ELSEVIER

European Journal of Pharmacology 279 (1995) 25–32

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SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs

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Received 25 January 1995; accepted 24 February 1995

Abstract

We have assessed the ability of amiodarone and the new amiodarone-like antiarrhythmic agent, SR 33589 (*N*,*N*-dibutyl-3-[4-((2-butyl-5-methylsulphonamido)benzofuran-3-yl-carbonyl)phenoxy]propylamine), to inhibit the effects of adrenoceptor stimulation in anaesthetized and conscious dogs. In anaesthetized, atropinized dogs, adrenoceptor stimulation was achieved (i) by i.v. administration of adrenaline and measurement of increased blood pressure (ii) by i.v. administration of isoprenaline and measurement of increased heart rate and decreased blood pressure. In conscious dogs, adrenoceptor stimulation was achieved by i.v. administration of isoprenaline and measurement of increased heart rate. In anaesthetized, atropinized dogs, both amiodarone and SR 33589 inhibited to similar extents, α-adrenoceptor stimulation (as indicated by attenuation of adrenaline-induced increases in blood pressure). The β_1-adrenoceptor inhibitory activity of SR 33589 (as demonstrated by blockade of isoprenaline-induced increases in heart rate) was significant, but less marked than amiodarone (heart rate elevation reduced by 39%, $P < 0.001$ with 10 mg/kg SR 33589 and by 52%, $P < 0.01$ with 10 mg/kg amiodarone). In contrast, its β_2-adrenoceptor antagonistic activity (as demonstrated by blockade of isoprenaline-induced reduction in blood pressure) was more marked (mean blood pressure decrease reduced by 69%, $P < 0.01$ with 10 mg/kg SR 33589 and by 31%, $P < 0.05$ with 10 mg/kg amiodarone). In conscious dogs, both SR 33589 and amiodarone (12.5, 25 and 50 mg/kg p.o.) inhibited isoprenaline-induced increases in heart rate by approximately the same amount for varying durations depending on the dose. Thus, like amiodarone, SR 33589 can partially inhibit the effects of stimulation of the adrenoceptor system that may play a pivotal role in the onset of severe ventricular rhythm disturbances.

Keywords: Amiodarone; SR 33589; Antiarrhythmic (class III); Anti-adrenoceptor activity

1. Introduction

Amiodarone is known to be one of the most effective antiarrhythmic agents currently available for clinical use (Gill et al., 1992). SR 33589 (*N*,*N*-dibutyl-3-[4-((2-butyl-5-methylsulphonamido)benzofuran-3-yl-carbonyl)phenoxy]propylamine) is a new antiarrhythmic agent structurally related to amiodarone with a similar pharmacological profile. Like amiodarone, SR 33589 has been shown to prolong action potential duration in anaesthetized rats (Manning et al., 1992) and to significantly reduce the incidence of life-threatening arrhythmias that arise upon reperfusion following a transient period of coronary artery occlusion in anaesthetized rats (Bruyninckx et al., 1992) and during myocardial ischaemia in anaesthetized pigs (Finance et al., 1993). In all these studies SR 33589 was shown to be effective at lower doses than amiodarone.

One of the mechanisms, in part responsible, for the antiarrhythmic actions of amiodarone may be its known partial antisympathetic activity (Charlier, 1970; Polster and Broekhuysen, 1976). For this reason in the present study we have compared the ability of SR 33589, in comparison to amiodarone, to inhibit the effects of adrenoceptor stimulation in dogs. Adrenoceptor stimulation was achieved by firstly, administration of adrenaline and measurement of the resultant hypertension and secondly, by administration of isoprenaline and measurement of increased heart rate and decreased blood pressure. Not only have we assessed these effects in anaesthetized dogs, we have also taken

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SSDI 0014-2999(95)00130-1

this work further and assessed this action following oral administration in conscious dogs.

2. Materials and methods

2.1. Effects of intravenous administration of amiodarone and SR 33589 on adrenoceptor stimulation in anaesthetized dogs

Surgical techniques and experimental protocol

Mongrel dogs, weighing between 4.0 and 12.5 kg, were anaesthetized with sodium pentobarbital (Nembutal, 30 mg/kg i.v.) and atropinized (1 mg/kg i.v.). Peripheral arterial blood pressure was measured via a catheter inserted into the femoral artery. Heart rate was determined from a limb-lead ECG recorded from lead II. These parameters were recorded on a Gould ES 2000.

