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QT-prolonging class I drug, disopyramide, does not aggravate but suppresses adrenaline-induced arrhythmias. Comparison with cibenzoline and pilsicainide

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Abstract

We investigated the effects of class I antiarrhythmic drugs on corrected QT (QTc) interval and adrenaline-induced arrhythmias in halothane-anaesthetized, closed-chest dogs. For this purpose, we plotted a dose–response curve for adrenaline by calculating the arrhythmic ratio, which is the number of ventricular ectopic beats induced by adrenaline divided by the total heart rate, and observed the changes in the arrhythmic ratio–adrenaline dose relation before and after administration of class I drugs. Disopyramide and cibenzoline decreased the arrhythmic ratio induced by adrenaline. Disopyramide prolonged the QTc interval by 20% ($P < 0.01$), but cibenzoline did not. Pilsicainide prolonged the QTc interval (12%), but this drug did not change the arrhythmic ratio. These results indicate that in contrast to the class III drugs which we have reported earlier, i.e. 1,3-dimethyl - 6 - {2 - [*N* - (2 - hydroxyethyl) - 3 - (4 - nitrophenyl) - propylamino]ethylamino}-2,4 (1*H*,3*H*)-pyrimidinedione hydrochloride (MS-551), 1-(2-amino-4-methanesulfonamidophenoxy)2-[*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino]ethane hydrochloride (KCB-328) and E-1-{[(5-(4-chlorophenyl)-2-furanyl)methylene]amino}-3-[4-(4-methyl-1-piperazinyl)butyl]-2,4-imidazolidinedione dihydrochloride (azimilide), class I drugs do not aggravate adrenaline-induced arrhythmias even though some drugs prolong the QTc interval. © 2000 Published by Elsevier Science B.V.

Keywords: Disopyramide; Cibenzoline; Pilsicainide; QTc; Adrenaline; (Dog)

1. Introduction

It is known that prolongation of cardiac repolarization can be associated with induction and aggravation of ventricular arrhythmias including premature ventricular complexes and, at the worst, torsade de pointes or ventricular fibrillation (Hondeghem and Snyders, 1990; Borggrefe et al., 1992). Class III antiarrhythmic drugs are inhibitors of K^+ channels and prolong the action potential duration. Indeed, we have shown that class III drugs, 1,3-dimethyl-6-{2-[*N*-(2-hydroxyethyl)-3-(4-nitrophenyl)-propylamino]-ethylamino}-2,4 (1*H*,3*H*)-pyrimidinedione hydrochloride (MS-551), 1-(2-amino-4-methanesulfonamidophenoxy) 2-[*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino]ethane hydrochloride (KCB-328), and E-1-{[(5-(4-chlorophenyl)-2-furanyl)methylene]amino}-3-[4-(4-methyl-1-piperazinyl) utyl]-2,4-imidazolidinedione dihydrochloride (azimilide), have proarrhythmic effects on the adrenaline-induced arrhythmias along with corrected QT (QTc) prolongation (Xue et al., 1998, 1999). The adrenaline-induced arrhythmia model mimics the clinical situation of sympathicotonia, and the human long QT syndrome is often associated with sudden death when sympathetic overactivity is present. Using the same model, we have shown that class II and class IV drugs suppress these adrenaline-induced arrhythmias (Hashimoto et al., 1991; Haruno and Hashimoto, 1993; Matsuzaki et al., 1993).

Although class I drugs act mainly by inhibiting Na^+ channels, it has been suggested that some of these drugs inhibit other channels such as K^+ channels and Ca^{2+} channels. Drugs classified as class IA, but not IC, are known to prolong action potential duration by inhibiting K^+ channels. For example, disopyramide blocks delayed rectifier K^+ channels and ATP-sensitive K^+ channels at

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therapeutic doses (Hiraoka et al., 1989; Wu et al., 1992) and the transient outward K^+ channels at higher doses, as class III drugs do (Virag et al., 1998). The resulting lengthening of cardiac repolarization can be proarrhythmic, while it is not clear whether the class I drugs, whose main effect is to suppress Na^+ channels, have similar proarrhythmic effects on adrenaline-induced arrhythmias. Therefore, in this study, we evaluated the effects of disopyramide, which has QT-prolonging effects, on adrenaline-induced arrhythmias, and compared it with two other class I drugs, cibenzoline and pilsicainide.

