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I_K independent class III actions of MS-551 compared with sematilide and dofetilide during reperfusion in anaesthetized rats

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1 The antiarrhythmic and haemodynamic effects of three class III antiarrhythmic drugs, MS-551, sematilide and dofetilide, were examined in the coronary artery, ligation-reperfusion model of pentobarbitone-anaesthetized rats, a species deficient in functional cardiac I_K. MS-551 is a non-selective potassium channel blocker, while both sematilide and dofetilide are selective delayed rectifier potassium (K) channel (I_K) blockers.

2 Before coronary ligation, 3 and 10 mg kg^{-1} MS-551 decreased the heart rate by 6% ($P<0.01$) and 12% ($P<0.01$), and increased mean arterial pressure (MAP) by 14% ($P<0.05$) and 33% ($P<0.01$), respectively. Sematilide at 10 and 30 mg kg^{-1} also decreased the heart rate by 4% ($P<0.01$) and 9% ($P<0.01$), respectively, and the higher dose of 30 mg kg^{-1} decreased MAP by 29% ($P<0.01$). Dofetilide, 1 mg kg^{-1}, decreased the heart rate ($P<0.01$), but had no significant effect on MAP.

3 The QT interval was increased by 10% ($P<0.01$) and 31% ($P<0.01$), when 3 and 10 mg kg^{-1} MS-551 were given. Sematilide and dofetilide had no effect on the QT interval.

4 Immediately after reperfusion, lethal ventricular fibrillation (VF) was induced in 80% of the saline group. MS-551 at 3 and 10 mg kg^{-1}, reduced the incidence of lethal VF to 50% and 20% ($P<0.05$). Neither dofetilide 1 mg kg^{-1} nor sematilide (10 and 30 mg kg^{-1}) decreased the incidence of lethal VF (70%, 80% and 50%, respectively). None of the three drugs had any effect on the occurrence of reperfusion-induced VT or the total incidence of VF. However, 10 mg kg^{-1} MS-551 delayed the onset of reperfusion-induced VF (27 ± 5 s compared with 12 ± 2 s of the control group, $P<0.05$).

5 In conclusion, in rats which are deficient in cardiac I_K MS-551 prolonged the QT interval and reduced the incidence of sustained VF after reperfusion. Blockade of channels other than I_K might participate in the defibrillatory effect of MS-551. Sematilide and dofetilide, which are selective I_K blockers, did not increase the QT interval nor did they show antiarrhythmic effects. Mechanisms other than K channel block may be involved in the different effects of the three drugs on blood pressure.

Keywords: Class III antiarrhythmic drugs; MS-551; sematilide; dofetilide; QT interval; I_K; I_{K1}; I_{to}

Introduction

Recently attention has been focused on the anti- or defibrillatory activities of class III antiarrhythmic drugs. Preliminary studies suggest that the class III agents generally demonstrate greater efficacy than conventional class I agents in preventing ventricular arrhythmias occurring during acute ischaemia or evoked by programmed electrical stimulation, while producing less cardiac depression than other classes of antiarrhythmic drugs (Lynch *et al.*, 1985; Kou *et al.*, 1987; Anderson, 1990).

Class III antiarrhythmic drugs block K currents (Colatsky *et al.*, 1990) and prolong action potential duration (APD) and QT interval without showing any effect on the impulse conduction (Vaughan Williams, 1970). In ischaemic hearts, where re-entrant excitation can easily occur due to abnormal conduction in and around the ischaemic myocardium (Janse *et al.*, 1986; Curtis & Hearse, 1989), class III agents may suppress re-entry arrhythmias by increasing the re-entry pathway through the prolongation of APD and effective refractory period (Singh & Nademanee, 1985; Gibson & Kertsen, 1990). However, all class III drugs are not the same. Cardiac K channels on which class III drugs are I_K, I_{K1}, I_{to} and additionally may be I_{KATP}. Almost all of the class III agents, such as sotalol (Komeichi *et al.*, 1990; Sanguinetti & Jurkiewicz, 1990), E-4031 (Sanguinetti & Jurkiewicz, 1990), MS-551 (Nakaya *et al.*, 1993; Hashimoto *et al.*, 1994; Sato *et al.*, 1995; Martin *et al.*, 1995), dofetilide (Gwilt *et al.*, 1991; Jurkiewicz & Sanguinetti, 1993), sematilide (Argentieri & Carroll, 1990; Sanguinetti & Jurkiewicz, 1990), N-acetylprocainamide (NAPA) (Komeichi *et al.*, 1990) and UK66, 914 (Rees & Curtis, 1993a) have been reported to inhibit I_K. There is no doubt that class III drugs prolong APD by inhibiting I_K which is mostly responsible for the initiation of repolarization. However not all the class III drugs are selective I_K blockers, and some also block other K channels such as I_{K1}, I_{to} and I_{KATP}. Therefore it is of interest to discover whether non-selective K channel blockers have different antiarrhythmic profiles compared with selective I_K blockers.