For each animal, a dose of adrenaline and isoprenaline was determined which produced substantial but submaximal effects, i.e. adrenaline-induced hypertension ranging from 85 to 150 mm Hg; isoprenaline-induced hypotension ranging from 35 to 75 mm Hg; and isoprenaline-induced tachycardia ranging from 60 to 120 beats per min. This was achieved using doses of adrenaline between 2.5–10 μg/kg i.v. and isoprenaline between 0.5 to 2 μg/kg i.v. These selected doses of catecholamines were injected at 10 min intervals. When two equal consecutive control responses were obtained, vehicle solution, amiodarone or SR 33589 was injected intravenously via the cephalic vein. The effects of the compounds on limiting the effects of catecholamine administration were then followed for a minimum of 55 min. Adrenaline and isoprenaline were both administered 3 times (at 5, 25 and 45 min for adrenaline; 15, 35 and 55 min for isoprenaline) following injection of amiodarone, SR 33589 or vehicle.

Chronotropic and pressor effects were the consequence of catecholamine-induced adrenoceptor stimulation, i.e.: (i) hypertension resulting from administration of adrenaline (mixed α and β receptor activity), (ii) increased heart rate induced by isoprenaline administration as a measure of β_1-adrenoceptor activity, (iii) decreased blood pressure induced by isoprenaline administration as a measure of β_2-adrenoceptor activity. The effects of amiodarone and SR 33589 were determined by measuring the changes in the maximal amplitude of these parameters.

Drug administration

Amiodarone and SR 33589 were administered intravenously at three different doses, 1 mg/kg, 5 mg/kg and 10 mg/kg. Each dose of compound was administered to a separate group of six dogs. Amiodarone was dissolved as a 1% solution in distilled water at the dose of 1 mg/kg i.v. and as a 5% solution in water at the higher doses. SR 33589 at 1 mg/kg i.v. was dissolved in distilled water and at the higher doses as a 3.33% solution in PEG 300 with distilled water (2/1).

2.2. Effects of oral administration of amiodarone and SR 33589 on isoprenaline-induced increases in heart rate in conscious dogs

Experimental protocol

Mongrel conscious dogs of either sex weighing between 8.0 and 14.1 kg were used in this study. Four electrodes were positioned (one attached to each limb) and connected to a physiograph to record a surface ECG. In each animal a dose of isoprenaline was determined which produced substantial but submaximal effects, i.e. isoprenaline-induced tachycardia ranging from 70 to 160 beats per min. This increase was achieved using doses of isoprenaline in the order of 1 to 2 μg/kg i.v. Consecutive, similar control responses were obtained for each dog the day before the study and repeated before oral administration of vehicle, amiodarone or SR 33589. The effects of amiodarone and SR 33589 on isoprenaline-induced tachycardia were determined by measuring the changes in the maximal amplitude of heart rate. Intravenous administration of isoprenaline via the cephalic vein was carried out before administration of the agents and repeated every hour during the first 7 h and after 24 h following administration of the compounds. The PQ, QRS and corrected QT intervals (QT_C) were also calculated from the surface ECG.

Drug administration

Amiodarone and SR 335589 were administered orally in the form of a capsule to non-fasting dogs. Amiodarone and SR 33589 were each administered orally at three different doses: 12.5 mg/kg, 25 mg/kg and 50 mg/kg. A period of 15 days was allowed between administration of the compounds to the same dog.

2.3. Statistical analysis

Statistical analysis of the results was undertaken using a Student's *t*-test for paired variables (vs. control time). Differences between mean values greater than $P < 0.05$ were considered statistically significant.

3. Results

3.1. Effects of intravenous administration of amiodarone and SR 33589 on adrenoceptor stimulation in anaesthetized dogs

Preliminary studies performed with PEG 300 and water showed that these solvents exerted no effect on adrenoceptor stimulation.

Effects on adrenaline-induced increases in mean blood pressure

The results are shown in Fig. 1. Amiodarone at 1 mg/kg i.v. decreased significantly the maximal degree of hypertension induced by the first administration of adrenaline but did not modify substantially the effects of further administration of this catecholamine (−17% $P < 0.01$; −7% and −5% NS). SR 33589 at 1 mg/kg i.v. showed a similar trend (−18% $P < 0.05$; −7% and −8% NS). The 5 mg/kg i.v. dose of amiodarone exerted a significant and greater effect on the maximal amplitude of adrenaline-induced hypertension (−35% $P < 0.05$; −17% $P < 0.05$; −12% NS). 5 mg/kg SR 33589 produced a larger decrease than the same dose of amiodarone (−54% $P < 0.001$; −20% $P < 0.001$; −13% $P < 0.05$). 10 mg/kg amiodarone induced a greater effect than lower doses of amiodarone (−66% $P < 0.001$; −34% $P < 0.05$; −19% NS). SR 33589 at 10 mg/kg exerted also a greater effect than lower doses of SR 33589 (−56% $P < 0.001$; −36% $P < 0.001$; −22% $P < 0.01$).

