Effects of the New Class III Antiarrhythmic Drug MS-551 and \textit{d}-Sotalol on Canine Coronary Ligation-Reperfusion Ventricular Arrhythmias

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ABSTRACT—The antiarrhythmic effects of a new class III antiarrhythmic agent, MS-551 \([1,3\text{-dimethyl-6-}\{2-[N-(2-hydroxyethyl)-3-(4-nitrophenyl)propylamino]ethylamino\}-2,4(1H,3H)\text{-pyrimidinedione hydrochloride}\) were investigated using canine coronary ligation-reperfusion arrhythmia models under slow and fast heart rate conditions and compared with those of \textit{d}-sotalol. Slow and fast heart rate conditions were produced by using different anesthetics; i.e., halothane anesthesia for the slow heart rate condition and pentobarbital \(\text{Na}\) anesthesia for the fast heart rate condition. MS-551 prolonged QTc and suppressed the occurrence of fatal ventricular fibrillation (VF) on coronary reperfusion under either halothane or pentobarbital anesthesia. However, it also showed proarrhythmic effects, i.e., induction of torsades de pointes-like arrhythmia in 1 of 6 halothane anesthetized dogs before coronary ligation. \textit{d}-Sotalol did not suppress the reperfusion VF in halothane anesthetized animals, nor did it show proarrhythmic effects. However, in the pentobarbital anesthetized animals, \textit{d}-sotalol suppressed reperfusion VF accompanied by proarrhythmic effects in 1 of 7 dogs. \(\textit{d}\)-Sotalol did not show reverse rate dependent QT prolongation. These results indicate that although both these class III drugs have similar electrophysiological properties, such as QTc prolongation, they have different antiarrhythmic effects. Also, antifibrillatory effects of class III drugs on coronary reperfusion apparently can not be explained solely by their QT prolonging effects.

\textbf{Keywords:} Antiarrhythmic drug (class III), \textit{d}-Sotalol, MS-551, Reperfusion ventricular fibrillation, QT prolongation

The occurrence of ventricular arrhythmias is a serious problem facing patients with coronary artery disease or myocardial infarction and most of these arrhythmias require treatment with antiarrhythmic agents, but the available antiarrhythmic agents, especially those of the class I type, are far from ideal with limited efficacy and serious side effects. Also, sudden death occurring in patients suffering from old myocardial infarction may result from long term use of class I antiarrhythmic agents. On the other hand, class III drugs, such as amiodarone and sotalol seem to be effective on these arrhythmias. MS-551 \([1,3\text{-dimethyl-6-}\{2-[N-(2-hydroxyethyl)-3-(4-nitrophenyl)propylamino]ethylamino\}-2,4(1H,3H)\text{-pyrimidinedione hydrochloride}\) is a newly synthesized class III antiarrhythmic agent with rapid onset of action (6–12) (Fig. 1). Electrophysiologically, MS-551 is similar to the standard class III drug, \(\textit{d}\)-sotalol, and it is classified as a highly potent K channel blocker in the classification proposed in the Sicilian Gambit. MS-551 preferentially blocks \(\text{i}_\text{K}\) channels without affecting Na and Ca channel activities, and thus prolongs the action potential duration (APD). MS-551 is reported to be effective on electrically induced ventricular tachycardia (VT) in dogs with previous myocardial infarction, but is not effective on spontaneously occurring VT produced by two-stage coronary ligation or digitalis intoxication. Similarly, \(\textit{d}\)-sotalol has been reported to be ineffective against spontaneously occurring VTs except for adrenergically-induced arrhythmias.

Class III agents prolong the ventricular effective refractory period and thus are thought to increase the excitation wave length and decrease the excitation gap in the reentry circuit and finally decrease the chance of maintenance or occurrence of reentry arrhythmias. Since coronary ligation-reperfusion arrhythmias in experimental animals are thought to be generated mainly by a reentry mechanism and another new class III agent, E-4031, has been shown by us to be effective in suppressing reperfusion ventricular fibrillation (VF), we examined the effects of MS-551 on arrhythmia models, i.e., canine coronary...
occlusion and reperfusion arrhythmia models, and compared them with those of the standard class III agent d-sotalol. In addition, as these new class III drugs are reported to have reverse use dependent QT or APD prolonging effects (19, 20), we examined the effects of the two drugs on the QT and the occurrence of reperfusion VF under different heart rate conditions by using two different anesthetics, halothane and pentobarbital. The heart rate under the former condition was slow and under the latter condition was fast. In comparison to the forced, direct electrical driving of the heart, the heart rate changes caused by anesthetics is spontaneous without adding experimental procedures, such as sinus node destruction, surgical production of AV block or introduction of electrodes, and is worth utilizing as an experimental model of tachycardia or bradycardia.