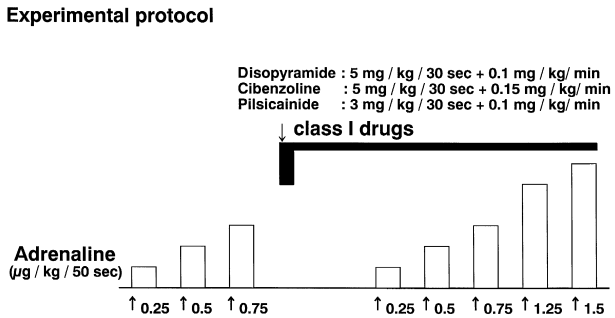

Fig. 1. Schema of experimental protocol to study the effect of disopyramide, cibenzoline, and pilsicainide on adrenaline-induced arrhythmias in dogs.

2. Materials and methods

2.1. Experimental preparation

These animal experiments were approved by the Yamanashi Medical University Animal Experimentation Committee and animals were obtained through the Animal Laboratory for Research of Yamanashi Medical University. Adult Beagle dogs of either sex, weighing 9–11.5 kg, were anesthetized initially with thiopental sodium. After tracheal intubation, 2.0% halothane, vaporized with 100% oxygen, was administered with a volume-limited ventilator (20 ml kg^{-1}, 15 strokes min^{-1}, Shinano, SN-480-4, Tokyo, Japan). Both vagi were cut at the mid-cervical region. The lead II electrocardiogram (ECG) and atrial electrogram from the catheter tip electrodes in the right atrium were continuously monitored. The QT interval was measured from the onset of the QRS complex to the end of the T-wave. The QTc interval was calculated using Bazett's formula, $QTc = QT/\sqrt{RR}$. The corrected JT (JTc) interval was calculated by the formula, $JTc = JT/\sqrt{RR}$, in which JT interval was calculated by subtracting the QRS duration from the QT interval. A femoral artery catheter was inserted for blood pressure monitoring. The ECG, atrial electrogram, and blood pressure were recorded with a polygraph system (Nihon Kohden, Tokyo, Japan). The femoral vein was also cannulated for administering drugs and adrenaline. Six dogs were used for each drug.

2.2. Production of adrenaline-induced arrhythmias

After surgical preparation, 30–45 min was allowed for stabilization, and then adrenaline diluted in 20 ml saline was intravenously infused for 50 s, according to the method of Hashimoto et al. (Hashimoto and Hashimoto, 1972; Matsubara et al., 1976). Fig. 1 shows the experimental protocol used in this study. The starting dose of adrenaline was 0.5 μg kg^{-1}. If 0.5 μg kg^{-1} adrenaline did not produce arrhythmia, the dose of adrenaline was increased by increments of 0.25 μg kg^{-1} until ventricular arrhythmias were induced. The maximum adrenaline dose in the control period was the dose, which produced severe ventricular tachycardia or occasionally fatal ventricular fibrillation. If 0.5 μg kg^{-1} adrenaline produced arrhythmia, a lower dose of 0.25 μg kg^{-1} adrenaline was infused. Between the challenges of the adrenaline infusion, a recovery period of about 10 min was allowed, during which time the hemodynamic parameters, e.g. heart rate and blood pressure, became stable. We defined the arrhythmia-inducing dose of adrenaline (referred to as the inducing dose) as the lowest dose which produced ventricular arrhythmias, including premature ventricular complexes, bigeminy or ventricular tachycardia defined as more than three consecutive premature ventricular complexes, and the non-arrhythmia-inducing dose of adrenaline (referred to as the non-inducing dose) as the highest dose which did not induce any arrhythmia.

As we previously showed (Xue et al., 1998), inducing and non-inducing doses of adrenaline were not changed by saline infusion, indicating the reproducibility of the arrhythmia.

Class I drugs were administered as follow, disopyramide, a bolus of 5 mg kg^{-1} i.v. followed by 0.1 mg kg^{-1} min^{-1} i.v. infusion for 40 min; cibenzoline, a bolus of 5 mg kg^{-1} i.v. followed by 0.15 mg kg^{-1} min^{-1} i.v. infusion for 40 min; pilsicainide, a bolus of 3 mg kg^{-1} i.v. followed by 0.1 mg kg^{-1} min^{-1} i.v. infusion for 40 min.