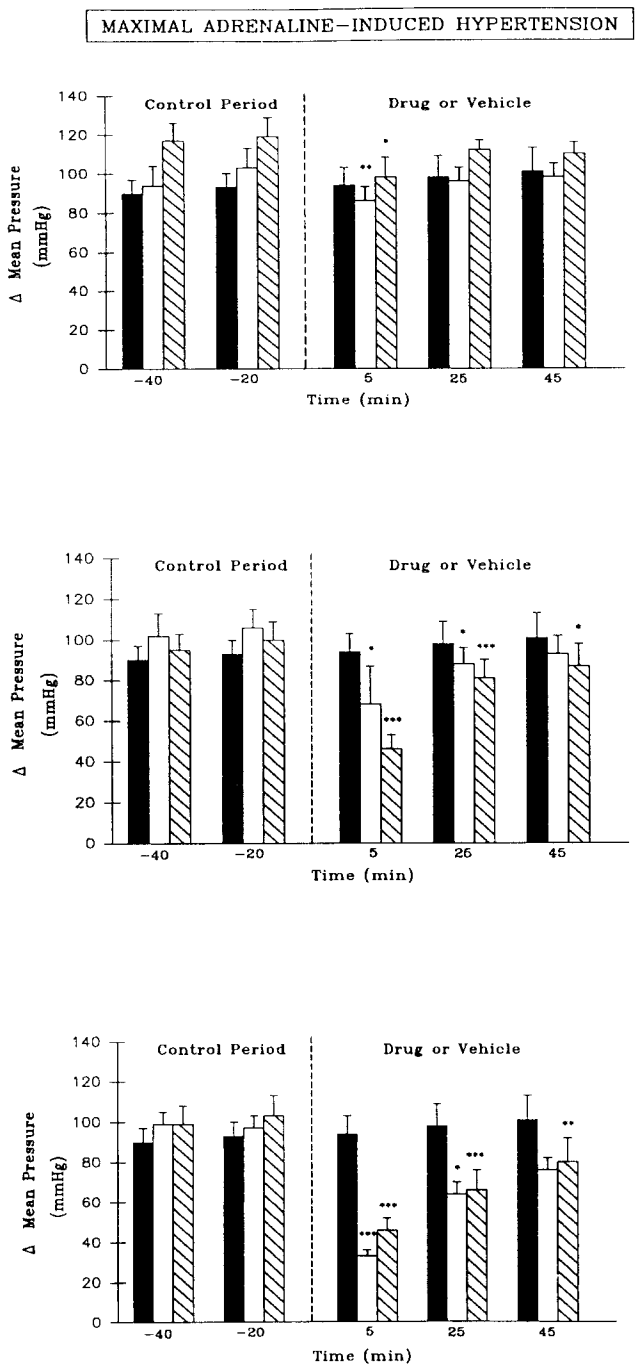

Fig. 1. Effects of vehicle, amiodarone and SR 33589 at 1 mg/kg (top), 5 mg/kg (middle) and 10 mg/kg i.v. (bottom) on maximal amplitude of adrenaline-induced hypertension in anaesthetized dogs. The results are shown as the mean ±S.E.M. (n = 6 in each group). Black columns: control, open columns: amiodarone, hatched columns: SR 33589. Asterisks indicate significant difference from the pre-drug value at the level: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Effects on isoprenaline-induced increases in heart rate

These results are shown in Fig. 2. Administration of 1 mg/kg amiodarone decreased significantly the increase in heart rate induced by the first administration of isoprenaline (−7% $P < 0.05$; −9% NS; −4% NS). SR 33589 at 1 mg/g i.v. did not cause any marked change in the increase in heart rate (−2% NS; 0% NS; +1% NS). Administration of 5 mg/kg amiodarone i.v. resulted in a significant and slightly greater inhibition of isoprenaline-induced tachycardia than 1 mg/kg (−28% $P < 0.05$; −14% NS; −1% NS). At the same dose, SR 33589 did not exert any significant effect on the maximal amplitude of isoprenaline-induced tachycardia (−25% NS; −8% NS; −2% NS). Administration of 10 mg/kg amiodarone i.v. produced a greater and more significant inhibition of isoprenaline-induced tachycardia (−52% $P < 0.01$; −37% $P < 0.05$; −31% $P < 0.05$). At the same dose, SR 33589 reduced significantly the elevation of heart rate induced by the first administration of isoprenaline but not the following two administrations (−39% $P < 0.001$; −10% NS; 0% NS).

Effects on isoprenaline-induced decreases in mean blood pressure

These results are shown in Fig. 3. Amiodarone at 1 mg/kg i.v. was without any marked effect on the maximal degree of hypotension provoked by isoprenaline (−2% NS; −2% NS; −1% NS). SR 33589 at 1 mg/kg i.v. also, did not cause any significant change to this index (−1% NS; −7% NS; 0% NS). Administration of 5 mg/kg amiodarone i.v. decreased the maximal amplitude of isoprenaline-induced hypotension. However, this effect only reached a level of statistical significance after the second administration of isoprenaline (−20% NS, −21% $P < 0.05$; −18% NS). At the same dose, SR 33589 produced a significant decrease after every administration of isoprenaline

