Use-dependent Electrophysiologic Effects of DL-sotalol and Modulation by Isoproterenol in the Human Ventricle

Naoki Naitoh, MD, Hiroshi Furushima, MD, Koji Ohira, MD, Koji Taneda, MD, and Yoshifusa Aizawa, MD

SUMMARY

The interaction between dl-sotalol and isoproterenol on the ventricular effective refractory period (VERP) and conduction were examined in an electrophysiologic study of 9 patients at drug-free baseline, after 14 days of dl-sotalol administration (320 mg/day), and after the administration of isoproterenol. In all 9 patients, ventricular tachyarrhythmia could not be induced after dl-sotalol treatment. Isoproterenol was administered as a loading dosage of 0.025 µg/kg for 5 min with a maintenance dosage of 0.0025 µg/kg/min. The VERP and the QRS duration were determined at paced cycle lengths of 600, 400 and 300 msec. DL-sotalol and dl-sotalol + isoproterenol had no effect on ventricular conduction at the three cycle lengths. The VERP was significantly prolonged after dl-sotalol treatment at paced cycle lengths of 600 (241 ± 16 to 302 ± 28 msec, p < 0.001), 400 (223 ± 21 to 280 ± 23 msec, p < 0.001) and 300 msec (202 ± 16 to 256 ± 24 msec, p < 0.005), but there was a parallel shift of the VERP, suggesting the absence of use-dependent effects on the VERP. The dl-sotalol-induced VERP prolongation was partially reversed by isoproterenol, but it remained significantly prolonged above baseline values at paced cycle lengths of 600 (241 ± 16 to 281 ± 18 msec, p < 0.01), 400 (223 ± 21 to 258 ± 20 msec, p < 0.01) and 300 msec (202 ± 16 to 247 ± 22 msec, p < 0.01). The shortening of the VERP was greater at longer basic cycle lengths (600 and 400 msec) than at the shorter paced cycle length (300 msec, p < .05), but the percentage increase of the VERP was similar at the three basic cycle lengths of 600 (16%), 400 (15%) and 300 (20%) msec, indicating the lack of reverse use-dependency. The absence of reverse use-dependency of dl-sotalol on the VERP, even after isoproterenol administration, may be beneficial in the therapy of ventricular tachyarrhythmias and may account in part for the high efficacy of this drug. (Jpn Heart J 1998; 39: 153–161)

Key words: DL-sotalol, Isoproterenol, Effective refractory period, Use-dependent effect

From the First Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan.
Address for correspondence: Naoki Naitoh, MD, First Department of Internal Medicine, Niigata University School of Medicine, 1–754 Asahimachi-dori, Niigata 951, Japan.
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THE negative results of the Cardiac Arrhythmia Suppression Trial using class Ic agents\(^1\) and the high efficacy of amiodarone\(^2\) and dl-sotalol\(^1,5\) in preventing sudden cardiac death have resulted in marked interest in the therapy of ventricular tachyarrhythmias based on lengthening ventricular repolarization or refractoriness. However, class III drugs such as amiodarone and dl-sotalol not only prolong ventricular refractoriness but also have other effects: dl-sotalol prolongs the action potential duration (APD) and has a β-blocking action.\(^6\)

It has been suggested that β-adrenergic agonists can reverse the electrophysiologic effects of antiarrhythmic agents,\(^7-11\) and they were reported to facilitate the induction of ventricular tachyarrhythmias during electrophysiologic studies.\(^7,8\) β-adrenergic agonists may modulate antiarrhythmic drug actions by affecting several currents in ventricular cells.\(^12\) The modulation of the electrophysiologic effects of these agents by β-adrenergic agonists may have important ramifications in regard to the clinical use of antiarrhythmic drugs.

It has been suggested that use-related electrophysiologic effects of amiodarone in the human ventricle might play an important role in the prevention of the induction of ventricular tachyarrhythmias.\(^11,16\) The purpose of the present study was to evaluate the use-related actions of dl-sotalol and its modulation by isoproterenol in patients who had ventricular tachyarrhythmia but were effectively controlled by dl-sotalol.

