Electrophysiological Effects of MS-551, a New Class III Agent: Comparison with dl-Sotalol in Dogs

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ABSTRACT
MS-551 is a newly synthesized, nonspecific K⁺ channel blocker. To elucidate its electrophysiological and potential proarhythmic effects relative to those of dl-sotalol in vivo, serial changes in ECGs, endocardial and epicardial monophasic action potential durations, and left and right ventricular pressures were measured simultaneously in pentobarbital-anesthetized open-chest dogs. Complete heart block was produced by the injection of 37% formaldehyde into the atrioventricular node. Intravenous administration of MS-551 produced prolongation of action potential duration at 90% repolarization time (APD90) immediately after the beginning of infusion and reached plateau at 10 min. MS-551 (1 mg/kg) caused 73 ± 8% increase in APD90 and 28 ± 5% increase in QT, at basic cycle length of 700 msec. The maximal prolongation of APD90 induced by 1 mg/kg MS-551 was 39% greater than that by the same dose of sotalol (P < .01). The dose-response curve of prolongation of ventricular effective refractory period produced by MS-551 was shifted significantly to the left compared with that induced by sotalol. The EC50 was 0.5 ± 0.1 mg/kg and 1.2 ± 0.2 mg/kg for MS-551 and sotalol, respectively (P < .05). When 0.5 mg/kg MS-551 doses were used, no ventricular arrhythmia was induced by stimulation at 200-msec basic cycle length. When 1.5 mg/kg sotalol was administered, 5 of 15 developed torsade de pointes, 2 of 15 developed ventricular fibrillation and 5 of 15 developed sustained ventricular tachycardia. The idioventricular rates and left ventricular pressures were reduced significantly by sotalol, not by MS-551. In conclusion, MS-551 is a potent class III antiarrhythmic agent that selectively prolongs repolarization in the ventricular myocardium and appears to be devoid of autonomic effects. Dose for dose, it is more potent in prolonging the APD90 and the right ventricular effective refractory period possibly with a lower tendency for the development of proarrrhythmia in a canine heart-block model.

In recent years, numerous class III agents have been synthesized and are being characterized experimentally and clinically (Colatsky et al., 1990). Interest in this series of compounds has stemmed from the clinical success with amiodarone and dl-sotalol in the treatment of lethal ventricular arrhythmias and sudden death (Mason and ESVEM Investigators, 1993). Although associated with a low to negligible incidence of proarrhythmia, amiodarone’s propensity to induce organ toxicity (pulmonary toxicity, neurotoxicity, the variegated and cumulative toxicity) that develops in a proportion of patients as a function of time limits the drug’s long-term usefulness (Weinberg et al., 1993) in many patients. dl-Sotalol, exhibiting beta blocking properties and producing a marked prolongation of the cardiac action potential duration in vitro and in vivo, has recently emerged as a potent antiarrhythmic agent (The CASCADE Investigators, 1993). It too is not ideal compound as in certain subsets of patients it has been associated with life-threatening ventricular arrhythmia, particularly TdP (Cui et al., 1994). It may also exacerbate heart failure, although the reported incidence of heart failure is lower than that for other beta blockers. Hence, the need to develop a potent and safer antiarrhythmic agent remains to be met. However, the quest for less toxic alternative class III agents has thus far been met with only a modest success (Kehoe et al., 1993). In recent years, there has been an increasing interest in the possibility of controlling cardiac arrhythmias, especially by homogeneously prolonging cardiac repolarization.

MS-551, a new investigational compound, is reported to be a potent class III antiarrhythmic agent, which prolongs the APD, QT, and VERP in rat (Chen et al., 1996), dog (Hashimoto et al., 1995) and human (Isomoto et al., 1995). Distinct from other class III agents, such as dofetilide and sotalol, MS-551 and sotalol are nonselective potent K⁺ channel blockers (Nakayas, 1993; Hashimoto et al., 1995; Sato et al., 1995) and share many antiarrhythmic activities (Nakaya et al., 1993; Singh, 1993; Hashimoto et al., 1995). Both drugs