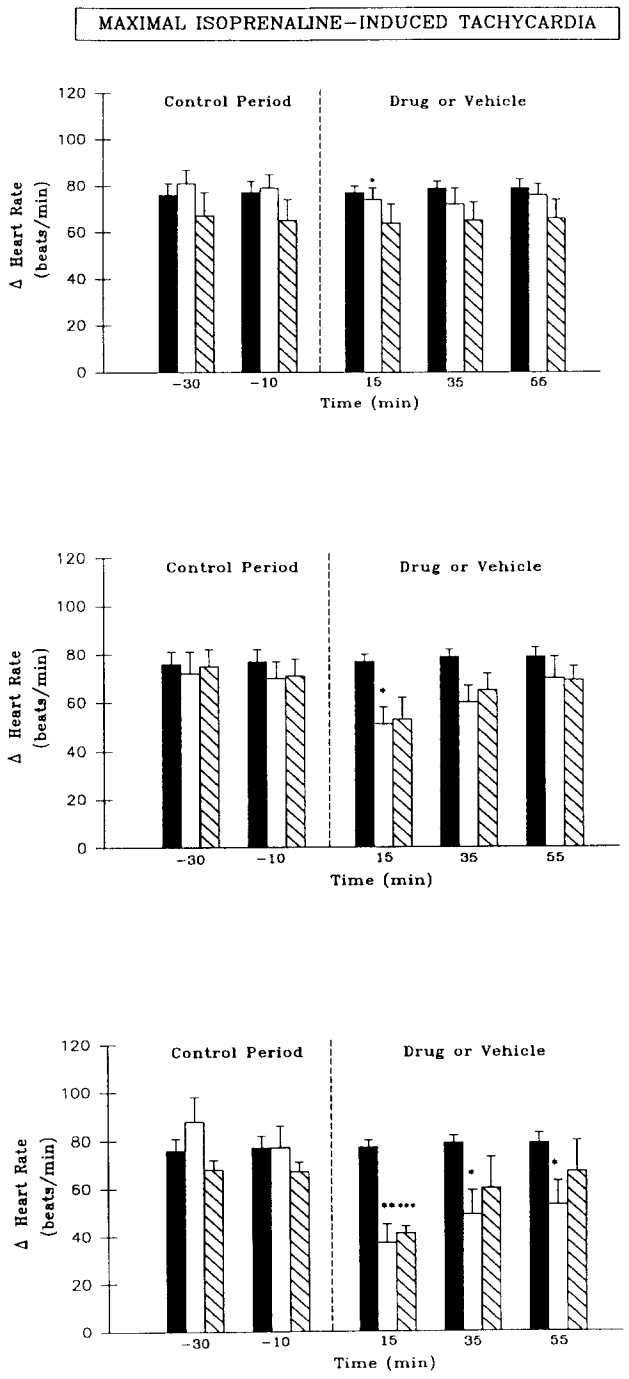

Fig. 2. Effects of vehicle, amiodarone and SR 33589 at 1 mg/kg (top), 5 mg/kg (middle) and 10 mg/kg i.v. (bottom) on maximal amplitude of isoprenaline-induced tachycardia in anaesthetized dogs. The results are presented as in Fig. 1.

(−34% $P < 0.05$; −25% $P < 0.05$; −20% $P < 0.05$). Administration of 10 mg/kg amiodarone induced a greater and more significant effect than the lower doses (−31% $P < 0.05$; −29% $P < 0.05$; −25% $P < 0.01$). At the same dose as amiodarone, SR 33589 exerted the larger and the more significant effect (−69% $P < 0.01$; −42% $P < 0.01$; −36% $P < 0.01$).

Effects on non-stimulated heart rate and blood pressure

Amiodarone and SR 33589 at 1 mg/kg i.v. were without any marked effect on heart rate. Administration of 5 mg/kg amiodarone i.v. induced a significant and sustained bradycardia (−19% after 55 min, from 177 to 144 beats/min, $P < 0.01$). At the same dose, SR 33589 exerted a slightly greater effect (−26% after 55 min, from 186 to 138 beats/min, $P < 0.001$). At the