**Materials and Methods**

**Patients:** Nine patients (8 males and one female) with a mean age of 57 ± 13 (range, 29 to 72) years underwent the electrophysiologic study. In the drug-free control state, the induced ventricular tachyarrhythmia in 6 patients was sustained monomorphic ventricular tachycardia (VT) with a mean VT cycle length of 318 ± 53 msec and was ventricular fibrillation (VF) in the other 3 patients. Four patients had coronary artery disease with previous myocardial infarction and one of these patients had a left ventricular aneurysm. One patient had dilated cardiomyopathy and one had cardiac surgery for subaortic stenosis. The remaining three patients had no demonstrable heart diseases, and their VT was not sensitive to verapamil. The mean left ventricular ejection fraction by echocardiography was 48 ± 17%.

**Electrophysiologic study:** After the purpose and possible risks of the study were explained to and informed consent was obtained from each patient, the electrophysiologic study was performed in the postabsorptive and nonsedated state. All antiarrhythmic agents were discontinued for two or three days before the baseline study. Quadripolar electrode catheters (6F multipurpose catheter, USCI, Boston, MA, USA) were placed against the right atrium, His-bundle
region, and the apex or the outflow tract of the right ventricle. Another quadripolar electrode catheter was positioned within the left ventricle. Stimulation with rectangular pulses of 2 msec duration at twice the diastolic threshold was administered by a programmable stimulator (Fukuda Denshi Cardiac Stimulator BCO2, Tokyo, Japan). The intracavitary electrograms were filtered at 30 to 500 Hz and stored on magnetic tape (TEAC Cassette Data Recorder XR-5000, Tokyo) simultaneously with surface electrocardiographic leads I, II, and V1. They were retrieved later on a recorder (Thermal Recorder RF-95, Fukuda Denshi Co.).

The protocol of ventricular tachyarrhythmia17) consisted of single and double (triple when necessary) extrastimuli after eight basic stimuli at two cycle lengths, 600 and 400 msec, and incremental pacing at cycle lengths from between 667 to 286 msec for 5–15 sec at two sites of the right ventricle and a single site of the left ventricle.

If ventricular tachyarrhythmia was not induced, isoproterenol was administered as a loading dosage of 0.025 μg/kg for 5 min with a maintenance dosage of 0.0025 μg/kg/min, and the programmed stimulation was repeated.

**Drug administration:** The initial dose of dl-sotalol was 80 mg and 160 mg per day for 7–14 days followed by the maximal dose of 320 mg per day for another 14 days. The stimulation protocol was then repeated in all patients to evaluate the efficacy of dl-sotalol.

**Definitions:** The ventricular effective refractory period (VERP) was measured at the apex of the right ventricle as the longest coupling interval which failed to capture the myocardium at the basic cycle lengths of 600, 400, and 300 msec before the induction of ventricular tachyarrhythmias.

The QRS duration was measured in lead V1 during sinus rhythm and during pacing from the apex of the right ventricle at cycle lengths of 600, 400 and 300 msec and was used as an index of the global ventricular conduction time. The pacing spike was used as the onset of the QRS duration.

The QT interval was measured from the onset of the QRS to the end of the T wave measured in V1 during sinus rhythm. The QT interval was corrected for heart rate with Bazett's formula.

**Analysis of data:** Electrophysiologic parameters are presented as mean ± standard deviation (SD). The changes in the sinus cycle length (SCL), the QRS duration, the QT interval and the corrected QT during sinus rhythm, and the change of VERP at the three basic cycle lengths of 600, 400 and 300 msec before and after dl-sotalol treatment and during the isoproterenol administration were analyzed by a paired t-test. The changes in the QRS duration and the VERP during dl-sotalol therapy and isoproterenol administration were compared at the three paced cycle lengths using repeated-measures ANOVA. A p-value <0.05.
Results

Effects of dl-sotalol on electrocardiographic parameters during sinus rhythm: The SCL was prolonged from \(831 \pm 104\) to \(1083 \pm 167\) msec \((p < 0.001)\) after dl-sotalol treatment. The QRS duration did not change significantly. The QT interval increased significantly from \(362 \pm 36\) to \(462 \pm 52\) msec \((p < 0.005)\), as did the corrected QT from \(400 \pm 51\) to \(446 \pm 53\) msec \((p < 0.01)\).

During isoproterenol administration, the SCL was decreased to \(944 \pm 194\) msec, but it was significantly prolonged compared with the control values \((p < 0.01)\). The QT interval and QTc were reversed to \(427 \pm 58\) msec \((p < 0.01)\) and \(442 \pm 54\) msec \((p < 0.05)\), respectively, while the QRS duration did not change from the control (Figure 1).