In our present study, we chose rats and produced reperfusion-induced arrhythmias. The rat ventricle possesses no functional I_K (Gwilt *et al.*, 1986; Tande *et al.*, 1990), so it is particularly suitable for detecting antiarrhythmic effects of blocking I_{K1}, I_{to} and I_{KATP}. In rats, defibrillatory activity (i.e. a shortening of the periods of sustained VF or a decrease in the occurrence of sustained VF), has been reported in isolated heart preparations subjected to coronary ischaemia and reperfusion for I_{to} blockers (Tsuchihashi & Curtis, 1991) and in isolated hearts subjected to regional coronary ischaemia (Rees *et al.*, 1993) and for I_{KATP} blockers in isolated heart subjected to reperfusion (Bril *et al.*, 1992), while I_{K1} blockers demonstrate antifibrillatory activity (i.e. a decrease in the total incidence of VF) in rat isolated hearts subjected to coronary ischaemia and reperfusion (Rees & Curtis, 1993b,c; 1995). We have addressed the question: is blockade of potassium currents other than I_K sufficient to affect reperfusion VF? To test this, using the anaesthetized *in vivo* rat, we examined whether the three new class III drugs have different anti- or defibrillatory effects on

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rat reperfusion arrhythmias, comparing MS-551, [1,3-dimethyl-6-{(2-[*N*-(2-hydroxyethyl)-3-(4-nitrophenyl)propylamino]ethylamino}-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride], a non-specific class III drug which inhibits I_K, I_{K1}, I_{to} and I_{KATP} (at high concentrations) (Nakaya 1993; Hashimoto *et al.*, 1994; Sato *et al.*, 1995; Martin *et al.*, 1995) and dofetilide and sematilide, which are specific I_K blockers (Argentieri & Carroll, 1990; Sanguinetti & Jurkiewicz, 1990; Gwilt *et al.*, 1991; Jurkiewicz & Sanguinetti, 1993).

Methods

Production of coronary ligation-reperfusion model in rat

As described earlier (Komori *et al.*, 1994), male Sprague-Dawley rats (220–300 g) were anaesthetized with 60 mg kg^{-1} sodium pentobarbitone intraperitoneally. The femoral vein was cannulated for drug administration, and the trachea was cannulated for artificial respiration. Systemic arterial pressure was continuously monitored via a catheter inserted into the carotid artery. A standard limb lead I ECG was continuously recorded together with arterial pressure on a recorder (Nihon Kohden RM 6200, Tokyo, Japan). Artificial respiration was started with room air, using a tidal volume of 2 ml 100 g^{-1} and a rate of 54 strokes min^{-1} in order to maintain arterial blood gases and pH within the normal ranges. The chest was opened by a left thoracotomy, followed by sectioning of the 4th and 5th ribs, approximately 2 mm to the left of the sternum. After incising the pericardium, the heart was exteriorized using gentle pressure on the rib cage. A 5/0 nylon suture attached to a 14 mm micropoint reverse cutting needle was placed under the left coronary artery. The heart was replaced back in the chest, and the rat was allowed to recover for 15 min. The rats that had arrhythmias and/or had a MAP less than 70 mmHg were not used.

Regional myocardial ischaemia could be produced by pulling the two ends of the suture through a plastic tube and pressing the tube against the surface of the myocardium and then clamping the tube together with the suture. As reported previously by Komori *et al.* (1994), we chose a 5 min duration of ischaemia for inducing maximal occurrence of reperfusion arrhythmias. Reperfusion was initiated by declamping and removing the tube.