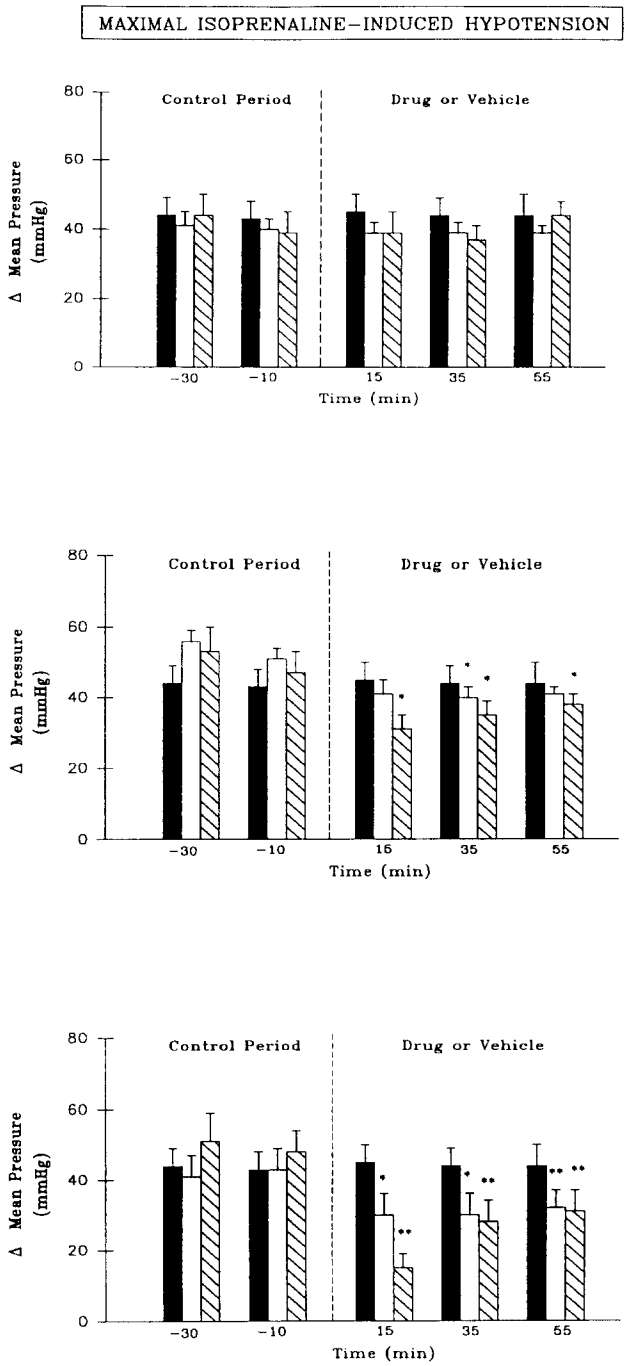

Fig. 3. Effects of vehicle, amiodarone and SR 33589 at 1 mg/kg (top), 5 mg/kg (middle) and 10 mg/kg i.v. (bottom) on maximal amplitude of isoprenaline-induced hypotension in anaesthetized dogs. The results are presented as in Fig. 1.

highest dose, the effects of amiodarone and SR 33589 were more marked (−83%, from 187 to 126 beats/min, and −36%, from 189 to 121 beats/min, respectively after 55 min, $P < 0.001$). Systolic blood pressure was not substantially modified by amiodarone, however SR 33589 at the highest dose induced a significant, but transient decrease in systolic blood pressure (−36% after 5 min, $P < 0.01$; −2% after 55 min, NS). Amiodarone exerted a significant, but transient decrease in diastolic blood pressure at the highest dose (−26% after 5 min, $P < 0.01$) while SR 33589 at 5 mg/kg and 10 mg/kg i.v. exhibited a similar trend (−20% after 5 min, $P < 0.01$; −46% after 5 min, $P < 0.001$ respectively).

3.2. Effects of oral administration of amiodarone and SR 33589 on isoprenaline-induced increases in heart rate in conscious dogs

Effects on isoprenaline-induced tachycardia

These results are shown in Fig. 4. Amiodarone at 12.5 mg/kg p.o. reduced significantly the elevation of heart rate induced by isoprenaline. This effect was observed between the 1st and 3rd h following drug administration (−26% after 2 h, $P < 0.001$; −8% after 4 h, NS). 12.5 mg/kg p.o. SR 33589 also caused a significant attenuation of isoprenaline-induced tachycardia between the first and fourth hour following drug administration (−17% after 2 h, $P < 0.01$; −8% after 6 h, NS).

Amiodarone at 25 mg/kg p.o. decreased significantly the maximal amplitude of isoprenaline-induced tachycardia. This inhibition was not observed at the end of the experimental protocol (−26% after 6 h, $P < 0.05$; +5% after 24 h, NS). Thus, 25 mg/kg amiodarone caused a significant attenuation of the effects of β_1-adrenoceptor stimulation between the 4th and 6th h following drug administration. SR 33589 at 25 mg/kg p.o. exhibited a similar level of inhibition of isoprenaline-induced tachycardia with a significant reduction (approximately 20%) after 1 and 2 h following drug administration (−20% after 2 h, $P < 0.05$).

Amiodarone at 50 mg/kg p.o. induced a greater and more significant decrease in the elevation of heart rate induced by isoprenaline, but as with the lower dose of amiodarone, this inhibition was not noted at the end of the observation period (−42% after 4 h, $P < 0.001$; −7% after 24 h, NS). However, at this dose, the duration of the effect was longer with a significant level of inhibition of approximately 6 h between the 2nd and 7th h following drug administration. The 50 mg/kg p.o. dose of SR 33589 produced also a greater inhibition of isoprenaline-induced tachycardia than the lower doses, but a slight, non-significant decrease was still present at the end of the experimental protocol (−38% after 5 h, $P < 0.05$; −17% after 24 h, NS). Thus 50 mg/kg SR 33589 caused a significant reduction of the effects of β_1-adrenoceptor stimulation between the 2nd and 7th h following oral administration.