2.3. Drugs

Disopyramide, cibenzoline, and pilsicainide were kindly provided by Chugai Pharmaceutical, Tokyo, Japan; Fujisawa Pharmaceutical, Osaka, Japan; and Suntory, Tokyo, Japan, respectively. These drugs were dissolved in saline. Thiopental sodium (Tanabe Seiyaku, Tokyo, Japan), halothane (Takeda Chemical Industries, Osaka, Japan), and adrenaline hydrochloride (Daiichi Pharmaceutical, Tokyo, Japan) were purchased.

2.4. Evaluation of antiarrhythmic effects

The arrhythmic ratio was calculated by dividing the number of premature ventricular complexes by the total heart rate, i.e. the number of premature ventricular com-

plexes plus the number of conducted beats, and the ventricular beats were judged by the different shape of the ventricular complex from the normal QRS complex. If the arrhythmic ratio and the number of the ranks expressing the severity of adrenaline-induced arrhythmias after drug administration were significantly lower than those of the control period, the drugs were judged to have antiarrhythmic effects.

2.5. Plasma drug assay

Heparinized arterial blood samples were centrifuged and the plasma samples were stored in a freezer at $-25°C$ before plasma drug analysis. Arterial blood samples were obtained before and after 5, 10, 30 and 40 min after injection.

Plasma disopyramide assay was carried out by the fluorescent polarization immunoassay method (Chen et al., 1987) using a commercially available kit (Dinabot, Tokyo, Japan). The limit of quantification was 0.04 $\mu g\ ml^{-1}$. Plasma concentrations of cibenzoline and pilsicainide were measured by high-performance liquid chromatographic methods at SRL (Tokyo, Japan).

2.6. Statistics

The hemodynamic and electrocardiographic parameters, and the arrhythmic ratio are expressed as means ± S.E.M. ($n = 6$). For the analysis of hemodynamic and electrocardiographic parameters, a repeated measured analysis of variance (ANOVA) was performed; when a statistical difference was detected, a Dunnett's multiple comparison test was used to determine the difference between the 0 time value and the other values. For the analysis of the arrhythmic ratio, paired Student's *t*-test was performed. The severity of arrhythmias was compared by the Wilcoxon signed-ranks test. Differences were regarded as significant if the P values were less than 0.05.

3. Results

3.1. Effects of disopyramide on ECG, hemodynamic parameters, and arrhythmic ratio

Disopyramide decreased mean blood pressure from 115 ± 4 to 89 ± 5 mmHg ($P < 0.01$) and heart rate from 137 ± 6 to 101 ± 2 beats min^{-1} ($P < 0.01$) and prolonged QT interval from 259 ± 13 to 356 ± 8 ms ($P < 0.01$) and JT interval from 193 ± 14 to 283 ± 10 ms ($P < 0.01$). Disopyramide also prolonged QTc interval from 391 ± 13 to 463 ± 13 ms $s^{-1/2}$ (by 19%) ($P < 0.01$) and JTc interval from 290 ± 17 to 368 ± 15 ms $s^{-1/2}$ (by 29%) ($P < 0.01$) at 10 min after the start of administration (Fig. 2). PQ interval and QRS duration were also prolonged by

