The antiarrhythmic efficacy of intravenous anipamil against occlusion and reperfusion arrhythmias

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1 Anipamil, a long acting analogue of verapamil, was tested for its actions against arrhythmias induced by ischaemia and reperfusion in conscious and anaesthetized rats, as well as for effects on epicardial intracellular action potentials.

2 When given 15 min or 4 h before coronary occlusion, 1 and 5 mg kg⁻¹ anipamil reduced ischaemia-induced arrhythmias in conscious rats. The same doses also reduced arrhythmias when given 15 min before occlusion in acutely-prepared anaesthetized rats. ED₅₀ values were between 1 and 5 mg kg⁻¹.

3 The incidence of reperfusion arrhythmias depended upon the period of regional ischaemia prior to reperfusion such that the peak incidence occurred after 5–7 min of ischaemia. Anipamil (2.5 mg kg⁻¹, i.v.) selectively abolished the reperfusion arrhythmias induced by short periods of ischaemia, although some antiarrhythmic effects were seen for all periods of ischaemia.

4 Anipamil slowed the rate of development of R-wave increases and S-T segment elevations induced by ischaemia, but did not reduce the maximum values they attained.

5 Anipamil (2.5 mg kg⁻¹ i.v.) lacked Class I or III electrophysiological actions on intracellular action potentials recorded *in vivo* from the epicardium of rat hearts.

6 In conclusion, the antiarrhythmic actions of anipamil appeared to depend upon calcium antagonism which may have reduced arrhythmias by a combination of anti-ischaemic and direct antiarrhythmic actions. Presumed anti-ischaemic actions changed the relationship between the duration of preceding ischaemia and resulting reperfusion arrhythmias.

Introduction

In a series of experiments (Curtis *et al.*, 1984; 1985; Curtis & Walker, 1986; 1988) we demonstrated that calcium antagonists have antiarrhythmic actions against arrhythmias induced in conscious rats by occlusion of a coronary artery. Both the racemate and enantiomers of verapamil were active with a potency order of (–) > (±) > (+) (Curtis & Walker, 1986; Au *et al.*, 1987). Two analogues of verapamil were also tested in the same model. Only anipamil, a long acting calcium antagonist (Dillon & Nayler, 1988) with cardiovascular actions, had antiarrhythmic activity when given orally (Curtis & Walker, 1986). In addition to antiarrhythmic actions, calcium antagonists also slowed the rate at which ischaemia-induced changes appeared on the ECG. In view of the above, further experiments were performed to investigate the antiarrhythmic efficacy of anipamil administered i.v., and to determine whether

the putative anti-ischaemic actions (Gries & Raschack, 1984; Raschack, 1984; Curtis & Walker, 1986) of anipamil influenced either ischaemia-induced or reperfusion arrhythmias.

In rat hearts, abrupt resumption of coronary flow after regional ischaemia lasting 2–20 min is associated with a burst of arrhythmias (Manning & Hearse, 1984; Curtis *et al.*, 1987; Curtis & Hearse, 1989). Such arrhythmias have been investigated in many species (Balke *et al.*, 1981; Dennis *et al.*, 1983; Benfey *et al.*, 1984) and in each species a characteristic period of ischaemia results in the maximum number of reperfusion arrhythmias. The period of ischaemia necessary for maximum reperfusion arrhythmias is longer in larger species (Berger *et al.*, 1982). The actions of drugs against reperfusion arrhythmias have been investigated despite difficulties in differentiating between drugs which are antiarrhythmic by virtue of anti-ischaemic actions, and those which act directly.

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In this study anipamil, a drug which appears to have anti-ischaemic as well as direct antiarrhythmic actions, was used to try to differentiate between primary and secondary antiarrhythmic actions. A secondary antiarrhythmic effect due to anti-ischaemic actions would be expected to reduce ischaemia-induced arrhythmias in the early period of irreversible ischaemia, but not in later periods. Thus the total number of arrhythmias would not be reduced by anti-ischaemic actions while the rate at which they appeared following the onset of ischaemia would be delayed. On the other hand, a direct antiarrhythmic action would be expected to reduce arrhythmias in all time periods. When tested against reperfusion arrhythmias, an anti-ischaemic drug would be expected to extend the period of occlusion required for maximization of reperfusion arrhythmias, i.e. it would shift the time-effect curve for reperfusion arrhythmias in the direction of longer times.