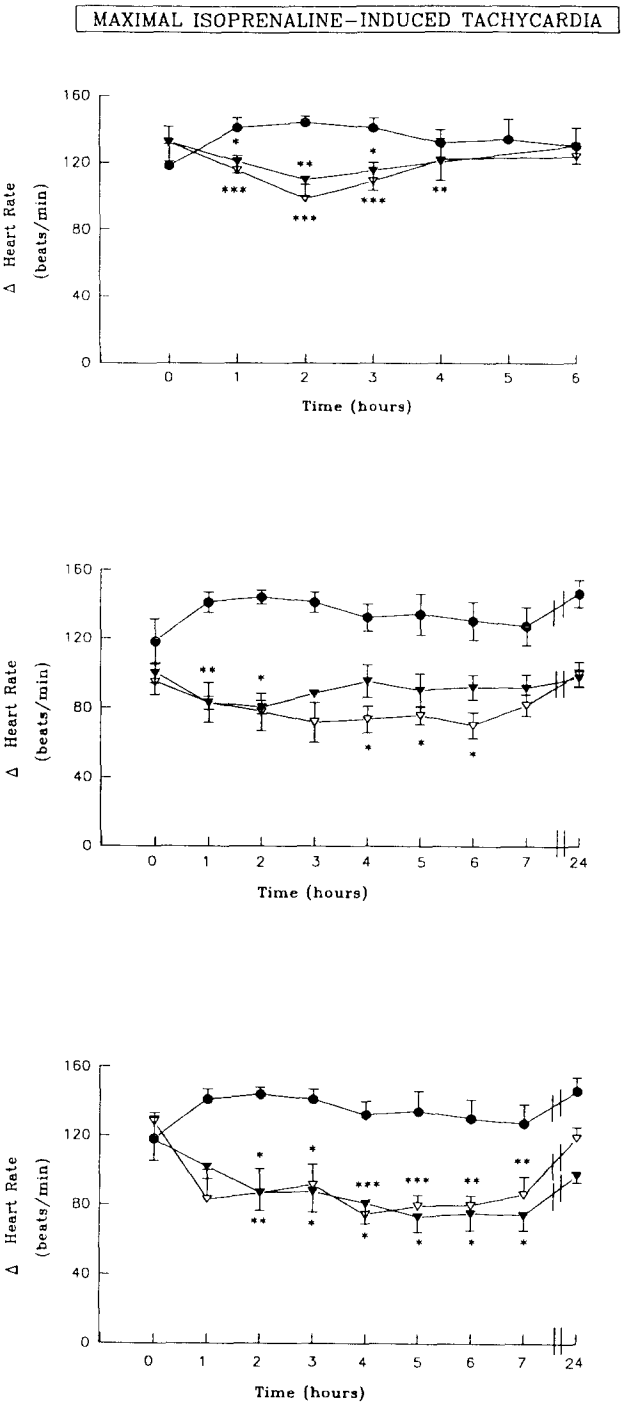

Fig. 4. Effects of vehicle, amiodarone and SR 33589 at 12.5 mg/kg (top), 25 mg/kg (middle) and 50 mg/kg p.o. (bottom) on maximal amplitude of isoprenaline-induced tachycardia in conscious dogs. ● Control, ▽ amiodarone, ▼ SR 33589B. The results are presented as in Fig. 1.

Effects on resting heart rate

Amiodarone at 12.5 mg/kg and 25 mg/kg p.o. exerted no significant effect on resting heart rate. SR 33589 at 12.5 mg/kg induced a small but significant tachycardia after 6 h following drug administration (+7%, from 111 to 119 beats/min, $P < 0.05$). However, SR 33589 at 25 mg/kg was without any significant effect on resting heart rate. The 50 mg/kg p.o. dose of amiodarone induced a slight, but significant, increase in heart rate which was the same as that found for the vehicle-treated group (+11% after 3 h, from 91 to 101 beats/min, $P < 0.05$). The highest dose tested of SR 33589 (50 mg/kg) also induced a significant increase in heart rate between the 2nd and 4th h following drug administration (+26% after 4 h, from 92 to 116 beats/min, $P < 0.05$).