ABBREVIATIONS: APD90, action potential duration at 90% repolarization time; LVP, left ventricular pressure; RVP, right ventricular pressure; TdP, torsade de pointes; IVR, idioventricular rate; VT, ventricular tachycardia; NSVT, nonsustained ventricular tachycardia; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; RVERP, right ventricular effective refractory period; MAP, monophasic action potential.
have been found to have antiarrhythmic action against atrial and ventricular arrhythmias in the conscious dog and isolated cardiac preparations (Hondegem and Synders, 1990; Kamiya et al., 1992). They both have been reported to be effective on electrically induced VT in dogs with previous myocardial infarction but are not effective on spontaneously occurring VT produced by two-stage coronary ligation or digitalis intoxication (Hashimoto et al., 1995). Both drugs reduce the incidence of sustained VP after reperfusion (Murakawa et al., 1997). The potent defibrillatory effect of MS-551 and sotalol has been thought to be related to the blockade of channels other than IK. Recently, Hashimoto et al. (1995) compared the reverse rate-dependent QT-prolonging effect of MS-551 and dl-sotalol in coronary ligation-reperfusion model at slow and fast heart rates. Yamada et al. (1996) compared the reverse frequency-dependent prolongation of effective refractory period of sinoatrial node, papillary muscle and atrioventricular node induced by MS-551, sematilide and E-4031. There is no report on comparison of simple antiarrhythmic molecules, such as MS-551, with single action vs those with more complex compounds that act by prolonging cardiac repolarization as their principal action, such as dl-sotalol.

The purposes of this study were to systematically evaluate the electrophysiological and proarrhythmic effects of MS-551 and dl-sotalol at comparable biological effective dose and to quantitatively compare the reverse frequency-dependent prolongation of cardiac refractoriness induced by these two drugs at precise and wider frequency range by using the complete AV block canine model.

Methods

Animal preparation. Thirty adult male mongrel dogs weighing 20 to 25 kg were studied after intravenous sodium pentobarbital anesthesia (30 mg/kg). The animals were intubated and artificially ventilated with room air using a positive-pressure Harvard respirator. The body temperature was kept within the physiological range. With the dogs right side up, thoracotomy was performed via the fifth right intercostal space, and the heart was suspended in a pericardial sling. Care was taken to minimize blood loss. The right and left femoral arteries and right jugular veins were exposed. A venous cannula in the femoral vein was used to infuse normal saline to replace spontaneous fluid losses and inject drugs. The Ag-AgCl bipolar dual purpose electrode catheter was inserted through the right jugular vein and advanced into the right ventricle. Its electrode tip was positioned in the right ventricular apex to record the endocardial MAPs during sinus rhythm and during pacing at various frequencies.

The Swan-Ganz and pigtail catheters were inserted via the femoral vein and artery and advanced into the right and left ventricular cavities to continuously monitor ventricular pressures. A customized flexible Ag-AgCl electrode was used to record the epicardial MAPs by directly attaching to the epicardium of the right ventricular apex. The electrode catheter position was placed in a similar position at the time for base-line electrophysiological study and during subsequent electrophysiological testing of drugs (MS-551 and dl-sotalol).

Electrodes were placed on the four limbs for monitoring the surface ECG. The surface ECG leads I, II and aVF and arterial blood pressure were simultaneously displayed on a multichannel oscilloscope (M3VR12; Etar, Beaverton, OR) screen and recorded on an ink-jet recorder at a paper speed of 50 to 100 mm/sec. The canine complete heart block model was used because it provides the choice of a wide range of stimulation frequencies, permitting the precise evaluation of the effects of heart rate on hemodynamic and electrophysiological parameters. Formaldehyde (0.1 ml, 37%) was directly injected into atrioventricular node through the groove between the right atrium and aorta before each experiment to produce total heart block (Steiner and Kovalik, 1968). After complete heart block was produced, the idioventricular rhythm that appeared immediately after atrioventricular block was monitored for stability for 30 min. If the rhythm tended to revert to normal sinus or if nodal tachycardia with narrow QRS complexes developed, a second injection of formaldehyde was given.