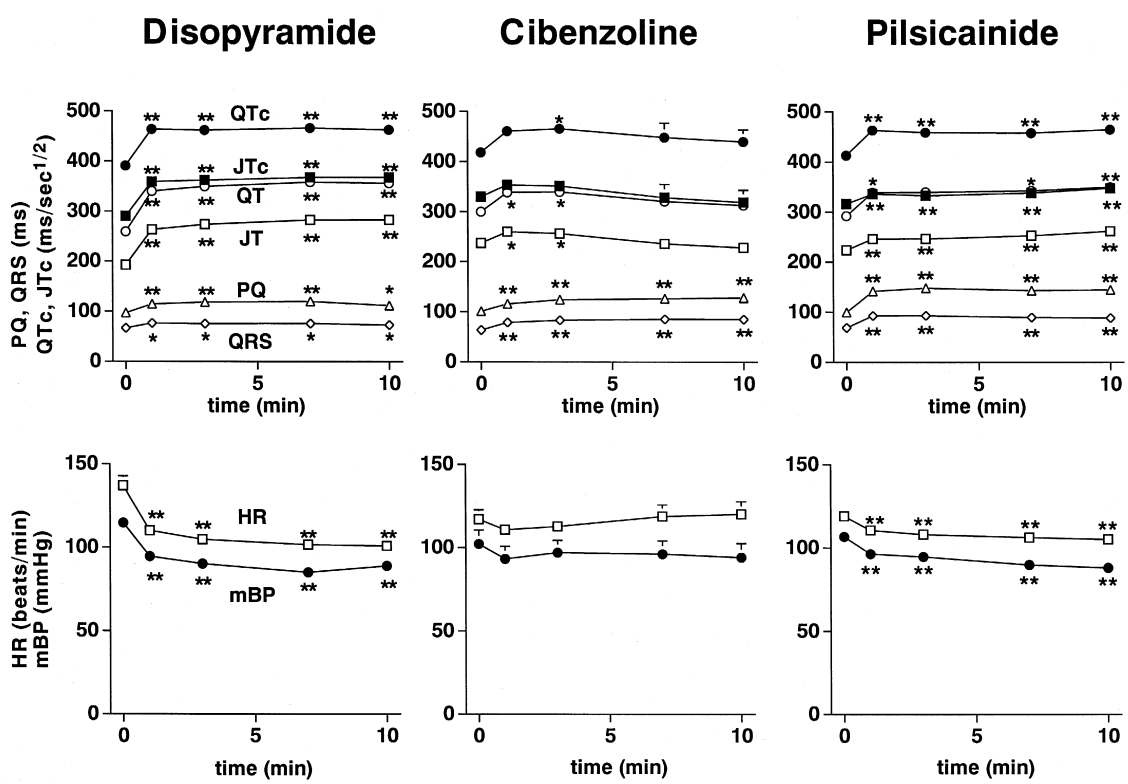

Fig. 2. Effects of disopyramide, cibenzoline, and pilsicainide on hemodynamic and electrophysiologic parameters in dogs. QTc: corrected QT interval, JTc: corrected JT interval, PQ; PQ interval, QRS: QRS duration, HR: heart rate, mBP: mean blood pressure. Data shown are the means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ by repeated measured ANOVA to compare the values before administration of drugs (time = zero).

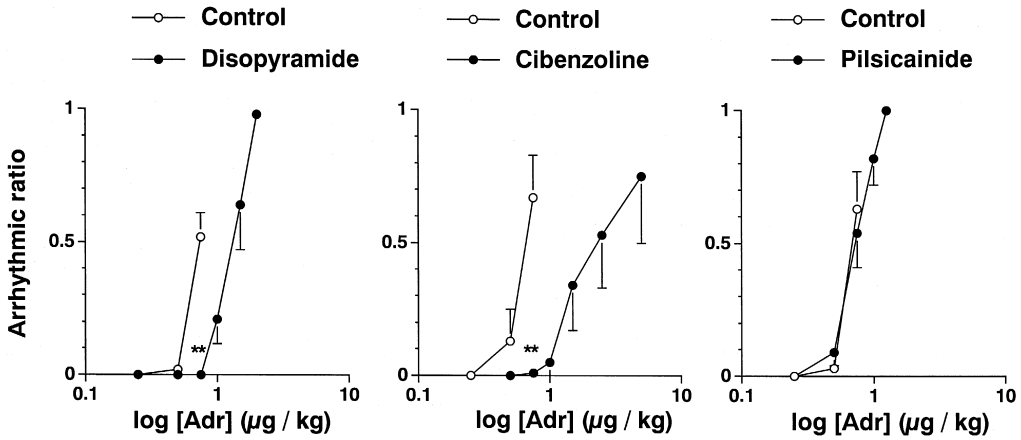

Fig. 3. Effects of disopyramide, cibenzoline, and pilsicainide on the arrhythmic ratio in dogs. The arrhythmic ratio in the drug-treated groups was compared with that in the control group at corresponding adrenaline doses. Each data point represents the mean, and vertical lines show S.E.M. $^{**}P < 0.01$, by paired Student's *t*-test to compare the arrhythmic ratio between drug-treatment and control.

disopyramide (PQ: from 97 ± 5 to 112 ± 7 ms, $P < 0.05$, QRS: from 67 ± 3 to 73 ± 3 ms, $P < 0.05$). Disopyramide suppressed adrenaline-induced arrhythmias, i.e. decreased the arrhythmic ratio attained using 0.75 μg kg^{-1} adrenaline ($P < 0.01$, Fig. 3), and abolished the arrhythmias produced by an inducing dose of adrenaline ($P < 0.05$, Fig. 4). Plasma concentrations of disopyramide were 0.1 ± 0.0, 10.1 ± 0.7, 8.0 ± 0.4, 7.2 ± 0.5 and 7.3 ± 0.6 μg ml^{-1} at 0, 5, 10, 30 and 40 min after the administration, respectively ($n = 6$).