Experimental protocol

After 15 min of stabilization, a saline or a drug solution was administered intravenously in the control or treated groups, respectively. The volume of injection was 0.5 ml and given for 30 s. Coronary ligation was started 5 min after the start of drug administration. Five min after ligation, reperfusion was performed. The ECG and blood pressure were continuously recorded throughout the experiment. Ischaemia and reperfusion were verified by the immediate changes in the shape of the lead I ECG, especially the height of the QRS complexes.

Sixty rats were used in this protocol. The rats were divided into 6 groups (10 rats/group) and were infused with the following drugs: group 1, saline; group 2, MS-551 (3 mg kg^{-1}); group 3, MS-551 (10 mg kg^{-1}); group 4, sematilide (10 mg kg^{-1}); group 5, sematilide (30 mg kg^{-1}); and group 6, dofetilide (1 mg kg^{-1}). The doses of MS-551 were chosen by their significant QT prolonging effect. Since sematilide did not prolong the QT interval, high doses up to those producing a transient hypotensive effect were chosen. The dose of dofetilide was the highest dose that could be dissolved in dilute hydrochloric acid, since dofetilide had no significant cardiovascular effects.

All experiments were performed in accordance with the Guidelines of the Animal Use and Care Committee of the Yamanashi Medical University.

ECG analysis of QT interval and arrhythmia

The heart rate and QT interval were measured from the ECG lead I just before the drug or saline injection (0 min) and 0.5, 1, 2, 3, 4, 5 min after the start of drug or saline injection. The QT interval was measured at the point of 90% repolarization and referred to as QT90 (Rees & Curtis, 1993b). Ventricular tachycardia (VT) was defined as a run of 4 or more ventricular premature beats (VPB). Ventricular fibrillation (VF) was defined as a rapid ECG waveform of QRS deflections varying in amplitude and coupling interval on a cycle to cycle basis. Because VF is not necessarily a terminal event in this rat model, we defined VF which lasted more than 3 min as a sustained VF and considered the rat suffering from the sustained VF as dead.

Drugs

MS-551, sematilide and dofetilide were kindly provided by Mitsui Pharmaceuticals Inc., Nippon Roussel K. K. and Pfizer Pharmaceuticals Inc., respectively. MS-551 and sematilide were dissolved in saline. Dofetilide was first dissolved in 0.01 N HCl solution and then diluted with saline to produce the final concentration.

Statistics

The haemodynamic and QT values and the latent period of VT and VF appearance are expressed as mean ± standard error of mean (s.e.mean) and the haemodynamic and QT values were subjected to ANOVA for repeated measures, followed by Dunnet's test. The latent period of VT and VF appearance was subjected to one-way ANOVA. Changes in the incidences were analysed by Fisher's exact probability test. Differences were regarded as significant if the P values were less than 0.05.

Results

Effects of MS-551, sematilide and dofetilide on heart rate (HR) and MAP

The baseline HR of thoracotomized, pentobarbitone-anaesthetized rats in the control, 3 and 10 mg kg^{-1} MS-551, 10 and 30 mg kg^{-1} sematilide and 1 mg kg^{-1} dofetilide group were 463±10, 454±12, 480±10, 463±6, 459±8 and 448±5 beats min^{-1} ($n=10$), and there were no significant differences among the 5 groups. The changes in HR were compared before and after drug (or saline)-treatment and there were almost no changes in the control group. A decrease in HR of −6±1, −12±1, −4±1, −9±1, −3±1%, was produced by 3 and 10 mg kg^{-1} MS-551, 10 and 30 mg kg^{-1} sematilide and 1 mg kg^{-1} dofetilide, respectively (Figure 1).

The baseline MAP in the control, 3 and 10 mg kg^{-1} MS-551, 10 and 30 mg kg^{-1} sematilide and 1 mg kg^{-1} dofetilide group were 103±6, 110±5, 99±7, 103±8, 117±4 and 105±5 mmHg ($n=10$), and there were no significant differences among the 5 groups. The MAP in the control group after saline-treatment tended to increased initially, then returned to the pretreatment value within 5 min. This statistically insignificant increase might be attributed to the saline added for drug administration. MS-551 increased the MAP at 10 mg kg^{-1}. Sematilide at the high dose of 30 mg kg^{-1}, on the other hand, decreased the MAP. Dofetilide, 1 mg kg^{-1}, did not change MAP (Figure 1).