Electrophysiological study. Electrophysiological study was performed in the base-line drug-free state. A 7F catheter with two platinum ring electrodes for pacing (located 2 mm from the catheter tip) and a pair of Ag-AgCl electrodes (at the distal tip and 5 mm proximal from the tip) (EP Technology, Palo Alto, CA) were used for the recording of MAPs at the right ventricular apex. This catheter permitted the determination of both the RVERP and the MAP duration at the same location (Franz et al., 1990). All pacing was performed with a pulse duration of 2 msec, at a current intensity of twice the late diastolic threshold, which was invariably ≤1 mA. Recordings were obtained at paper speeds of 50 to 100 mm/sec (PPG VR-16 or MIDAS, Lenexa, KA). MAP duration was determined after steady state right ventricular pacing at cycle lengths of 700, 600, 500, 400, 300, 250 and 200 msec for 60 complexes at twice diastolic threshold. Steady state recordings were obtained after 7 min of pacing at each new rate. The amplitude of the MAP was determined from the diastolic base line to the plateau and the APD∞ from the initial MAP upstroke to the point where repolarization was 90% complete. Three APD complexes at each paced cycle length were measured and mean values were calculated.

The RVERP was measured at the same catheter position as the MAP recordings before and after the test drugs. After a basic drive run of 10 S1 beats and an extrastimulus (S2) was applied during late diastole with successive decrement of the coupling interval of the extra stimulus by 5 msec. One-second pause was used between runs. When S2 extrastimulus failed to elicit a propagated response on two successive attempts, the S1-S2 interval was taken as the RVERP.

MAP recordings and RVERP determinations were obtained both at base line and after an intravenous bolus with MS-551 or dl-sotalol. The pacing protocol was identical for each dog for the investigation of both MS-551 and dl-sotalol on different days. The end point of the pacing protocol was the completion of the entire protocol.

The ECG standard was the same as that used in the initial study. The QT interval was measured from the surface ECG obtained just before the electrophysiology study. The lead with the most prominent T wave and the termination of which could be easily defined was chosen at base line for the evaluation of changes due to drug effects. The QT interval was measured in six successive complexes, and each measurement was corrected by the Bazett’s formula for the preceding RR interval (e.g., QTc = QT/√RR) (Bazett, 1920). The mean of the six measurements was used for comparisons between controls and drug-induced changes.

Drug protocol. Each dog was randomly assigned to sequential drug testing with MS-551 and dl-sotalol using a cross-over protocol. After control measurements had been obtained, MS-551 or dl-sotalol was administrated as an intravenous bolus of 0.1, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg body weight. Each intravenous bolus was completed in 5 min. The interval between two doses was 1.5 hr. The electrophysiological parameters were measured and recorded 1, 2, 3, 4, 5, 10, 15, 15 and 60 min after the beginning of each dose of testing drug bolus. The design of this study allowed a comparison of the individual change induced by MS-551 and dl-sotalol with respect to their effects on refractoriness, repolarization and the tendency to produce ventricular arrhythmias. To compare the relative degree of reversal of the electrophysiological effects of MS-551 and dl-sotalol by catecholamine administration, all parameters were recorded before and after >15 min of epinephrine (50 mg/kg/min) infusion. All drugs were dissolved directly in distilled water immediately before use.
Definitions. VT was defined as five or more consecutive ventricular complex at a rate of >120 beats/min and was considered sustained when it persisted for >30 sec or required direct current cardioversion for termination. VT was considered to be nonsustained if it lasted ≥10 beats and reverted spontaneously to the original rhythm within 30 sec. TdP was considered when ECG monitoring revealed the spontaneous occurrence of a polymorphic VT containing at least one change in the mean QRS axis during the course of the arrhythmia and with seven consecutive beats with an excessive QT interval prolongation immediately before the onset of the tachycardia. VF was defined as a ventricular tachyarrhythmia characterized by disorganized electrical activity on the surface ECG.

Materials. MS-551 was a gift from Mitsui Pharmaceuticals (Mobar, Japan).

Statistical analysis. Results are expressed as mean ± S.D. as an index of dispersion of values around the mean. Student’s paired t test was used for mean values of data, and Fisher’s exact test was used to analyze categorical data. Mean values of electrophysiological and hemodynamic data, changes in RVERP, APD₉₀, QTc, and RVERP/APD₉₀ ratio during drug tests and consistency of these changes compared with base line and drug tests as function of the paced cycle length were evaluated using repeated measures ANOVA with the Greenhouse-Geiser correction for within subject correlations. Differences were considered significant at P < .05.