3.2. Effects of cibenzoline on ECG, hemodynamic parameters, and arrhythmic ratio

In contrast to disopyramide, cibenzoline did not change the mean blood pressure and heart rate 10 min after its administration. QT, JT, QTc and JTc intervals were also not changed by cibenzoline, whereas cibenzoline significantly prolonged PQ interval from 101 ± 4 to 128 ± 6 ms ($P < 0.01$) and QRS duration from 63 ± 3 to 85 ± 4 ms ($P < 0.01$) (Fig. 2). Cibenzoline decreased the arrhythmic ratio attained using 0.75 μg kg^{-1} adrenaline ($P < 0.01$, Fig. 3) and suppressed the arrhythmias produced by an inducing dose of adrenaline ($P < 0.05$, Fig. 4). Plasma concentrations of cibenzoline were 0.2 ± 0.1, 4.1 ± 0.4, 3.5 ± 0.4, 3.2 ± 0.3 and 3.0 ± 0.1 μg ml^{-1} at 0, 5, 10, 30 and 40 min after administration, respectively ($n = 5$–6).

3.3. Effects of pilsicainide on ECG, hemodynamic parameters, and arrhythmic ratio

As shown in Fig. 2, at 10 min after administration, pilsicainide decreased mean blood pressure from 107 ± 4 to 88 ± 4 mmHg ($P < 0.01$) and heart rate from 119 ± 3

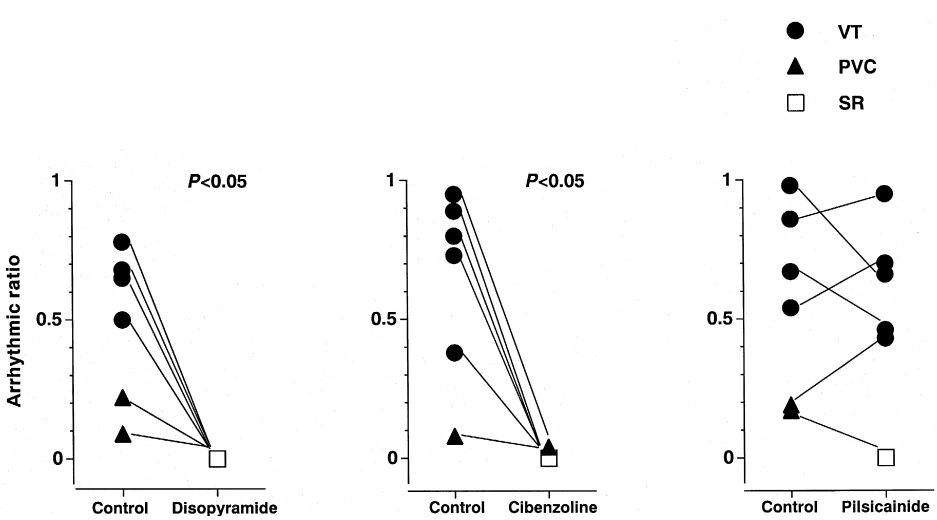

Fig. 4. Effects of disopyramide, cibenzoline, and pilsicainide on the changes of the severity of arrhythmia elicited by the arrhythmia-inducing dose of adrenaline in dogs. VT: ventricular tachycardia, PVC: premature ventricular complexes, SR: sinus rate. The severity of arrhythmias was compared by Wilcoxon signed-ranks test.

to 105 ± 3 beats min^{-1} ($P < 0.01$). QT interval and JT interval were also prolonged by pilsicainide from 292 ± 9 to 350 ± 16 ms ($P < 0.01$) and 224 ± 6 to 262 ± 13 ms ($P < 0.01$), respectively. Pilsicainide prolonged QTc and JTc intervals, from 413 ± 10 to 464 ± 16 ms $s^{-1/2}$ (by 12%) ($P < 0.01$) and from 316 ± 6 to 347 ± 13 ms $s^{-1/2}$ (by 10%) ($P < 0.01$), respectively. PQ interval and QRS duration were increased from 100 ± 4 to 145 ± 6 ms ($P < 0.01$), 69 ± 7 to 88 ± 6 ms ($P < 0.01$), respectively, 10 min after administration. In contrast to both disopyramide and cibenzoline, pilsicainide did not change the arrhythmic ratio, as shown by the adrenaline dose–arrhythmic ratio curve (Fig. 3) and the arrhythmias produced by an inducing dose of adrenaline (Fig. 4). Plasma concentrations of pilsicainide were 0.1 ± 0.0, 4.8 ± 0.4, 4.4 ± 0.3, 3.9 ± 0.4 and 4.1 ± 0.4 $\mu g\ ml^{-1}$ at 0, 5, 10, 30 and 40 min after administration, respectively ($n = 5–6$).