MATERIALS AND METHODS

Coronary ligation and reperfusion arrhythmias

Sixty-four beagle dogs of either sex, weighing 7 – 10 kg, were used. Dogs of the halothane anesthetized group were anesthetized initially with intravenous thiopental Na, 30 mg/kg, and intubated. Anesthesia was maintained by 1.0% halothane, vaporized with 100% oxygen using a volume-limited ventilator (20 ml/kg, 15 strokes/min). Dogs of the pentobarbital anesthetized group were given an intravenous bolus injection of 30 mg/kg pentobarbital Na followed by an infusion of 5 mg/kg/hr.

In both groups, the chest was opened, and the left anterior descending coronary artery (LAD) was isolated just proximal to the first diagonal branch. MS-551 was infused intravenously at a speed of 3.6 mg/kg/hr. d-Sotalol was infused intravenously at a speed of 10 mg/kg/hr. Since the incidence of occurrence of coronary ligation-reperfusion arrhythmias is known to be quite variable (21), experiments were randomized using a pair of beagles (by coin-flip); one received the drug infusion, and the other received 0.9% NaCl (saline) infusion. The speed of infusion was 1 ml/min. After 30 min of the start of either MS-551, d-sotalol or saline infusion when their effects on QTc became stabilized, the LAD ligation was performed using a silk thread for 30 min and then released to examine reperfusion responses. The drug solution was infused during the whole course of the experiment.

Pairs of epicardial electrodes were sutured on the border zone of the ischemic area of the left ventricle to continuously record the ventricular electrograms. QT interval was assessed from the lead II ECG and the ventricular surface electrogram monitored at a fast 100 cm/sec recording speed. The QTc interval was calculated by Bazett's formula, QTc=QT/√RR. Effects on the heart rate were assessed using a tachograph triggered by the ECG, and effects on the blood pressure were continuously monitored through a double lumen arterial cannula in the femoral artery. Arterial blood samples were obtained through another lumen of the cannula just before 1) the start of MS-551 or d-sotalol infusion, 2) LAD occlusion and 3) LAD reperfusion.

The experiment was approved by the Animal Use and Care Committee of the Yamanashi Medical University and performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical University.

Drugs

The following drugs were used: pentobarbital sodium (Tokyo Kasei, Tokyo), thiopental sodium (Tanabe Seiyaku Co., Osaka), halothane (Takeda Chem. Ind., Osaka), adrenaline injection (1 mg/ml) (Daichi Seiyaku Co., Tokyo) and ouabain octahydrate (Sigma Chemical Co., St. Louis, MO, USA). MS-551 and d-sotalol were gifts from Mitsui Pharmaceuticals, Inc., Tokyo and Bristol-Myers-Squibb K.K., Tokyo, respectively.

Determination of MS-551 plasma levels

Arterial blood samples were collected into heparinized syringes at a predetermined time and centrifuged at 3000×g for 5 min. The plasma was stored at about -80°C until analysis at the Institute of Biological Science, Mitsui Pharmaceuticals, Inc. (Mobara). Concentrations of MS-551 were determined by an HPLC procedure. MS-551 in the plasma was extracted with a Bond Elut CH column (Varian Associates, Inc., Harbour City, CA, USA). HPLC analysis was performed with the Inertsil ODS-2 column, 4.6 mm × 150 mm, 5-mm particle size; GL Sciences, Inc., Tokyo. The mobile phase was 0.1 M ammonium acetate / methanol / acetonitrile, 64/18/18, and the flow rate was 0.8 ml/min. The elution profile was monitored at 270 nm. MS-12-514, 1,3-dimethyl-6-[(2-[N-
(2-hydroxyethyl)-3-(4-nitrophenyl)butylamino)-2,4-(1H,3H)-pyrimidinedione hydrochloride, was used as an internal standard. The peak area ratio was used for quantitative calculation.