In vivo electrophysiological analyses were also performed in this study to determine whether anipamil had Class I or III antiarrhythmic effects on intracellular potentials which would explain its antiarrhythmic actions.

Methods

Chronically prepared conscious rats subject to irreversible ischaemia

Anipamil (1 or 5 mg kg⁻¹ i.v.) was administered 15 min or 4 h before occlusion of the left anterior descending (LAD) coronary artery in conscious chronically prepared rats. The model has been previously described in detail (Johnston *et al.*, 1981; 1983) and uses male rats (250–300 g) surgically-prepared 7 days before occlusion. On the day of occlusion blood pressure and ECG were continuously recorded for 30 min before, and for 4 h after occlusion of the LAD coronary artery which was accomplished by traction on an implanted occluder. After 24 h of occlusion, animals were monitored for a further 30 min before they were killed and hearts perfused for estimation of occluded zone size by dye exclusion (Johnston *et al.*, 1983).

Acutely prepared anaesthetized rats subject to irreversible ischaemia

Anipamil (1 and 5 mg kg⁻¹ i.v.) was also given 15 min prior to occlusion in a series of rats acutely prepared and occluded in the manner we have previously described (Au *et al.*, 1979; 1983). These

rats were anaesthetized with pentobarbitone (50 mg kg⁻¹) i.p.

Chronically-prepared conscious rats subject to reperfusion

In a separate series of experiments in which rats were given 2.5 mg kg⁻¹ i.v. anipamil, the coronary artery occluder was rapidly released following a carefully timed period of ischaemia. The dose of 2.5 mg kg⁻¹ was chosen as the probable ED₅₀ for the antiarrhythmic actions of anipamil against ischaemia-induced arrhythmias, and because its use was not associated with excessive cardiovascular depression which might be expected to impair an animal's ability to withstand reperfusion. Ischaemia was maintained for 3, 5, 7, 10 or 20 min prior to the abrupt release of the occluder. The method used was somewhat similar to that described by Kinoshita *et al.* (1988), but with technical modifications (MacGeough, MacLeod, Moulton & Walker, unpublished observations). To ensure parity of reperfusion, a set of exclusion criteria was developed on the basis of initial experiments. These were: (1) Following initiation of ischaemia the characteristic ECG pattern of occlusion had to occur within 1 min. (2) Physical release of the occluder had to be rapid and complete such that initiation of reperfusion could be presumed to have occurred within 10 s. (3) Reperfusion had to induce a rapid return of the ECG toward normal, i.e., both elevated S-T segment and R-wave had to return rapidly towards normal. (4) After reperfusion, each animal had to have an occluded zone, defined by dye exclusion *in vitro*, which was 25–30% of total ventricular mass.

Exclusion criteria were applied blindly.

As in the experiments in which occlusion was maintained and not released, all animals undergoing non-spontaneously reversing ventricular fibrillation were subjected to manual defibrillation. This has been shown to be effective in reducing mortality in control animals from 80% to 30% or less (Johnston *et al.*, 1983; Curtis & Walker, 1986).

Anipamil (Knoll, Ludwigshafen, W. Germany) was solubilized in HCl acidified (pH 3.0) water at a temperature of 50–60°C. The volume of injection never exceeded 10 ml kg⁻¹ and all injections were made over a 3 min period. Control animals received an appropriate volume of acidified water. Altogether five different dose regimens of anipamil were used. These were: 1 mg kg⁻¹ either 15 min or 4 h before occlusion, 5 mg kg⁻¹ given in the same manner or 2.5 mg kg⁻¹ given 15 min before occlusion.

Electrophysiological experiments

The effects of anipamil on intracellular potentials recorded from the epicardial surface of intact rat

hearts were determined by a recently developed procedure (MacLeod & Walker, unpublished observations). This involved exposing the heart by means of a mid-line incision in pentobarbitone (50 mg kg^{-1} , i.p.)-anaesthetized rats. Under positive pressure ventilation the heart was suspended in a pericardial cradle and a section of the exposed epicardial surface of the left ventricle firmly sutured to a specially shaped Ag/AgCl₂ electrode holder. Conventional 'floating' fibre-filled 3 M glass electrode tips were used to record epicardial potentials before and at various times after administration of 2.5 mg kg^{-1} i.v. anipamil.