4. Discussion

In the present study, disopyramide (class IA) and cibenzoline (class IC) suppressed the arrhythmias induced by adrenaline, while pilsicainide (class IC) failed to suppress the arrhythmias. Prolongation of QTc interval was observed with disopyramide and pilsicainide but not with cibenzoline. These results are opposite to those obtained with class III drugs such as MS-551, KCB-328, and azimilide, drugs that prolonged QTc and which aggravated the adrenaline-induced arrhythmias, showing that class I drugs do not aggravate the arrhythmias regardless of their effects on the QTc interval.

The plasma concentration of disopyramide during the administration of adrenaline was between 7.2 and 8.0 $\mu g\ ml^{-1}$ in this study, which is close to the concentrations which produce a 50% reduction of canine two-stage coronary-ligation and digitalis-induced arrhythmias (IC_{50}, 6.9 and 5.9 $\mu g\ ml^{-1}$, respectively), as we previously reported (Hashimoto et al., 1991). Similar results were obtained for plasma concentrations of cibenzoline and pilsicainide. The concentrations of cibenzoline were between 3.2 and 3.5 $\mu g\ ml^{-1}$ during administration of adrenaline, and IC_{50}s for digitalis and two-stage coronary ligation-induced arrhythmias were 0.9 and 3.7 $\mu g\ ml^{-1}$. The concentrations of pilsicainide were between 3.9 and 4.4 $\mu g\ ml^{-1}$ during administration of adrenaline, and IC_{50}s for digitalis and two-stage coronary ligation-induced arrhythmias were 3.1 and 5.8 $\mu g\ ml^{-1}$. These results suggest that under our experimental conditions, plasma concentrations of these class I drugs are within effective plasma concentrations for dogs.

The proarrhythmic effects of class I and III drugs have been recognized in a number of clinical studies and we have also shown that class III drugs prolong QTc interval and aggravate adrenaline-induced arrhythmias in halothane-anesthetized dogs (Xue et al., 1998, 1999). The mechanism of this model is thought to be abnormal automaticity and triggered activity via the augmentation of cardiac Ca^{2+} channels (Hashimoto and Hashimoto, 1972; Hashimoto et al., 1982; Wit and Rosen, 1992), and halothane is known to interfere with cell-to-cell coupling (Hashimoto and Hashimoto, 1972; Spray and Burt, 1990). This model mimics the clinical situation of sympathetic overactivity. The proarrhythmic effects of class III drugs on this model may be induced by early afterdepolarizations associated with excessive action potential prolongation due to K^+ channel inhibition with the reverse use dependent property of these drugs (Xue et al., 1998). It is likely that drugs that inhibit the K^+ channel have a proarrhythmic potential in the adrenaline-induced arrhythmia model. Disopyramide, classified as class IA, inhibits K^+ channels, including the delayed rectifier K^+ channel (I_{Kr}), the transient outward current (I_{Kto}), and the ATP-sensitive K^+ channel ($I_{K,ATP}$) (Hiraoka et al., 1989; Wu et al., 1992; Virag et al., 1998), at therapeutic concentrations. These effects of disopyramide resulted in prolongation of the QTc interval (by about 20%) and JTc interval (by about 30%) in this study, suggesting prolonged repolarization. Although the extent of QTc-prolongation was similar to that induced by class III drugs, which exert arrhythmogenic effects (Xue et al., 1998), disopyramide decreased the arrhythmic ratio at the dose of 0.75 $\mu g\ kg^{-1}$ adrenaline and suppressed the arrhythmias elicited by the inducing dose of adrenaline.