Effects of MS-551, sematilide and dofetilide on QT interval

The baseline QT intervals in the control, 3 and 10 mg kg^{-1} MS-551, 10 and 30 mg kg^{-1} sematilide and 1 mg kg^{-1} dofetilide group were 45±3, 46±4, 51±4, 45±3, 39±4 and 43±3 ms ($n=10$), and there were no significant differences among the 5 groups. As shown in Figure 1, there was almost

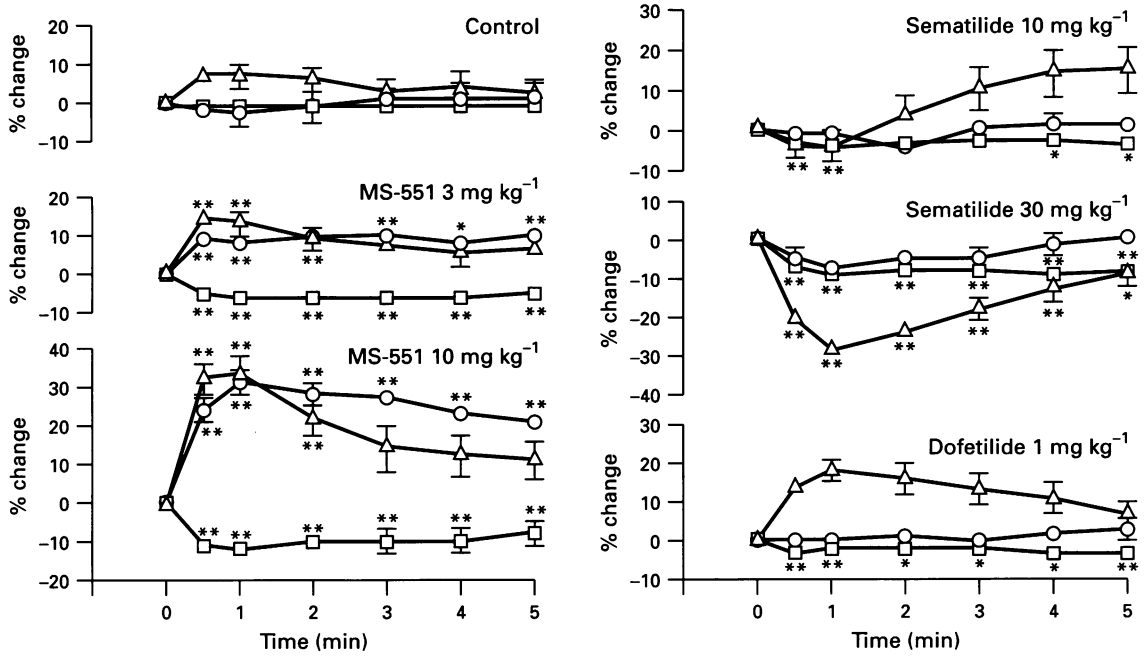

Figure 1 Effects of three class III agents, MS-551, sematilide and dofetilide on the heart rate (□), mean blood pressure (△) and the QT interval (○) in pentobarbitone-anaesthetized rats (10 rats/group). The changes of the heart rate and QT interval were compared before and after saline or drug-treatment. The changes in the mean blood pressure of drug-treated groups were compared with the control group at corresponding time points. $^*P<0.05$, $^{**}P<0.01$.

no change in the QT interval in the control, dofetilide or 10 and 30 mg kg^{-1} sematilide groups. However 3 mg kg^{-1}, MS-551 increased QT interval by 10%, and at 10 mg kg^{-1}, it was increased by 31%. The QT prolonging effect of MS-551 lasted at least up to the ligation time (5 min after the administration).

Effects of MS-551, sematilide and dofetilide on the latency of the induction of reperfusion-induced arrhythmias (Figure 2)

MS-551 significantly prolonged the latent period between the onset of reperfusion and the appearance of VF at a higher dose of 10 mg kg^{-1} (27±5 s compared to 12±2 s of the control group). Sematilide and dofetilide neither delayed nor hastened the onset of reperfusion-induced arrhythmias.