Experimental design and statistics

The experimental design was blind and random with the rigid application of exclusion criteria. In each animal, blood pressure, and ECG were recorded together with occluded zone. Arrhythmias in the 0–30 min and 30–240 min post-occlusion periods were recorded in animals subjected to permanent occlusion (Johnston *et al.*, 1981; 1983). In animals subjected to temporary occlusion and subsequent reperfusion, ischaemia-induced arrhythmias were recorded in the usual manner, whereas only the occurrence and not number or duration of each type of reperfusion arrhythmia was recorded.

Data analyses were by previously described statistical procedures (Johnston *et al.*, 1983). Altogether, 6 groups ($n = 9$ rats) of chronically-prepared conscious rats were subjected to irreversible occlusion; 2 control groups, 2 groups treated (1 or 5 mg kg^{-1} i.v. anipamil) 15 min before occlusion and a similar 2 groups treated 4 h before occlusion. In acutely-prepared anaesthetized animals, 3 groups ($n = 9$) were studied; a control group and 2 groups treated with 1 or 5 mg kg^{-1} i.v. anipamil 15 min before occlusion.

Ten groups ($n = 9$) were subjected to reperfusion. They consisted of 5 control groups and 5 groups treated with 2.5 mg kg^{-1} i.v. anipamil 15 min before occlusion. One control and one treated group was subjected to either 3, 5, 7, 10 or 20 min of ischaemia prior to reperfusion.

The data for each separate group of conscious rats subjected to irreversible ischaemia were initially analysed separately, but, where no statistically significant ($P < 0.05$) differences were found, treatment groups receiving the same dose, but at different times prior to occlusion, were combined to give a single group of 18 rats. Statistically significant differences were never found between the two control groups and so these were combined ($n = 18$). With reperfusion, groups could not be combined because of the dependency of reperfusion arrhythmias on the duration of the preceding ischaemic period.

Figure 1 The effects of anipamil on blood pressure (a) and heart rate (b) before and after permanent occlusion of the LAD coronary artery in conscious and anaesthetized rats. Each column is mean (s.e. mean shown by vertical bars) ($n = 6-9$) of blood pressure (mmHg) in (a) and heart rate (beats min^{-1}) in (b). The time periods for measurements were 1 min before occlusion (filled columns) and 4 h after occlusion (cross-hatched columns). Data were divided on the basis of when anipamil was given, i.e. either 15 min (e) or 4 h (l) before occlusion, and whether rats were chronically-prepared and conscious (C) or acutely-prepared and anaesthetized (A). Doses of (1) or (5) mg kg^{-1} i.v. were given 15 min or 4 h before occlusion in conscious animals or 15 min before occlusion in anaesthetized rats. * $P < 0.05$ from appropriate controls.

Results

Cardiovascular effects of anipamil and occlusion

As shown in Figure 1 (a and b) anipamil tended to cause a fall in blood pressure and heart rate, especially at the higher dose and in the presence of anaesthesia. The hypotensive effects of anipamil were prolonged for up to 8 h. Occlusion of the LAD produced further falls in blood pressure in both the control and treated groups. The fall in blood pressure after occlusion was due to the functional loss of myocardium due to the formation of ischaemic zones (occluded zones). The size of the occluded zones (as percentage by weight of total ventricular weight) was not altered by any of the treatments or by conditions (i.e., maintained ischaemia or reperfusion). Values for the various control groups varied between 31.7 ± 2.2

Table 1 Summary of the antiarrhythmic effects of anipamil in rats subjected to permanent occlusion of the LAD coronary artery

n	AS	VT	VF	Mortality	VPB	Treatment
A 0–30 min post-occlusion arrhythmias						
<i>Conscious animals</i>						
18	3.6 ± 0.5	17	15	0	1.9 ± 0.1	Control
18	3.4 ± 0.5	15	9*	1	1.9 ± 0.2	1 mg kg ⁻¹
18	2.0 ± 0.5*	12	4*	0	2.0 ± 0.2	5 mg kg ⁻¹
<i>Anaesthetized animals</i>						
9	4.1 ± 0.6	9	4	0	2.0 ± 0.2	Control
9	3.1 ± 0.3*	9	2	1	1.8 ± 0.2	1 mg kg ⁻¹
9	2.1 ± 0.3*	6	0*	3†	1.7 ± 0.2	5 mg kg ⁻¹
B 30–240 min post-occlusion arrhythmias						
<i>Conscious animals</i>						
18	3.6 ± 0.6	14	14	1	2.6 ± 0.6	Control
17	2.4 ± 0.6	9	6*	0	2.6 ± 0.6	1 mg kg ⁻¹
18	2.0 ± 0.6*	12	4*	0	2.5 ± 0.3	5 mg kg ⁻¹
<i>Anaesthetized animals</i>						
9	4.1 ± 0.6	9	4	2	3.0 ± 0.3	Control
8	0.4 ± 0.4*	1*	0*	0	0.8 ± 0.3*	1 mg kg ⁻¹
6	1.0 ± 0.6*	0*	0*	0	0.7 ± 0.2*	5 mg kg ⁻¹