Effects of dl-sotalol on the incremental ventricular pacing: At baseline, complete ventricular capture at a paced cycle length of 286 msec during incremental ventricular pacing was observed in all 9 patients. Complete ventricular capture was possible at a paced cycle length of 286 msec in six patients after dl-sotalol, while it was not achieved at a paced cycle length of 400, 375 or 353 msec in the remaining three patients (mean \(319 \pm 47\) msec). In one of these three patients, complete capture was possible at a paced cycle length of 286 msec during isoproterenol infusion, and it was achieved at a paced cycle length of 316

Figure 1. Effect of dl-sotalol on the QRS duration. The lack of a use-dependent effect of dl-sotalol on the QRS duration and after dl-sotalol plus isoproterenol administration is shown. Dl-sotalol had no effect on the QRS duration at the three basic cycle lengths.
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Figure 2. Effect of dl-sotalol on the right ventricular effective period. The use-dependent effect of dl-sotalol on the right ventricular effective refractory period (VERP) and after dl-sotalol plus isoproterenol administration is shown. DL-sotalol significantly increased the VERP; the effect was attenuated by isoproterenol but remained significantly prolonged above the baseline values.

Effects of dl-sotalol on conduction: At the three basic cycle lengths of 600, 400 and 300 msec, there were no significant changes in the paced QRS duration after dl-sotalol treatment or even after the use of isoproterenol compared with baseline values. DL-sotalol had no effect on ventricular conduction, and isoproterenol did little to modify the paced QRS duration. In addition, there was no use-dependent slowing of ventricular conduction even after dl-sotalol and isoproterenol administration.

Effects of dl-sotalol on the right ventricular refractoriness: The effects of dl-sotalol on the VERP at basic cycle lengths of 600 to 300 ms are graphically illustrated in Figure 2. The stimulation site did not show any abnormal electrical activity or fragmentation.

There were significant increases in the VERP at all three basic cycle lengths of 600, 400, and 300 msec after dl-sotalol treatment: 241 ± 16 vs. 302 ± 28 msec ($p < 0.001$), 223 ± 21 vs. 280 ± 23 msec ($p < 0.001$), and 202 ± 16 vs. 256 ± 24 msec ($p < 0.005$), respectively. However, the magnitude of the dl-sotalol-induced VERP prolongation was not significantly different among the three basic cycle lengths (Figure 2). The mean percent increases of the VERP from baseline were 25%, 26%, and 26% at the paced cycle lengths of 600, 400, and 300 msec,
respectively. There was no significant difference in the percent increase in the VERP at the cycle lengths examined.

The VERP during isoproterenol administration was partially reversed at the three basic cycle lengths of 600, 400 and 300 msec, but the values were significantly prolonged compared with the baseline values: 241 ± 16 vs. 281 ± 18 msec ($p < 0.01$), 223 ± 21 vs. 258 ± 20 msec ($p < 0.01$), and 202 ± 16 vs. 247 ± 22 msec ($p < 0.01$), respectively. However, the magnitude of the dl-sotalol-induced VERP prolongation showed no cycle length-dependency. The mean percent increase of the VERP from baseline was 16%, 15%, and 20% at the paced cycle lengths of 600, 400, and 300 msec. Reverse use-dependent effects of dl-sotalol on the VERP were not observed.

The mean shortening of the VERP by isoproterenol at the three basic cycle lengths of 600, 400 and 300 msec was by 7%, 8% and 4%, respectively. There was a greater shortening of the VERP at the basic cycle lengths of 600 and 400 msec compared to that at 300 msec ($p < 0.05$).

**DISCUSSION**

The modulation of the action potential duration (APD) is recognized as a mechanism of the effect of some antiarrhythmic drugs. In vitro and in vivo studies have shown a close correlation between the ventricular APD and ERP, and the two parameters progressively shorten with a decrease in ventricular paced cycle lengths. The effects of various antiarrhythmic agents on repolarization have demonstrated that the prolongation of the APD might be attenuated at short paced cycle lengths, a phenomenon which is known as reverse use-dependency. Pure class III antiarrhythmic drugs such as E-4031 and dofetilide were recently shown to specifically prolong the APD with a preferential block of the potassium channel. Moreover, these class III drugs lengthen action potentials in a “reverse” use-dependent manner, and a greater effect was observed at a lower rate.