Results

Effects of MS-551 and dl-sotalol on QT and QTc. The QT intervals were measured at base line and during right ventricular pacing at a basic cycle length of 700 msec. Both the uncorrected QT interval and QTc according to the Bazett’s formula demonstrated variable increases induced by MS-551 as well as dl-sotalol. QT and QTc prolongation induced by MS-551 was evident at dose as low as 0.1 mg/kg. These effects began to develop at the start of the bolus injection, followed by a slight gradual decrease in the rate of the idioventricular rhythm, reaching a steady state at 10 min from the commencement of the bolus injection. When the heart was paced through the right ventricle at a basic cycle length of 700 msec, MS-551 produced a dose-dependent prolongation of the QT interval that was 87% greater than that on dl-sotalol at the peak effect of the drugs. Of note, the QTc interval was prolonged more strikingly after MS-551 than that after dl-sotalol (+31.6 vs. +14%, at 2 mg/kg). The EC₅₀ was 0.65 ± 0.07 mg/kg on MS-551 (n = 15) and 1.59 ± 0.17 mg/kg for sotalol (n = 15, P < .01). The overall changes as a function of dose are shown on figure 1.

Effects of MS-551 and dl-sotalol on the right ventricular MAP. The mean data derived from studies with MS-551 and dl-sotalol with respect to the changes in APD₉₀ relative to the time course of effect are shown in figure 2. A and B. MS-551, 1 mg/kg, prolonged the APD₉₀ with an acute onset of action (within 1 min) after the intravenous infusion. This effect reached the steady state at ~10 min (fig. 2A). The APD₉₀ was increased by 73 ± 6% (n = 15, P < .01). In contrast, the increase in the APD₉₀ induced by sotalol was more gradual and reached plateau effect at ~75 min. The maximal change in APD₉₀ induced by sotalol was 37% less than that induced by MS-551 at 1 mg/kg. Figure 2B shows the dose-response curves with respect to the changes in the APD induced by MS-551 and sotalol. The maximal prolongation of APD induced by MS-551 was 67% greater than that induced by dl-sotalol. The EC₂₅ was 0.65 ± 0.07 mg/kg for MS-551 (n = 15) and 1.59 ± 0.17 mg/kg for sotalol (n = 15, P < .01), which were correspondingly similar to those observed for the prolongation of QTc in the case of the two drugs.

Frequency-dependent effects of MS-551 and dl-sotalol on APD₉₀ during steady state ventricular pacing. As shown in Figure 3, both MS-551 and sotalol produced a significant prolongation of the APD₉₀ compared with the base line during ventricular pacing at all cycle lengths tested. The increment in APD₉₀ over control was significantly greater in the MS-551 group than that in the sotalol group at cycle lengths from 200 to 700 msec (ANOVA, P < .01). However, the effects of both MS-551 and sotalol on APD₉₀ were reverse frequency dependent. The percent increases from the base line in the APD₉₀ in MS-551 group were 32% at 200 msec cycle length and 79% at 700 msec cycle length. Sotalol produced an 8% increase in APD₉₀ at 200 msec cycle length and 43% increase at 700 msec cycle length. The frequency-dependent curve of sotalol was approximately parallel to that on MS-551, indicating that the two drugs exerted quantitatively but not qualitatively differing effects on APD₉₀. Thus, they both exerted the phenomenon of reverse frequency-dependency of action with respect to ventricular repolarization.

Effect of MS-551 and dl-sotalol on the RVERP. The changes in the RVERP induced by MS-551 and sotalol were compared after complete AV block was established. As with the APD₉₀, intravenous administration of 0.1 to 8 mg/kg of MS-551 or sotalol produced a dose-dependent prolongation of RVERP at all paced cycle lengths compared with the base line. The maximal effect of MS-551 on RVERP was 67%
higher than that after sotalol \((n = 15, P < .01)\). The EC\(_{50}\) was 0.57 ± 0.06 mg/kg for MS-551 and 1.47 ± 0.15 mg/kg for sotalol. The mean data are summarized in figure 4A relative to varying doses given by the method of cumulative addition.

Consistent with the finding with respect to the APD\(_{90}\), the effect of dl-sotalol on the RVERP was also reverse-frequency dependent \((r = .04; P < .01)\) (fig. 4B). However, the percent increments in the RVERP induced by MS-551 were smaller for any given decrease in the pacing cycle length compared with the effects induced by dl-sotalol \((r = .09; P < .05)\).