**Determination of d-sotalol plasma levels**

Arterial blood samples were collected into heparinized syringes at a predetermined time and centrifuged at 3000×g for 5 min. The plasma was stored at about -80°C until analysis at the Preclinical Research Laboratories, Bristol-Myers-Squibb K.K. (Okazaki). Concentrations of d- and l-sotalol in the plasma were determined by a stereospecific HPLC procedure. The d- and l-sotalol in the plasma were extracted by using a Sep-Pak C18 column and then derivatized with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC). HPLC analysis was performed on a STR ODS II column, 4.6×150 mm, 5-mm particle size; Shimadzu Techno Research, Kyoto. The mobile phase was 0.02 M NH4H2PO4/ acetonitrile, 60/40, and the flow rate was 1.0 ml/min. The chromatogram was monitored with an UV-detector at 225 nm. p-Hydroxybenzoic acid isoamyl ester was used as an internal standard. The relative peak area was used for quantitative calculation.

**Statistics**

Analysis of variance was used to compare QTc, heart rate and blood pressure values between the drug-treated and saline-treated experiments. Incidence of arrhythmias was compared by the chi squared test. Results are expressed as means±standard deviation. A P value less than 0.05 was considered significant at each time point.

**RESULTS**

**MS-551 in halothane anesthetized beagles**

In the preliminary dose finding experiments using lower speeds of MS-551 infusion, for example, 0.6 mg/kg/hr, the occurrence of reperfusion VF was as that in high as that in control group, so we decided to employ a 3.6 mg/kg/hr infusion speed. In 12 beagles anesthetized by halothane, the heart rate and mean blood pressure were measured under saline and MS-551 (3.6 mg/kg/hr) treatments. The results are shown in Table 1.

**Table 1. Effects of MS-551 on canine coronary ligation-reperfusion ventricular arrhythmias**

|                          | Saline  | MS-551 (3.6 mg/kg/hr) |
|--------------------------|---------|-----------------------|
| **Halothane anesthesia, n=** | 6       | 6                     |
| Before administration (0 min) |         |                       |
| Heart rate (beats/min)    | 106±6   | 110±10                |
| Blood pressure (mmHg)     | 103±6   | 95±8                  |
| QTc (sec¹/²)               | 0.27±0.01 | 0.29±0.05             |
| Before occlusion (30 min)  |         |                       |
| Heart rate (beats/min)    | 98±7*   | 86±9**                |
| Blood pressure (mmHg)     | 99±11   | 88±6                  |
| QTc (sec¹/²)               | 0.27±0.02 | 0.43±0.01**            |
| VPC during 30-min occlusion (beats) | 517±641 | 222±339               |
| VF on reperfusion          | 5/6     | 1/6*                  |
| **Pentobarbital anesthesia, n=** | 6       | 6                     |
| Before administration (0 min) |         |                       |
| Heart rate (beats/min)    | 207±28  | 219±29                |
| Blood pressure (mmHg)     | 132±13  | 134±8                 |
| QTc (sec¹/²)               | 0.31±0.02 | 0.32±0.02             |
| Before occlusion (30 min)  |         |                       |
| Heart rate (beats/min)    | 210±26  | 189±25*               |
| Blood pressure (mmHg)     | 133±14  | 136±4                 |
| QTc (sec¹/²)               | 0.31±0.02 | 0.36±0.03*            |
| VPC during 30-min occlusion (beats) | 862±753 | 239±131               |
| VF on reperfusion          | 5/6     | 2/6*                  |

*P<0.05, **P<0.01, versus values of before administration. VPC=ventricular premature contraction, VF=ventricular fibrillation.
108±8 beats/min and 99±10 mmHg, respectively. As shown in Table 1, the QTc interval in the saline injected beagles did not change. As shown in Fig. 2, 30 min of infusion of MS-551 induced in one beagle ventricular arrhythmias of torsades de pointes type VT (Fig. 3), but no arrhythmias occurred with saline infusion. During the 30 min of complete LAD occlusion, ventricular arrhythmias including ventricular premature contractions (VPCs) and VT, defined as more than three consecutive VPCs, occurred in both the MS-551 and saline treated beagles, but there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion as shown in Table 1. Immediately after reperfusion MS-551 suppressed the occurrence of VF. These fatal VF occurred within 6 min of reperfusion. The QTc interval in the MS-551 injected beagles increased 48%. The heart rate decreased in the MS-551 treated group just before LAD occlusion. The mean blood pressure did not change in either the saline- or MS-551-treated groups. The MS-551 plasma concentrations at the start of infusion, at the 15th, 25th min after the start of infusion, 5 min before reperfusion (55th min) and 25 min after reperfusion (85th min) were 0.00±0.00 (n=6), 1.66±0.58 (n=6), 1.80±0.81 (n=6), 2.01±0.90 (n=6) and 1.93±0.87 (n=4) μg/ml, respectively. MS-551 linearly increased QTc as the plasma concentration increased (n=27, r=0.89, P<0.01). The linear regression was expressed as (%QTc increase) = 18.4 × (MS-551 plasma concentration in μg/ml) + 5.2 (Fig. 4).