The arrhythmias induced by ischaemia in the 0–30 min and 30–240 min periods of occlusion were recorded as the incidence in the group of animals having one or more episodes of ventricular tachycardia (VT), or ventricular fibrillation (VF) and as the number of ventricular premature beats (VPB) (expressed as log₁₀ of the number of VPBs in the observation period considered). The total arrhythmic history of each rat was summarized as an arrhythmia score (AS). Values are given either as number in group or $\bar{x} \pm \text{s.e.mean}$, of size = *n*. *P* < 0.05 when compared with the appropriate control. † All deaths in this group were due to cardiac output failure.

and 41.2 ± 1.5 ($\bar{x} \pm \text{s.e.mean}$). The values in the treated groups varied from 35.0 ± 2.2 to 42.6 ± 0.6 . Analysis of variance failed to show treatment to be a source of variance.

Antiarrhythmic effects

The overall antiarrhythmic effects of anipamil treatment on arrhythmias induced by permanent occlusion are summarized in Table 1. Anipamil dose-dependently reduced the incidence of severe arrhythmias such as ventricular tachycardia and particularly ventricular fibrillation, as well as arrhythmia scores which are overall summaries of an animal's arrhythmic history. There were no statistically significant reductions in the number of ventricular premature beats (VPB), except in anaesthetized animals. Antiarrhythmic effects of anipamil may have been more pronounced in such animals.

Since the ischaemic time-dependency of major tachy-arrhythmias gives insight as to possible mechanisms involved in antiarrhythmic drug action, the time-dependency curves for ischaemia-induced arrhythmias are shown in Figure 2. The data are plotted to show group incidences of major arrhythmias in each of the important time periods after occlusion (a) as well as their cumulative incidence (b). A selective reduction in incidence during the early

period of occlusion, but no change in the overall cumulative incidence, would be assumed to reflect underlying anti-ischaemic actions. A non-selective decrease in all time periods would reflect direct anti-arrhythmic actions. Anipamil had two effects. It reduced the cumulative incidence of major arrhythmias in all time periods but in addition was most effective against the arrhythmias occurring early after occlusion. With ventricular tachycardia only, there was a tendency for its incidence to increase in later time periods but this was not statistically significant.

In Table 2 the occurrences of ventricular fibrillation and ventricular tachycardia with reperfusion are shown. The table illustrates the time-dependency of reperfusion arrhythmias which peaked after 5–7 min of ischaemia in controls, and were both less severe (VT, rather than VF) and less frequent after 20 min of ischaemia. Anipamil 2.5 mg kg^{-1} tended to reduce reperfusion arrhythmias in all time periods, but this tendency was most marked for the 3 min period.

Effects of anipamil on ECG changes induced by ischaemia

Although anipamil reduced arrhythmias, there were no corresponding effects on mortality since a

Figure 2 Incidence of major arrhythmias after various periods of ischaemia in conscious rats. The incidence of arrhythmias is given as number of animals having the major arrhythmias of ventricular tachycardia (a and b) or ventricular fibrillation (c and d) in groups of $n = 18$. In (a) and (c) incidences in the various separate time periods after occlusion are plotted while in (b) and (d) cumulative incidences at noted times after occlusion are given. In all panels, incidences are shown for controls (filled columns), 1 mg kg^{-1} i.v. anipamil (open columns) and 5 mg kg^{-1} i.v. anipamil (hatched). * $P < 0.05$ from control.

reduction in VF-induced mortality was associated with an increase in non-arrhythmic mortality (Table 3). The lack of effect of anipamil upon occluded zone size did not explain variations in mortality, although it was consistent with its failure to reduce the maximum value attained either by the R-wave or S-T segment elevation following permanent occlusion (Table 3). Anipamil treatment had no effect on the time to appearance of Q-waves (index of

infarction), but it did, at 5 mg kg^{-1} i.v., reduce the number of animals that showed such a wave. Anipamil treatment also influenced the rate at which ECG changes appeared following the onset of ischaemia. This delaying effect is clearly illustrated in Figure 3 where anipamil, in a dose-related manner, reduced the rate at which S-T segment elevations developed. A similar delayed increase in R-wave was also seen (data not shown).