Effects on ECG intervals

These results are shown in Table 1. Amiodarone at the two lowest doses increased slightly, but significantly the PQ interval (+5% after 4 h, $P < 0.05$ at 12.5 mg/kg and +8% after 3 h, $P < 0.05$ at 25 mg/kg). However, at the highest dose, no statistically significant increase was observed (+15% after 4 h, NS). SR 33589 at all three doses increased significantly the PQ interval (+9% after 3 h, $P < 0.05$; +8% after 5 h, $P < 0.05$; +12% after 6 h, $P < 0.05$ at the doses of 12.5 mg/kg, 25 mg/kg and 50 mg/kg respectively). Amiodarone at the lowest dose was without any significant effect on QRS complex. However at the two highest doses, a slight but significant lengthening of the QRS complex was noted (+9% after 7 h, $P < 0.05$; +3% after 4 h, $P < 0.05$ at the doses of 25 mg/kg and 50 mg/kg p.o. respectively). SR 33589 was without any significant effect on the QRS interval. Amiodarone at 12.5 mg/kg p.o. produced a slight, but significant, lengthening of the QT_c interval (+9% after 2 h, $P < 0.05$). However, no statistically different changes were observed at the two highest doses. SR 33589 at 12.5 mg/kg p.o. was without any significant effect on the QT_C interval while a slight, but significant lengthening of this parameter was noted at the two highest doses (+8% after 4 h, $P < 0.05$; +6% after 7 h, $P < 0.05$ at the doses of 25 mg/kg and 50 mg/kg p.o., respectively).

4. Discussion

The results of this study indicate that SR 33589 can inhibit, in a similar manner to amiodarone, activation of the adrenoceptor system by catecholamines. Although it can not be assumed that adrenoceptor stimulation by adrenaline is solely an α-adrenoceptor response, the ability of SR 33589 and amiodarone to effectively block this action does suggest a significant blockade of the α-adrenoceptor receptors. Inhibition of isoprenaline-induced tachycardia indicates a partial inhibition of β_1-adrenoceptor responses and an inhibition of isoprenaline-induced decreases in blood pressure suggests an action on β_2-adrenoceptor responses.

This inhibition of adrenoceptor stimulation by SR 33589 is a potential mechanism by which this agent could reduce the severity of life-threatening arrhythmias. Various studies have shown that sympathetic activity can induce arrhythmias in the absence of any demonstrable degree of myocardial ischaemia. Electrical stimulation of specific areas of the brain is known to provoke cardiac arrhythmias (Evans and Gillis, 1978) and hypothalamic stimulation has been shown to lower the threshold for ventricular fibrillation in intact animals (Verrier et al., 1975). These effects were observed in vagotomized animals and are thus independent of changes in heart rate or blood pressure. The link between the sympathetic nervous system and psycho-

Table 1
Heart rate (before and following drug administration) and electrocardiographic intervals in dogs treated orally with vehicle, amiodarone and SR 33589

Treatment	Vehicle	Amiodarone			SR 33589		
		12.5 mg/kg	25 mg/kg	50 mg/kg	12.5 mg/kg	25 mg/kg	50 mg/kg
Heart rate (beats / min)							
Control	112 ± 6	115 ± 7	93 ± 5	91 ± 7	111 ± 6	92 ± 6	92 ± 7
Maximal change	127 ± 9 *	117 ± 6	99 ± 5	101 ± 5 *	119 ± 6 *	102 ± 3	116 ± 5 *
PQ (ms)							
Control	118 ± 7	103 ± 3	120 ± 6	121 ± 3	94 ± 4	116 ± 8	119 ± 2
Maximal change	115 ± 5	108 ± 3 *	130 ± 6	139 ± 6	102 ± 3 *	125 ± 6	133 ± 6
QRS (ms)							
Control	36 ± 4	22 ± 2	33 ± 1	33 ± 2	27 ± 1	33 ± 1	30 ± 1
Maximal change	35 ± 3	23 ± 2	36 ± 1 *	34 ± 2 *	25 ± 1	33 ± 2	31 ± 2
QTC (ms)							
Control	272 ± 7	252 ± 10	293 ± 4	287 ± 7	263 ± 11	290 ± 9	285 ± 10
Maximal change	277 ± 9	274 ± 10 *	306 ± 7	298 ± 8	268 ± 12	313 ± 10 *	303 ± 9 *

The results are shown as the mean ± S.E.M. ($n = 6$ in each group). Asterisks indicate a significant difference from the pre-drug value at the level of $P < 0.05$.

logical, stress-induced cardiac arrhythmias has been also noted in several other studies (Lynch et al., 1977). In particular, Matta et al. (1976) showed that dogs submitted to a psychologically stressful environment exhibited a reduced threshold for repetitive extrasystoles. The increase in vulnerability to arrhythmias in this study appeared to be mediated by the sympathetic nervous system, as a complete cessation of this phenomenon was noted following β-adrenoceptor blockade. Many previous studies have focused on the role of the autonomic nervous system on the occurrence of ischaemia and reperfusion-induced arrhythmias, such that the importance of the autonomic nervous system in modulating arrhythmias occuring during acute myocardial ischaemia and reperfusion is now well established (Corbalan et al., 1976; Corr and Gillis, 1978; Manning and Hearse, 1984).