Effects of MS-551 and dl-sotalol on the relation of RVERP and APD\(_{90}\). Figure 5A shows the values for the RVERP against APD\(_{90}\) at each cycle length (250–600 msec) in 15 dogs before and after MS-551 or sotalol infusion. There was a significant correlation for APD\(_{90}\) and RVERP before and after MS-551 or sotalol infusion \((r = .06, P < .01)\). Under control conditions, the correlation between RVERP and APD\(_{90}\) was linear. The RVERP-APD\(_{90}\) relation curve for MS-551 (2 mg/kg) was significantly shifted to the left compared with control \((P < .05)\). The slope factor of the RVERP-APD\(_{90}\) relation curve was slightly increased in MS-551 group compared with that at control but did not reach the statistically significant difference \((P > .05)\). In contrast, the RVERP-APD\(_{90}\) relation curve was shifted to the right in the case of
the sotalol group (P < .05), and the slope factor was the same as that for control.

The RVERP/APD<sub>90</sub> ratio, measured at twice diastolic threshold, is presented in figure 5B. As the pacing rate was increased under basal conditions, the APD<sub>90</sub> and RVERP shortened. Because the RVERP shortened to a lesser degree, the ratio increased toward unity at the shortest paced cycle lengths at control condition. In the presence of MS-551, the ratio was not changed by increasing pacing cycle lengths. However, sotalol had a similar profile as that in control condition. Therefore, the change of RVERP/APD<sub>90</sub> ratio induced by MS-551 from control condition at each cycle length was less in shorter cycle lengths and greater in longer cycle lengths (ANOVA, P < .05). Thus, at the longer cycle lengths examined, the MS-551-induced prolongation of the RVERP did not appear to be entirely secondary to increases in the APD<sub>90</sub>.

**Effects of MS-551 and dl-sotalol on IVR.** After the interruption of AV conduction, all animals developed a stable escape rhythm with uniform QRS complexes. Sotalol prolonged the RR interval of the IVR by ≈22% within 2 min after the initiation of the bolus injection and showed a very gradual decrease thereafter. The prolongation of the RR intervals of the IVR complexes after dl-sotalol was significantly greater than that after MS-551 (P < .01) (fig. 6A).

**Effect of MS-551 and dl-sotalol on ventricular pressure.** The animals receiving sotalol showed a significantly greater depressant effect on ventricular pressures compared with those treated with MS-551. As shown in figure 6B, the left ventricular pressure was reduced 14% by sotalol (P < .01). There was no effect noted in MS-551-treated dogs over a wide range of doses (0.1–8 mg/kg). Sotalol also produced a 10% reduction in right ventricular pressure but not MS-551 (data not shown).

**Comparative proarrhythmic effects of MS-551 and dl-sotalol.** The overall arrhythmogenic data for 0.5 mg/kg MS-551 (ED<sub>50</sub> for RVERP) in comparison to 1.5 mg/kg (ED<sub>50</sub> for RVERP) sotalol and 2 mg/kg sotalol, which produced the same degree of prolongation of the ERP, are summarized in table 1. At a dose of 0.5 mg/kg MS-551, no ventricular arrhythmias were induced by stimulation at 200-msec basic cycle length. At a dose of 1.5 mg/kg sotalol, ventricular arrhythmias that met the criteria for TdP was induced in 5 of 15 dogs, 2 developed ventricular fibrillation and 5 developed sustained ventricular tachycardia. However, when 2 mg/kg MS-551 was infused, TdP was induced by pacing at a 200 msec cycle length in 9 of 15 dogs. This pattern was similar to that when 4 mg/kg sotalol was used (13 of 15 dogs developed TdP, 1 of 15 developed sustained ventricular tachycardia). An example of stable escape rhythm after successful AV block is shown in figure 7A, and a representative recording of TdP is shown in fig. 7B.

**Relative effect of epinephrine on APD<sub>90</sub> and RVERP during MS-551 and dl-sotalol testing.** After the maximal effects of MS-551 or sotalol on APD<sub>90</sub> and RVERP were attained, epinephrine was infused at 50 ng/kg/min for 15 min. Epinephrine shortened the MS-551- induced prolongation of RVERP and APD<sub>90</sub> determined at a cycle length of 600 msec by 69 ± 12% and 58 ± 13%, respectively. Similar results were obtained when APD was obtained at a cycle length of 400 msec. However, epinephrine did not attenuate sotalol-induced lengthening of the RVERP and APD<sub>90</sub>. The mean data are summarized in fig. 8, A and B.

