in the conscious dog, 3–5 days after coronary ligation. The induction of the arrhythmia is thought to depend on a combination of direct myocardial stimulation, an increase in blood pressure and depression of sinus node function (Maling & Moran, 1957). In this respect, the model may be considered similar to the halothane-adrenaline arrhythmia where direct sinus slowing may be pro-

duced by halothane. One major difference, however, is the presence of intact autonomic reflexes in the conscious model after coronary artery ligation. These reflexes may be responsible for the increases in heart rate seen with UK-52046 and the combination of UK-52046 with atenolol, by mediating a tachycardia in response to a fall in resting blood pressure. The fact that antiarrhythmic doses of UK-52046 were associated with attenuation of the pressor response in both this and the halothane-sensitized model serves to emphasize the importance of a rise in blood pressure in the genesis of both arrhythmia models. In the present study we have demonstrated that while atenolol ($100\,\mu g\,kg^{-1}$) can significantly reduce ectopic response (84%) to adrenaline, it is less effective than UK-52046 where a dose of $3.7 \pm 1.4\,\mu g\,kg^{-1}$ prevented the arrhythmia in 6/6 dogs. The combination of both drugs was no better than UK-52046 alone. Whilst these results are at variance with the synergy observed in the halothane-adrenaline model, they confirm an enhanced role for α-adrenoceptors following myocardial infarction (Sheridan *et al.*, 1980).

Unlike the automaticity nature of the arrhythmia occurring 24 h after coronary artery ligation, the early arrhythmias of acute coronary ischaemia have been shown to depend on a re-entrant basis arising from epicardial delay in the ischaemic zone (Scherlag *et al.*, 1974). Further analysis of these early arrhythmias has demonstrated two periods of maximal arrhythmic activity. The immediate ventricular arrhythmias (IVA, or 1a) occur from 2–10 min after ligation and the delayed ventricular arrhythmias (DVA, or 1b) from 12–30 min (Kaplinsky *et al.*, 1979). Previous studies have emphasized the role of both endogenous and neurogenic catecholamines in the genesis of the acute arrhythmias (Ebert *et al.*, 1970) and our results confirm that the α_1-adrenoceptor antagonist UK-52046 is effective in the model employed. This is in agreement with similar studies with alternative α-antagonists in the dog (Benfey *et al.*, 1984), the guinea-pig (Penny & Sheridan, 1982), the cat (Sheridan *et al.*, 1980; Davey, 1981) and the pig (Benfey *et al.*, 1984). It would also appear that the protective effect of the agents used in these experiments is independent of any changes in regional myocardial blood flow (Davey, 1981), or any other non-specific actions of the drugs (Sheridan *et al.*, 1980).

Programmed electrical stimulation in the chronic canine model provides the opportunity to study the effects of antiarrhythmic drugs on reproducible arrhythmias which have been shown to share the same re-entrant mechanisms that are responsible for sudden death in man (El Sherif *et al.*, 1977; Josephson *et al.*, 1978). The pharmacological requirements for drug efficacy in such models remain unclear, but recent studies from this laboratory have demonstrated signficant antiarrhythmic protection with R-tocainide (Uprichard *et al.*, 1988) and atenolol (Uprichard & Harron, 1988). The present study failed to demonstrate significant antiarrhythmic effects with UK-52046 and are similar to those of Wilber and co-workers (1987) who demonstrated no protection against the arrhythmias of programmed electrical stimulation in conscious dogs dosed with prazosin. In the same study, however, prazosin afforded significant protection against the arrhythmias of acute ischaemia, in this case ischaemia produced by the introduction of a 150 μA current to the left circumflex coronary artery. The administration of UK-52046 during programmed stimulation in a chronic model was not associated with any alterations in electrocardiographic parameters or refractory periods, suggesting that the potential of the drug against re-entrant arrhythmias may be operative only at the time of acute ischaemia, either by a direct (as yet unidentified) electrophysiological action or by antagonism of the deleterious influence of α_1-stimulation.

The present studies have demonstrated significant haemodynamic effects as the result of UK-52046 administration. In some of the models such changes occurred only at doses exceeding those at which antiarrhythmic effects were apparent, but it does appear that the cardioselectivity of UK-52046 is a relative phenomenon.

In conclusion, UK-52046 is effective against the arrhythmias occurring 24 h after experimental coronary artery ligation. It is equally effective in preventing adrenaline-induced arrhythmias in the halothane-sensitized model and following coronary artery ligation. Atenolol has no effect on the arrhythmia 24 h after coronary artery ligation and is less effective in arrhythmias induced by adrenaline after coronary artery ligation than in the halothane-sensitized model. A combination of the two drugs is synergistic in the halothane-adrenaline model but after coronary artery ligation the combination appears no better than UK-52046 alone. UK-52046 is effective against the re-entrant arrhythmias of acute coronary ischaemia in anaesthetized dogs, but is less effective against similar arrhythmias when generated by programmed electrical stimulation in the conscious state. In several of the models studied there occurred haemodynamic changes in keeping with peripheral α-adrenoceptor antagonism. These results confirm an important role for α-adrenoceptors following myocardial ischaemia and infarction and suggest that α_1-receptor antagonists may prove to be valuable antiarrhythmic agents.

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All studies described were carried out as far as possible in accordance with the Lambeth Conventions.

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