Hondcghem and Snyders suggested that an ideal antiarrhythmic drug was one that prolongs APD not at a normal but at a fast heart rate. Agents that lengthen the APD by blocking mainly outward potassium channels usually exhibit marked lengthening of the APD at longer cycle lengths, but the effect would be attenuated at shorter cycle lengths. Such a reduction in the magnitude of APD at shorter cycle lengths suggests that a reverse use-dependency might lead to a decrease in efficacy in the treatment of ventricular tachyarrhythmias and lead to an increase in proarrhythmia. A drug which inhibits the slow component of the delayed rectifier current ($I_{Ks}$) might thus be desirable.

Sager and colleagues showed that the human right ventricular APD at
90% repolarization (APD<sub>90</sub>) was significantly prolonged by sematilide (mean increase, 7 ± 1%), a selective potassium channel blocker, and amiodarone (mean increase, 12 ± 1%), a nonselective potassium channel, sodium channel and β-adrenergic blocker at paced cycle lengths of 300 to 500 msec. However, while sematilide-induced APD<sub>90</sub> prolongation was fully reversed to baseline values during isoproterenol infusion, the APD<sub>90</sub> in patients receiving amiodarone remained significantly prolonged by a mean of 6 ± 1% compared with baseline.

In the present study, the human right ventricular ERP was significantly prolonged by dl-sotalol (mean increase, 26%) at the clinical dose of 320 mg per day, and the ERP remained significantly prolonged by a mean of 17 ± 3% during isoproterenol infusion at paced cycle lengths of 300 to 600 msec. Therefore, the use-related electrophysiologic effects of dl-sotalol on the human right ventricular APD or ERP were greater than those of sematilide or amiodarone.

In three of the 9 patients in the present study, ventricular pacing failed to stimulate the right ventricle after dl-sotalol treatment at a basic cycle length of 300 msec and the mean VERP was longer than the 256 ± 24 msec obtained from the remaining six patients. The percentage increase in the VERP at a cycle length of 300 msec was thus >26%.

In contrast to the results obtained with a selective blocker of the rapid component of the delayed rectifier current (I<sub>k</sub>),<sup>12,21,29</sup> the dl-sotalol-induced prolongation of the VERP was partially reversed by isoproterenol, but the VERP remained significantly prolonged beyond the baseline. Thus, dl-sotalol, with a β-blocking action, still exerted significant pharmacological effects even during β-adrenergic stimulation. The partial reversal of repolarization or refractoriness by isoproterenol during dl-sotalol therapy may be explained by the nonselective blockade of the potassium channel<sup>12,18</sup> and the effect of isoproterenol on I<sub>k</sub>s, which leads to a lack of use-dependent blockade on refractoriness or repolarization.<sup>12,16,21,26</sup>

The use-related effect of dl-sotalol on the VERP in patients who were effectively treated for the prevention of ventricular tachyarrhythmia induction showed a lack of reverse use-dependency in this study. Whether the absence of reverse use-dependency on the prolongation of VERP in humans has clinical significance remains to be studied.<sup>26,29</sup>

**Limitations:** The present study had several limitations. 1) It was impossible to assess the VERP at < 300 or > 600 msec, and the range of the study was thus limited.

2) We measured the VERP at the right ventricular apex, but the response to dl-sotalol or isoproterenol may be different in the substrates of ventricular tachyarrhythmias. It is possible that such diseased or/partially depolarized tissue might respond in a different manner to dl-sotalol or to isoproterenol.
3) The number of patients in this study was small and limited to those who were effectively treated by dl-sotalol for the prevention of ventricular tachyarrhythmia induction.

CONCLUSIONS

The purpose of this study was to clarify the interaction between dl-sotalol and isoproterenol. In patients in whom ventricular tachyarrhythmia was effectively prevented, dl-sotalol showed a marked prolongation without a reverse use-dependent effect on the VERP. In addition, the dl-sotalol-induced prolongation of the VERP was not reversed by isoproterenol, and the lack of a reverse use-dependent effect of dl-sotalol on the VERP was confirmed by isoproterenol administration.

REFERENCES

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