Effects of MS-551, sematilide and dofetilide on the incidences of VT, total incidence of VF and incidence of sustained VF induced by coronary reperfusion (Figure 3)

The control incidences of reperfusion-induced VT, total VF and sustained VF were high. MS-551, 3 mg kg^{-1}, did not significantly reduce the incidence of these arrhythmias. A higher dose of 10 mg kg^{-1} MS-551 did not reduce the incidence of VT, but significantly reduced the incidence of sustained VF. Sematilide and dofetilide had no effects on the incidence of these reperfusion-induced arrhythmias.

Effects of MS-551, sematilide and dofetilide on the incidence of VT or VPB induced by 5 min coronary occlusion

During the 5 min between the drug administration and the start of coronary occlusion, there were no occurrences of arrhythmia. The occurrence of VT or VPB during the 5 min coronary occlusion was 3/10 in the control saline-treated group and 4/10, 2/10, 4/10, 3/10 and 2/10 in MS-551 3 mg, 10 mg, sematilide 10 mg, 30 mg and dofetilide 1 mg kg^{-1}, respectively. There were no statistically significant differences among these results.

Discussion

Class III agents are pharmacologically heterogeneous, varying in their relative selectivity of blockade for I_K, I_{K1} and I_{to} (Colatsky *et al.*, 1990), and I_K blockade appears to be a specific antiarrhythmic mechanism for arrhythmias occurring in rat isolated hearts subjected to coronary reperfusion (Rees & Curtis, 1993b). However, additional I_{K1}, I_{to} or I_{KATP} blockade may also play some role in the antiarrhythmic mechanism. In the present study, we used rats *in vivo* to examine and compare the effects among the new class III drugs, MS-551, sematilide and dofetilide. Since the rat ventricle has been reported to be deficient in I_K (Gwilt *et al.*, 1986; Tande *et al.*, 1990), the animal is suitable for examining the role of I_K blockade in the antiarrhythmic mechanism of these class III drugs. It has been reported that sematilide (Argentieri & Carroll, 1990; Sanguinetti & Jurkiewicz, 1990) and dofetilide (Gwilt 1991; Jurkiewicz & Sanguinetti, 1993) are selective I_K blockers, but MS-551 has additional I_{K1} or I_{to} blocking and also I_{KATP} actions (Nakaya *et al.*, 1993; Sato *et al.*, 1995). We chose doses of MS-551, sematilide and dofetilide based on the relative potency of the three drugs. Previous *in vitro* and *in vivo* studies indicated that it is approximately 0.03-0.1: 0.03-0.1: 1 for MS-551: sematilide: dofetilide for I_K blockade or QT prolongation (Gwilt *et al.*, 1992; Nakaya *et al.*, 1993; Lee *et al.*, 1993; Sato *et al.*, 1995; Martin *et al.*, 1995; Ishii *et al.*, 1995). The doses were also determined from our previous experiments on ischaemic arrhythmias in rats (1–10 mg kg^{-1} MS-551; Watanabe *et al.*, 1996) and dogs (3.6 mg kg^{-1} MS-551, 1–3 mg kg^{-1} sematilide and 0.1 mg kg^{-1} dofetilide; Hashimoto *et al.*, 1995; Xue *et al.*, 1996; Chen *et al.*, 1996). The doses of sematilide and dofetilide were maximal or supermaximal doses, because they had no QT prolonging and anti- or defibrillatory effects.

In the present experimental protocol, reperfusion after 5 min of ischaemia induced a high incidence of sustained VF and other arrhythmias, such as VT and non-sustained VF, in the control group. Using this arrhythmia model, it is possible to evaluate the antiarrhythmic effect of the drug immediately after reperfusion. During the ischaemic period, there was a low incidence of arrhythmia (3 out of 10 rats showed VT or VPB) in the control group, so it could also be used to observe