MS-551 in pentobarbital anesthetized beagles

In pentobarbital anesthetized beagles, we examined the same 3.6 mg/kg/hr infusion of MS-551. The heart rate and mean blood pressure of 12 beagles were 213±28 beats/min and 133±10 mmHg, respectively. Thirty minutes of infusion of MS-551 and saline did not induce any ventricular arrhythmias. As shown in Table 1, VPCs occurred in both the MS-551 (3.6 mg/kg/hr) - and saline-treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion. MS-551 (3.6 mg/kg/hr) suppressed the occurrence of VF immediately after reperfusion. The QTc interval in the MS-551 (3.6 mg/kg/hr)-injected beagles increased significantly, but only 12%. The heart rate decreased in the MS-551-treated group. The blood pressure did not change in either the saline- or MS-551-treated group. The MS-551 plasma concentrations at the start of infusion, 2 min before coronary occlusion (28 min after the start of infusion) and 2 min before reperfusion (58 min after the start of infusion) were 0.00±0.00,
Dog treated with MS-551 (3.6 mg/kg/hr) before occlusion

Fig. 3. Proarrhythmic effects of intravenous infusion of MS-551. This torsades de pointes-like VT occurred before ligating the LAD.

1.31 ± 0.26 and 1.65 ± 0.42 μg/ml (n = 6), respectively. MS-551 linearly increased QTc as the plasma concentration increased (n = 17, r = 0.83, P < 0.01). The linear regression was expressed as (％QTc increase) = 7.4 × (MS-551 plasma concentration in μg/ml) + 0.59 (Fig. 4).

d-Sotalol in halothane anesthetized beagles

In the preliminary dose finding experiments using lower speeds of d-sotalol infusion, for example 1 – 5 mg/kg/hr, the QTc did not increase significantly, thus a 10 mg/kg/hr infusion speed was employed. The heart rate and mean blood pressure of 12 beagles anesthetized with halothane were 133 ± 16 beats/min and 117 ± 15 mmHg, respectively. Thirty minutes of infusion of d-sotalol and saline did not induce any ventricular arrhythmias. During the 30 min of LAD occlusion, ventricular arrhythmias including VPCs and VT occurred in both the d-sotalol- and saline-treated beagles as shown in Table 2. However, immediately after reperfusion, there were no differences in the occurrence of VF in the d-sotalol- and the saline-treated groups. The low incidence of VF in the control group...
made it quite difficult to show the efficacy of d-sotalol to suppress VF in the present relatively small number of dogs. The QTc interval in the d-sotalol-injected beagles increased 17%. The heart rate decreased in the d-sotalol-treated dogs. The mean blood pressure did not change in either the saline- or d-sotalol-treated dogs.

Since there was no antifibrillatory effect by d-sotalol at 10 mg/kg/hr, which is the maximum dose when given as a bolus in the previous studies (4), another experiment using d-sotalol at 15 mg/kg/hr was performed. Immediately after reperfusion, again partly due to the low incidence of VF, 2 of 6 beagles in the saline-injected group, there was no suppression of VF by the higher dose of d-sotalol, 2 of 6 beagles. The initial QTc interval in the d-sotalol (15 mg/kg/hr)-injected beagles was 0.31±0.04 sec\(^{1/2}\), and it increased further just before LAD occlusion to 0.39±0.05 sec\(^{1/2}\) (26%, \(P<0.01\)). The d-sotalol plasma concentrations at the start of infusion, 1 min before coronary occlusion (29 min after the start infusion) and 1 min before occlusion (59 min after the start of infusion) were 0.15±0.38, 15.51±1.80 and 19.42±5.02 μg/ml (n=6),