Table 2 Group incidence of major arrhythmias with reperfusion after various preceding periods of ischaemia in control (C) and anipamil (2.5 mg kg^{-1}) (A) treated rats

Arrhythmia	Group	Ischaemic period					Total No.
		3 min	5 min	7 min	10 min	20 min	
Ventricular fibrillation	C	6	9	8	6	0	29
	A	0*	5	7	2*	0	14*
Ventricular tachycardia &/or fibrillation	C	6	9	9	9	5	38
	A	1*	8	8	6	3	26*

The incidence in the group ($n = 9$) of major arrhythmias which occurred within 1 min of reperfusion after the specified period of preceding ischaemia are given together with the cumulative total for all time groups ($n = 45$).

* $P < 0.05$ compared with appropriate control.

Table 3 Mortality and ECG changes (maximum R-wave size and S-T segment elevation, Q-wave) in control (C) and anipamil (A) treatment groups

	Mortality		ECG changes – maximum values obtained			
	Arr.	Non-Arr.	R-wave mV	S-T % of R	Q-wave Incidence	Time (h)
Control	1	0	1.2 ± 0.1	40 ± 3	14	1.9 ± 0.1
A 1 mg kg ⁻¹	0	1	1.4 ± 0.2	40 ± 3	14	2.1 ± 0.1
A 5 mg kg ⁻¹	0	3	1.3 ± 0.1	37 ± 3	8*	2.3 ± 0.2

Mortality in the 0–4 h post-occlusion period is expressed as the incidence in groups of 18, or arrhythmia-(Arr.) or non-arrhythmia-(Non-Arr.) related death. The maximum values for R-wave size and S-T segment elevation were found by inspection of each individual rat's ECG trace, and the mean values ($\pm$ s.e.mean) calculated for group size of $n = 18$. Q-wave occurrence was recorded as both the incidence in the group, and as the time at which it was first detected in those animals which developed Q-waves.

Effects on epicardial intracellular potentials

Anipamil treatment did not reduce the major characteristics of resting or action potentials recorded *in*

Figure 3 The rate of development of S-T segment changes following occlusion in control and anipamil-treated animals. In (a) the group mean size of the S-T segment elevation (as % of R-wave size) at the various time periods after occlusion are shown ($n = 18$). (Δ) control; ($\circ$) 1 mg kg⁻¹; ($\blacktriangle$) 2.5 mg kg⁻¹ and ($\bullet$) 5 mg kg⁻¹. $t_{1/2}$ values were calculated from the data in (a) on the assumption that there was a saturation function adequately described by $t_{1/2}$ values. Such calculated values were replotted in (b).

vivo (Table 4). Neither the depolarization and/or late repolarization phases were affected. However, anipamil produced a change in the configuration of the phase 2 portion of the action potential in the earliest phases of repolarization (Figure 4). The change proved very difficult to quantitate in a consistent manner and only a qualitative description can be given. Anipamil modified the shoulder of the action potential such that phase 1 appeared to become more pronounced while the 'plateau' portion appeared to be depressed.

Discussion

This study established that anipamil *i.v.* dose-dependently reduced arrhythmias due to LAD occlusion in conscious and anaesthetized rats. This agrees with a previous study in which anipamil was antiarrhythmic if given orally 4 h before occlusion (Curtis & Walker, 1986). The present study further defined this antiarrhythmic effect and showed it to be dose-dependent and occurring in more than one rat model. It also illustrated the long duration of action of anipamil since anipamil given either 4 h or

Figure 4 Epicardial action potential recorded *in vivo* before and after administration of anipamil. An example of intracellular potentials recorded from the epicardial surface of a rat heart before and after administration of anipamil (2.5 mg kg⁻¹) is shown.