**Discussion**

The principal findings of this study are (1) MS-551 produced a rapid onset and dose-dependent increase in the QT/QTc, and in right ventricular APD<sub>90</sub> and RVERP, with the maximal effects being significantly greater than those on sotalol. (2) MS-551 shifted the dose-response curves for APD<sub>90</sub> and RVERP prolongation significantly to the left compared with sotalol. (3) The effects of both MS-551 and sotalol on APD<sub>90</sub> and RVERP were reverse frequency dependent. (4) The RVERP/APD<sub>90</sub> ratio in MS-551 group was significantly higher than that in the sotalol group and at control. Unlike those in the sotalol group, the RVERP/APD<sub>90</sub> ratio was not changed by the differing cycle lengths. (5) For a given degree of APD prolongation, MS-551 appeared to exert less proarrhythmic effect than dl-sotalol. (6) The cycle length of ventricular escape rhythm was much (4–7 times) longer in the dogs that received sotalol than those given MS-551 group. (7) MS-551 exerted no significant effect on the LVP that, however, was lowered by sotalol. The overall data, therefore,
indicate that despite the fact that both drugs prolonged the time course of ventricular repolarization, there were significant differences between the effects of dl-sotalol and MS-551. Such differences appeared to stem largely from the lack of beta-blocking activity in the case of MS-551, which, in our studies, functioned essentially as a pure class III antiarrhythmic compound. The data provide the basis for a comparison of the properties of MS-551 with dl-sotalol (racemate) and d-sotalol, which is devoid of beta-blocking activity. Such a comparison is likely to be of much theoretical as well as of practical therapeutic significance in light of the evolving data that deal with differences between simple antiarrhythmic molecules with single actions vs those with more complex compounds that act by prolonging cardiac repolarization as their principal actions.

**Significance of antiadrenergic properties in a class III compound.** The comparative data on the electrophysiological effects of MS-551 and dl-sotalol must be interpreted in light of the emerging clinical experience, which has emphasized the preeminent role of sotalol and amiodarone in the control of life-threatening ventricular arrhythmias (Singh, 1996). Amiodarone and sotalol share the common property of lengthening repolarization and refactoriness. However, both also have potent antiadrenergic actions, as do beta blockers; amiodarone has additional electrophysiological effects together with an exceedingly complex pharmacokinetics and membrane effects. The antiadrenergic actions of sotalol and amiodarone are not readily nullified by exercise or by the administration of concomitant catecholamines. Thus, their class III actions are largely preserved despite catecholamine stimulation. In contrast, the effects of other antiarrhythmic agents that act by prolonging repolarization are offset or even reversed as sympathetic activity is increased (Waldo et al., 1996). The clinical profiles of sotalol and amiodarone do not, however, allow conclusions regarding which components of their electrophysiological properties are linked meaningfully to their clinical antifibrillatory and proarrhythmic actions. Nevertheless, an understanding of the mechanisms of action and of the clinical effects of the so-called pure class III compounds (Singh, 1996) is likely to provide insights into the significance of lengthening of APD in preventing VF. Their development stemmed from the need to circumvent the perceived shortcomings of sotalol (beta blocker side effects and

**Fig. 6.** A, Dose-dependent changes in heart rate induced by dl-sotalol and MS-551. Each item of datum was plotted as the percentage of changes in the idioventricular rate induced by MS-551 and dl-sotalol over that under control conditions. B, Time course of the changes in left ventricular pressure induced by dl-sotalol (2 mg/kg) and MS-551 (1 mg/kg).

**Fig. 7.** A, Typical recordings of the surface ECG, ventricular pressures, and monophasic action potentials after the creation of complete AV block in the dog by the direct injection of formaldehyde into the AV node. The ECG, endocardial (End) and epicardial (Epi) MAPs and right (RV) and left (LV) ventricular pressures were recorded simultaneously. B, A typical example of TdP induced by MS-551. The arrhythmia was induced by stimuli at 250 msec cycle length after 2 mg of MS-551 had been given.
and RVERP (B) induced by at 600 msec basic cycle length. MS-551 (4 mg/kg, M) increased both epinephrine.

In such a framework, MS-551 and the dextro-isomer of sotalol, dl-sotalol, function as pure class III agents, both being devoid of any other major associated pharmacological effects. Within this context, the theoretically lower incidence of TdP that might be encountered with pure class III agents such as dl-sotalol (S) on both APD<sub>90</sub> and RVERP could not be reversed by epinephrine. C, control; E, epinephrine.