### Table 2. Effects of d-sotalol on canine coronary ligation-reperfusion ventricular arrhythmias

|                  | Saline    | d-sotalol (10 mg/kg/hr) |
|------------------|-----------|------------------------|
|                  | 7         | 7                      |
| **Halothane anesthesia, n=7** |           |                        |
| Before administration (0 min) |           |                        |
| Heart rate (bpm)  | 130±19    | 137±13                 |
| Blood pressure (mmHg) | 118±18   | 119±10                 |
| QTc (sec\(^{1/2}\)) | 0.35±0.04 | 0.35±0.04              |
| **Before occlusion (30 min)** |           |                        |
| Heart rate (bpm)  | 128±27    | 106±10*                |
| Blood pressure (mmHg) | 111±20   | 104±8                  |
| QTc (sec\(^{1/2}\)) | 0.34±0.03 | 0.41±0.04**            |
| VPC during 30-min occlusion (beats) | 259±351 | 82±103                 |
| VF on reperfusion | 3/7       | 3/7                    |
| **Pentobarbital anesthesia, n=7** |           |                        |
| Before administration (0 min) |           |                        |
| Heart rate (bpm)  | 179±26    | 175±26                 |
| Blood pressure (mmHg) | 119±18   | 125±9                  |
| QTc (sec\(^{1/2}\)) | 0.34±0.03 | 0.35±0.02              |
| **Before occlusion (30 min)** |           |                        |
| Heart rate (bpm)  | 184±18    | 125±17**               |
| Blood pressure (mmHg) | 128±20   | 121±3                  |
| QTc (sec\(^{1/2}\)) | 0.35±0.03 | 0.39±0.02**            |
| VPC during 30-min occlusion (beats) | 266±273 | 189±261 (n=6)          |
| VF on reperfusion | 4/7       | 1/6*                   |

\(^*P<0.05, ~**P<0.01,\) versus values of before administration. VPC=ventricular premature contraction, VF=ventricular fibrillation.

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Fig. 5. Linear relationship between QTc prolongation and d-sotalol plasma concentration. In both halothane and pentobarbital anesthetized groups, QT prolonged linearly with d-sotalol concentration, indicating no reverse rate dependency in QT prolongation.
respectively. d-Sotalol linearly increased QTc as the plasma concentration increased (n=18, r=0.85, P<0.01). The linear regression was expressed as (%QTc increase) = 1.2 × (d-sotalol plasma concentration in μg/ml) + 0.4 (Fig. 5).

d-Sotalol in pentobarbital anesthetized beagles

In pentobarbital anesthetized beagles, we examined the effects of 10 mg/kg/hr d-sotalol. The heart rate and mean blood pressure of 14 beagles were 177±25 beats/min and 123±14 mmHg, respectively. Thirty minutes of infusion of d-sotalol induced VPCs and VT in one beagle. During the 30 min of LAD occlusion, VPCs and VT occurred in both the d-sotalol (10 mg/kg/hr)- and saline-treated beagles, and there were no statistically significant differences in the number of total VPCs in the 30 min of occlusion (Table 2), but one beagle in the d-sotalol group died of VF. However, immediately after reperfusion, d-sotalol at 10 mg/kg/hr suppressed the occurrence of VF. The QTc interval in the d-sotalol (10 mg/kg/hr)-injected beagles increased only 11%. The heart rate decreased in the d-sotalol (10 mg/kg/hr)-treated group. The blood pressure did not change in either the saline- or d-sotalol-treated beagles. The d-sotalol plasma concentrations at the start of infusion, 2 min before coronary occlusion (28 min after the start of infusion) and 2 min before reperfusion (58 min after the start of infusion) were 0.43±0.61, 8.25±1.20 and 12.40±1.57 μg/ml (n=6). d-Sotalol linearly increased QTc as the plasma concentration increased (n=17, r=0.84, P<0.01). The linear regression was expressed as (%QTc increase) = 1.9 × (d-sotalol plasma concentration in μg/ml) − 1.9 (Fig. 5).