Autonomic neural influences on arrhythmogenesis appear to be mediated principally by catecholamine stimulation of α- and β-adrenoceptors. Many studies, although not all, have demonstrated, in various species, an antiarrhythmic effect of α_1-adrenoceptor blockade during both acute ischaemia and reperfusion (Sheridan et al., 1980; Benfey et al., 1984). Efficacy of α_2-adrenoceptor blocking agents in preventing reperfusion arrhythmias in isolated rat hearts has also been suggested (Thandroyen et al., 1983). Blockade of β-adrenoceptors has also been shown to decrease the risk of arrhythmias. β-Adrenoceptor antagonists such as propranolol and atenolol have demonstrated significant antiarrhythmic activity in preventing ventricular arrhythmias arising during both myocardial ischaemia and reperfusion (Echt et al., 1983; Manning and Hearse, 1984; Uprichard and Harron, 1989). Such evidence strongly implicates a role for sympathetic activation in the genesis of arrhythmias under these conditions and the beneficial activity of adrenoceptor blockade. In Langendorff perfused, guinea pig hearts submitted to ischaemia and reperfusion, phentolamine and propranolol both prevented ventricular fibrillation and significantly reduced the incidence of ventricular tachycardia during ischaemia and reperfusion (Penny, 1984). In the same study, myocardial catecholamine depletion induced by 6-hydroxydopamine reduced significantly the incidence of arrhythmias. This suggests that release of endogenous myocardial catecholamines contributes through α- and β-adrenoceptor stimulation to arrhythmia formation during myocardial ischaemia and reperfusion.

Amiodarone is known to have multiple electrophysiological effects including prolongation of ventricular refractoriness and action potential duration (Singh and Vaughan Williams, 1970). In addition, amiodarone exhibits a clearly defined antisympathetic activity demonstrated previously in animal preparations (Charlier, 1970; Polster and Broekhuysen, 1976). It has been suggested that this ability to inhibit activation of the adrenoceptor system may be responsible for some of the early electrophysiological effects of amiodarone (Kobayashi et al., 1983; Kadish et al., 1990). However, the pharmacological activity of amiodarone is known to differ following long-term drug administration, such that antiarrhythmic efficacy is enhanced (Gill et al., 1992). At present it is not known if chronic administration of SR 33589 affords greater antiarrhythmic potency than acute administration. However, it has been demonstrated that, like amiodarone, the electrophysiological properties of SR 33589 are not immediately demonstrated but are revealed, even following intravenous administration, relatively slowly (Manning, 1995). In addition, on a purely structural level, the fact that both compounds are substituted benzofurans would suggest similar properties. Thus, although the present study has been devoted solely to the immediate adrenoceptor antagonistic effects of amiodarone and SR 33589 and we have no results following long-term administration, the current body of evidence points towards similar properties for the two compounds following chronic treatment.

Recently, the presence and time course of β-adrenoceptor antagonism produced by amiodarone in response to graded doses of isoproterenol have been evaluated in patients treated with oral amiodarone for sustained ventricular tachycardia (Kadish et al., 1990). In this study, amiodarone limited the increase in heart rate produced by isoproterenol. This effect was present on the second day of amiodarone administration. In addition, ventricular ectopic activity in response to isoproterenol was abolished after 4 days of amiodarone therapy. Thus, these observations indicate that oral amiodarone therapy exerts significant β-adrenoceptor antagonism manifested by limitation of isoproterenol-induced increases in heart rate and premature ventricular complexes. As this adrenoceptor antagonism is present after only 2 days of therapy, it may be responsible for some of the early clinical effects of amiodarone and its unique antiarrhythmic efficacy.

This present study was carried out in dogs to determine the ability of SR 33589, in comparison with amiodarone, to inhibit the effects of adrenoceptor stimulation. SR 33589 has been shown to possess a similar pharmacological profile to that of amiodarone when given intravenously. In particular, this compound has been shown to prolong action potential duration in anesthetized rats (Manning et al., 1992), to prolong atrial, AV node and ventricular refractory periods in dogs (Manning, 1995) and to exhibit, in several different preparations, antiarrhythmic properties that are at least equivalent or more potent than those of amiodarone in terms of either dosage used or suppression of arrhythmias. In particular antiarrhythmic effects of SR 33589 have been demonstrated against reperfusion-

induced arrhythmias in anaesthetized rats (Bruyninckx et al., 1992) and ischaemia-induced arrhythmias in anaesthetized pigs (Finance et al., 1993).

Thus, in conclusion, this study demonstrates that SR 33589, like amiodarone, possess an ability to partially inhibit the effects of sympathetic activation, when given both intravenously or orally. This activity may well be partly responsible for the antiarrhythmic actions of SR 33589.

Acknowledgements

The help of Ms A. Haly, Mr J. Houthuys and M. Baetens is gratefully acknowledged. This work was supported in part by a grant from the 'Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture' (I.R.S.I.A.).

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