Cibenzoline did not prolong the QT interval, the JT interval, the QTc interval or the JTc interval, but suppressed the arrhythmias induced by 0.75 $\mu g\ kg^{-1}$ adrenaline and arrhythmias produced by the inducing dose of adrenaline. We have already reported that a bolus injection of cibenzoline (5.0 $\mu g\ ml^{-1}$ i.v.), but not of disopyramide and pilsicainide, suppresses severe ventricular tachycardia or ventricular fibrillation induced by 2.5 $\mu g\ kg^{-1}\ min^{-1}$ adrenaline infusion (Shibuya et al., 1983; Hashimoto et al., 1985, 1987), re-confirming that cibenzoline suppresses arrhythmia induced by adrenaline.

It is known that cibenzoline and disopyramide have anticholinergic effects. However, these effects may not be the reason for the antiarrhythmic effects because both vagi were cut in this study, and 0.1 mg kg^{-1} atropine did not suppress the adrenaline-induced arrhythmias (data not shown, $n = 3$). The mechanisms of the antiarrhythmic effects of disopyramide and cibenzoline were not determined in this study. However, we have examined the effects of various antiarrhythmic drugs on adrenaline-induced arrhythmias and reported that class II (β-blockers) and class IV (Ca^{2+} channel blockers) antiarrhythmic drugs suppress adrenaline-induced arrhythmias (Hashimoto et al., 1991; Haruno and Hashimoto, 1993; Matsuzaki et al., 1993). Therefore, the antiarrhythmic effects of disopyramide and cibenzoline might be due to their additional effects of inhibiting cardiac Ca^{2+} channels. It has been

suggested that disopyramide at near therapeutic concentrations (2.0–5.0 μM) depresses the Ca^{2+} current and delayed outward K^+ current (Hiraoka et al., 1989), and Sato et al. (1994) suggested that cibenzoline inhibited the Ca^{2+} current ($K_d = 14.4$ μM) and delayed rectifier K^+ current ($K_d = 23$ μM). In fact, the plasma concentrations of disopyramide and cibenzoline measured in this study were very close to the in vitro Ca^{2+} channel-blocking concentrations.

The Ca^{2+} channel-blocking effect might have resulted in prolongation of the PQ interval observed in the case of disopyramide and cibenzoline. Inhibition of Na^+ channels also may partly contribute to the prolongation of the PQ interval by prolonging the intra-atrial and proximal His region conduction time. Prolonged QRS duration may be due to the inhibition of Na^+ channels.

Pilsicainide, a Na^+ channel inhibitor (Inomata et al., 1987), did not suppress arrhythmias induced by adrenaline, whereas QTc was prolonged by 12%. These results suggest that Ca^{2+} channel inhibition may be important in suppressing the adrenaline-induced arrhythmias, because only pilsicainide lacks Ca^{2+} channel-blocking activity at a therapeutic concentration ($IC_{50} = 55$ μM) (Inomata et al., 1987). Though pilsicainide prolonged the PQ interval, this may have been partly caused by prolongation of the intra-atrial and proximal His region conduction time, which are sodium channel-dependent (Ino et al., 1998). Pilsicainide prolonged QT and JT intervals, concomitantly decreasing the heart rate, but QTc and JTc intervals were also prolonged. Prolongation of QRS, in part, might have contributed to the prolongation of QTc. However, the prolongation of JTc interval was unexpected, because there were no reports suggesting inhibition of K^+ channels or the prolongation of action potential duration by this agent. Therefore, further studies are needed to clarify the mechanisms of prolongation of JTc by pilsicainide.

In this study, we did not observe proarrhythmic effects of disopyramide, cibenzoline, and pilsicainide by themselves, whereas we have reported the proarrhythmic effect of MS-551 and KCB-328 before adrenaline administration (Xue et al., 1998, 1999). However, it may be that higher plasma concentrations of these class I drugs prolong QTc interval more extensively and induce proarrhythmic effects, because we have shown that 5 mg kg^{-1} pilsicainide bolus infusion induces ventricular fibrillation (Hashimoto et al., 1985).

In conclusion, disopyramide suppressed adrenaline-induced arrhythmias with a prolongation of the QTc interval, whereas pilsicainide had no effect even with a prolongation of the QTc interval. Cibenzoline suppressed the arrhythmias without prolongation of the QTc interval. These results suggest that there is a dissociation between QTc prolongation and proarrhythmic effects among class I drugs. Multiple effects on cardiac ion channels, probably inhibition of Ca^{2+} currents, might have counteracted the arrhythmogenic effects of K^+ current inhibition and might have resulted in suppression of adrenaline-induced arrhythmias.

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