DISCUSSION

The results of the present investigation indicate that MS-551 was effective in suppressing the occurrence of coronary reperfusion VF in the low heart rate halothane anesthetized beagles, but d-sotalol was not effective, partly due to the lower occurrence of reperfusion VF in the control group (3 out of 7 beagles). However, when pentobarbital sodium was used as an anesthetic, d-sotalol as well as MS-551 were effective in suppressing the VF. Although the rate of occurrence of reperfusion VF was not high (59% in all 32 control beagles of the present study) and variable as has already been reported (21), the suppression of VF by these drugs might be related to the prolongation of the refractory period. It is because new class III antiarrhythmic drugs are reported not to suppress either cardiac Na or Ca channels and thus had no antiarrhythmic effects on automaticity arrhythmias such as those produced by two-stage coronary ligation or digitalis in dogs (6). On the contrary, the mechanism of the occurrence of the coronary reperfusion arrhythmias is thought to be re-entry of excitation in and around the acutely infarcted myocardium (16, 17). We observed that pronounced QTc prolongation, as much as 48% by MS-551, was accompanied by the suppression of the VF in low heart rate halothane anesthetized dogs. This is consistent with our previous findings that a similar new class III drug, E-4031, prolonged QTc 39% and suppressed the occurrence of reperfusion VF (18). With d-sotalol, the extent of QTc increase, 17% in halothane anesthetized beagles, was far smaller in comparison to that of the two drugs, and it did not suppress the occurrence of VF. However, in high heart rate pentobarbital anesthetized beagles, d-sotalol and MS-551 suppressed reperfusion VF with only an 11% and 12% increase of QTc, respectively. The fact that the effect of MS-551 in prolonging QTc was attenuated under the high heart rate condition, indicates that a reverse use dependent effect of this new class III drug (Fig. 4) was also observed under in vivo as well as under in vitro conditions (19, 20). However, unlike the reports by others, d-sotalol did not show reverse use dependency of its QT prolongation (Fig. 5). The discrepancy between our results and those of others (19, 20) may indicate that anesthetics affect not only the heart rate, but possibly also cardiac excitation and conduction. Further experiments using other methods of altering the heart rate may be needed to clarify this problem. From our data, it is difficult to correlate the lack of reverse use dependent QT prolongation of d-sotalol with its lack of VF suppression in halothane anesthetized beagles in the present study. Also it is difficult to explain from our data why a smaller degree of QT prolongation was enough to suppress the occurrence of VF in the high heart rate pentobarbital anesthetized beagles.

d-Sotalol was reported not to suppress reperfusion VF after 20 min coronary occlusion in dogs by intravenous doses up to 10 mg/kg, but it suppressed the occurrence of ventricular arrhythmias during coronary occlusion (22). The same group also reported that during the LAD occlusion, ventricular arrhythmia was suppressed by 5 mg/kg d-sotalol in pentobarbital anesthetized dogs (23). Lynch et al. (24) also reported that in dogs with old anterior myocardial infarction, cumulative doses up to 8 mg/kg of d-sotalol suppressed electrical stimulation-induced VT and VF, in dogs under pentobarbital anesthesia. Our present finding that d-sotalol was not effective in suppressing arrhythmias during occlusion, but suppressed reperfusion VF is different from those reports despite the use of the same anesthesia. The reason for the difference is difficult to explain, but it may be related to the different protocols among these studies.

As for the arrhythmogenic effect of MS-551 in the control period of halothane anesthetized beagles, VT similar
to torsades de pointes occurred before applying the coronary ligation (1 out of 6 beagles), but none of the pentobarbital anesthetized beagles showed such responses except for one dog each for the halothane and pentobarbital anesthetized groups which showed VPC or non-lethal VTs. This may be due to the use of halothane, because the severe arrhythmogenic effect could also be seen in our halothane anesthetized dogs that had been given E-4031 (18). Halothane is known not only to decrease the sinoatrial rate, but is also known to sensitize the cardiac cell to the arrhythmogenic effect of catecholamines, probably because halothane interferes with the cell to cell coupling and thus decreases the conduction velocity (25). So with the concomitant use of halothane, new class III drugs showed arrhythmogenic effects, and such side effects may occur in clinical situations where the QT interval is dramatically increased after the use of class III drugs.

We must identify the extent of QT prolongation responsible for induction or suppression of arrhythmias or determine the reason for the different effectiveness of d-sotalol using two different anesthetics. However, it is interesting that electrophysiologically similar MS-551 and d-sotalol are quite different from other classes of antiarrhythmic drugs in their effectiveness on canine ventricular arrhythmia models. The spontaneously occurring arrhythmias, such as digitalis-induced, two-stage coronary ligation induced- and halothane-adrenaline-induced- VTs, are useful in detecting the antiarrhythmic effects of class I, II and IV drugs, but are not suited for demonstrating the antiarrhythmic effect of class III drugs. It is interesting to know whether such data will be obtained in clinical situations and to determine whether these drugs will be particularly effective for suppressing postinfarction VF or to prevent sudden death.

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