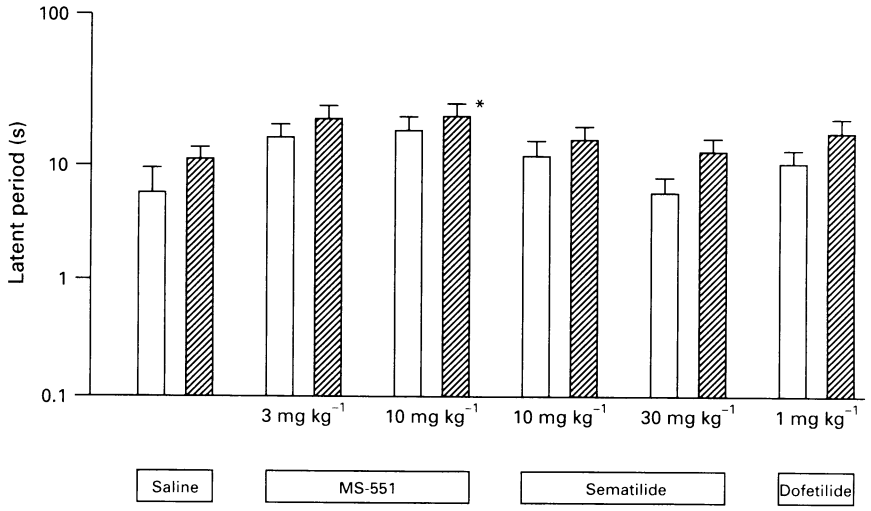

Figure 2 Effect of MS-551, sematilide and dofetilide on the interval between the reperfusion and the onset of VT (open columns) and VF (hatched columns) in anaesthetized rats. $*P<0.05$ compared with control value.

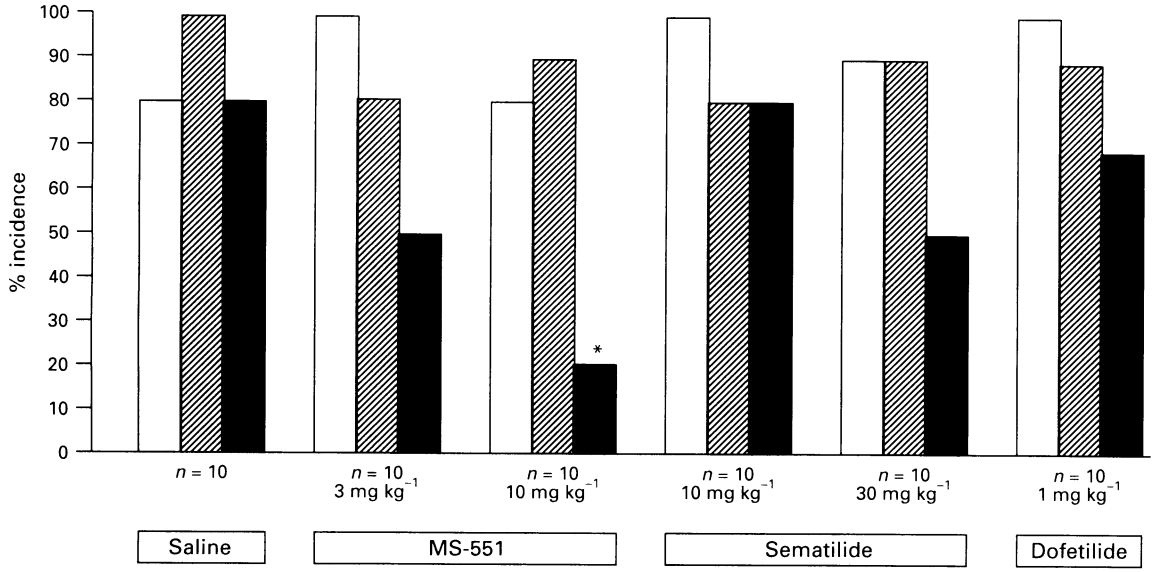

Figure 3 Effects of MS-551, sematilide and dofetilide on % incidence of reperfusion-induced VT (open columns), total VF (hatched columns) and sustained VF (solid columns) in rats. $*P<0.05$ compared with control values.

proarrhythmic effects of drugs during the first 5 min of ischaemia. However, in this short period of drug administration of 10 min, including the 5 min of occlusion time, we did not see any proarrhythmic effect of the three class III drugs. This does not, however, account for any effects on arrhythmias in the later stages of ischaemia. The disadvantage of this rat coronary ligation-reperfusion model was that the QT interval after coronary ligation could not be measured because of the marked shape changes in the ECG, including an increase in the amplitude of the QRS complexes. This is due both to the direct effect of ischaemia on the ECG and to the change of heart position after clamping the suture.