Table 4 Action potential characteristics recorded *in vivo* before and after 2.5 mg kg⁻¹ anipamil i.v. (A)

Time period	RMP (mV)	AP (mV)	MRR (V s ⁻¹) at 50% repolarization	AP duration (ms)
Control	75 ± 5	85 ± 5	164 ± 10	12 ± 3
5 min after A	73 ± 5	90 ± 5	166 ± 12	13 ± 3
30 min after A	72 ± 4	90 ± 4	171 ± 10	12 ± 4

Epicardial potentials were recorded by a floating microelectrode technique in 5 open-chest pentobarbitone anaesthetized rats. Where possible, a single cell potential was held before and after administration of anipamil. When multiple impalements were made only average values for individual rats were used in the calculation of group $\bar{x} \pm \text{s.e.mean}$.

15 min before occlusion was equally efficacious. Antiarrhythmic effects were not associated with a reduction in occluded zone size, although they were associated with possible anti-ischaemic effects as inferred from ECG evidence. Such evidence has previously been reported for anipamil following its oral administration (Curtis *et al.*, 1986).

The antiarrhythmic effectiveness of anipamil can usefully be compared with those of verapamil enantiomers. In conscious rat (-), (+) and (+)-enantiomers had ED₅₀ values of 2, 6 and 20 mg kg⁻¹, respectively (Curtis *et al.*, 1984; Curtis & Walker, 1986), which are close to that for anipamil (between 1 and 5 mg kg⁻¹). Antiarrhythmic efficacy of both verapamil and anipamil was associated with hypotension and bradycardia and this depression of the cardiovascular system increased the possibility of death due to cardiac output failure following coronary occlusion.

The mechanisms underlying anipamil's antiarrhythmic activity may involve more than one action. We previously suggested that the antiarrhythmic efficacy of calcium antagonists in conscious rats relates to inhibition of calcium currents in ventricular tissue (Curtis *et al.*, 1984; Curtis & Walker, 1986). Such a mechanism may also be involved in the antiarrhythmic action of anipamil, but unfortunately the full pharmacological profile of this drug is unknown, although it is a calcium antagonist (Dillon & Nayler, 1988). Effects on intracellular potentials were suggestive of Class IV rather than Class I or III actions since a reduced calcium current during Phase 2 of the action potential would accentuate repolarization processes only.

The present experiments suggested that the putative anti-ischaemic actions of anipamil participated in antiarrhythmic actions. If delays in the development of ischaemia-induced changes in the ECG (Figure 3) indicated an anti-ischaemic action, one would expect anipamil to be more efficacious against arrhythmias appearing very early after the onset of ischaemia. Figure 2 suggests that this was partly the case since arrhythmias occurring in the period when ECG changes were noticeably delayed appeared more sensitive to the antiarrhythmic

actions of anipamil. However, particularly with the 5 mg kg⁻¹ dose and incidence of VF, anipamil reduced arrhythmias in all time periods thus concordance between ECG effects and the time dependency of arrhythmias was not complete. If all of the antiarrhythmic actions of anipamil were due to the same process as that which delayed the development of R-wave or S-T segment elevation, then one would expect Figure 3a and Figure 2b and d to show overall concordance. This was not the case since, in both cases, the slopes of the time-dependency were depressed by anipamil whereas the maxima they achieved were only depressed in Figure 2b and d. Thus, both an anti-ischaemic and direct antiarrhythmic action appeared to be involved.

Anti-ischaemic actions may have accounted for the reduction in reperfusion arrhythmias seen in rats subjected to 3 or 5 min ischaemic periods, but not for the reductions after more prolonged periods of ischaemia (Table 2). A complete analysis would require a more extensive time series study to differentiate clearly between secondary antiarrhythmic actions due to anti-ischaemic effects, and those due to direct actions. Antiarrhythmic actions against reperfusion arrhythmias are complicated by the fact that such arrhythmias depend on a number of factors (see review by Manning & Hearse, 1984). These include not only the extent, intensity and duration of the preceding period of ischaemia, but also the speed and efficacy of reperfusion. A drug influencing any of the foregoing could be antiarrhythmic by virtue of reducing the initial arrhythmic stimulus and not by direct antiarrhythmic actions.

In conclusion, anipamil given intravenously, has antiarrhythmic actions against both occlusion and reperfusion arrhythmias in the conscious rat. These antiarrhythmic actions may involve both primary antiarrhythmic, and secondary antiarrhythmic actions. The latter is presumed to be due to 'anti-ischaemic' effects. The duration of the antiarrhythmic actions of anipamil was very prolonged.

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