**Fig. 8.** A, Reversal effect of epinephrine-induced changes in APD<sub>90</sub> (A) and RVERP (B) induced by dl-sotalol and MS-551. The hearts were paced at 600 msec basic cycle length. MS-551 (4 mg/kg, M) increased both APD<sub>90</sub> and RVERP significantly compared with that in control (C). This effect was reversed by epinephrine (50 ng/kg/min for 15 min) intravenous infusion. However, the effects of the same dose of dl-sotalol (S) on both APD<sub>90</sub> and RVERP could not be reversed by epinephrine. C, control; E, epinephrine.

TdP) and amiodarone (complex side effect profile). For this reason, there has been an intense focus on simpler molecules that have the propensity to lengthen repolarization without any other major associated pharmacological effects. Within such a framework, MS-551 and the dextro-isomer of sotalol, dl-sotalol, function as pure class III agents, both being devoid of significant beta blocking activities.

It is thus of major clinical significance that dl-sotalol and MS-551 have an intense focus on simpler molecules that have the propensity to lengthen repolarization without any other major associated pharmacological effects. Within such a framework, MS-551 and the dextro-isomer of sotalol, dl-sotalol, function as pure class III agents, both being devoid of significant beta blocking activities.

Proarrhythmic actions of MS-551 and dl-sotalol. The occurrence of the proarrhythmic reactions in the form of TdP is now considered the Achilles’ heel of class III compounds (Hohnloser and Singh, 1995). In our experimental model, the frequency of the arrhythmia for a given dose was twice as common with dl-sotalol than with MS-551. Furthermore, the phenomenon of reverse frequency-dependence of APD<sub>90</sub> or RVERP, described for a number of newer class III agents (Sager et al., 1993; Tande et al., 1990) was less striking and the VERP/APD<sub>90</sub> ratio (an unexplained finding because the drug does not exhibit class I actions) was greater in the case of MS-551 compared with the corresponding parameters on sotalol. Similarly, often with a marked slowing of the heart rate accompanied by excessive prolongation of repolarization as might occur with sotalol (and not with pure class III agents), given the appropriate clinical milieu, the proclivity for the development of TdP will be augmented. On the other hand, the theoretically lower incidence of TdP that might be encountered with pure class III agents such as dl-sotalol, MS-551 and dofetilide, as a class, in concert with their potentially beneficial antiarrhythmic actions may be negated by catecholamine surges and fast heart rates, as was demonstrated in the case of MS-551 in our experimental model. Our experimental findings in the current study with dl-sotalol are consistent with the clinical data that the presence of sympathetic inhibitory effect in the setting of the lengthening of the action potential duration may be essential for affecting a favorable change in mortality in patients with ischemic heart disease.

Effects on idioventricular escape rhythm and ventricular pressures. The observed effects of dl-sotalol and MS-551 on these measured parameters appeared to stem largely from their differing antisympathetic actions. Sotalol increased sinus cycle length significantly, an effect that was paralleled by an increase in the sinus node recovery time in our anesthetized open-chest canine preparation. Depression of sinus node automaticity as a result of beta blocking activity has been observed in numerous investigations (The CASCADE Investigators, 1993). Intravenous sotalol also had a marked negative chronotropic action on the IVR. However, the corresponding decrease induced by MS-551 was relatively small, consistent with the drug being devoid of anti-
sympathetic activity. The cycle length of ventricular escape rhythm was much longer (4–7 times) in the dogs that received sotalol compared with that in the MS-551 group. The ventricular pressures (right and left) were significantly reduced by sotalol but not by MS-551, again reflecting the differing antisypathetic activities of the two compounds. The action of MS-551 on cardiac hemodynamics was extremely weak compared with those of dl-sotalol and resembled those of d-sotalol reported previously (Holubarsch et al., 1995).

Summary and conclusions. In an open-chest anesthetized canine model in which AV block was produced by formaldehyde injection, the electrophysiological effects of MS-551 were compared with those of dl-sotalol. Dose for dose, MS-551 was more potent than sotalol in prolonging the APD and VERP; it exerted less reverse use and rate dependency on repolarization with a lower proarrhythmic tendency and less depressant effect on ventricular pressure and on escape ventricular rhythm after AV block compared with dl-sotalol. The experimental findings in this study establish the electrophysiological profile of MS-551 as a pure class III agent, but its clinical properties and utility remain to be defined by controlled studies.

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