In our experiments, even though we could not measure the QT interval just before the reperfusion, the effect of drug intervention on QT interval was observed before the start of coronary ligation, and the changes appeared to be related to the protection of reperfusion-induced sustained VF. For example, MS-551 at higher doses significantly increased the QT interval and decreased the incidence of sustained VF, whereas sematilide and dofetilide neither increased the QT interval nor decreased the incidence of sustained VF. Therefore we propose that the QT interval prolongation and defibrillatory effect of MS-551 is due to repolarization delay. This presumably occurred because of I_{K1} or I_{to} blockade (and perhaps also I_{KATP} blockade), because there is no functional cardiac I_K in the rat ventricle (Gwilt *et al.*, 1986; Tande *et al.*, 1990). It is reported that selective I_{to} blockers possess defibrillatory, but no antifibrillatory activity in rat isolated hearts subjected to coronary ischaemia and reperfusion (Tsuchihashi & Curtis 1991) or subjected to coronary ischaemia (Rees *et al.*, 1993) and this is also true for I_{KATP} blockers in rat isolated hearts subjected to coronary ischaemia (Bril *et al.*, 1992). On the other hand I_{K1} blockers are reported to be antifibrillatory in rat isolated hearts subjected to ischaemia and reperfusion (Rees & Curtis, 1993b,c) and subjected to ischaemia (Rees & Curtis, 1995). Since the present experiments showed that a high dose of MS-551 had defibrillatory effect, i.e. decreasing the incidence of sustained VF without decreasing the total incidence of VF, MS-551 might have blocked I_{to} and/or I_{KATP}. If I_{to} does not flow at the terminal phase of repolarization, we can speculate that the antiarrhythmic mechanism of MS-551 is through its blockade of I_{KATP}. *In vitro* studies have shown that I_{KATP}

blockade requires higher concentrations of MS-551 (30–100 μM; Martin *et al.*, 1995), which are higher than those necessary to block I_{to} (10 μM; Nakaya *et al.*, 1993). Our previous study in dogs indicates that an intravenous dose of 3.6 mg kg^{-1} MS-551 resulted in a plasma concentration of 2 μg ml^{-1}, which is about 5 μM (Hashimoto *et al.*, 1995). It is difficult to speculate whether the present 30 mg kg^{-1} intravenous dose of MS-551 in rats results in a plasma concentration of up to 10 μM, but it is within a range not very far from that expected from canine experiments. However, it is difficult to be certain which K current was primarily responsible for the QT-prolongation and defibrillatory activity of MS-551 from our *in vivo* study.

With regard to the haemodynamic effect of class III agents, our study showed that MS-551, sematilide and dofetilide had negative chronotropic effects. K currents exist in sinoatrial node cells, and contribute to repolarization (Noma & Irisawa, 1976; Yanagihara & Irisawa, 1980). Although the negative chronotropic effect of the class III drug can be explained by K channel blockade (Yang *et al.*, 1991), precise electrophysiological analysis of class III drugs on the sinoatrial node has not been performed. MS-551, sematilide and dofetilide had different effects on the blood pressure. MS-551 increased the MAP, an effect which is inconsistent with the results obtained in dogs (Hashimoto *et al.*, 1994), where MS-551 decreased the MAP. The defibrillatory effect of MS-551 on the reperfusion VF may not be due to an anti-ischaemic effect of the drug, because it is neither a vasodilator, nor is it a potent bradycardic agents such as β-blockers or Ca channel blockers (Hashimoto 1994). Dofetilide had no significant effect on the MAP which is consistent with the results obtained in dogs (Spinelli *et al.*, 1992). Sematilide had a biphasic effect on the MAP, namely an increase was produced by a low dose, whereas a decrease was produced by a high dose. There have been several reports (Chi *et al*, 1990; Fish *et al.*, 1990; Greenberg *et al.*, 1992) showing similar transient decreases in MAP, but there were no reports of an increasing effect. It is not clear what produced such different results on the blood pressure and whether they are related to the K channel blockade. Even though the effects on MAP of the three drugs indicate the existence of some other cardiovascular effects, changes in haemodynamics have been found to be transient and minimal in conscious dogs and man (Greenberg *et al.*, 1992). Because maximal doses were used in our experiments, these effects should be of little importance in the clinical use of these drugs.

In conclusion, the non-selective potassium channel blocker, MS-551 prolonged the QT interval and reduced the incidence of reperfusion-induced sustained VF in rats. Sematilide and dofetilide had no effect on the QT interval and on the occurrence of arrhythmias in rats. Thus additional defibrillatory efficacy may be expected by blockade of potassium channels other than I_K.

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