Comparison of Efficacy of Sotalol and Nifekalant for Ventricular Tachyarrhythmias

Hiroshi Watanabe, MD*,**; Masaomi Chinushi, MD†; Takashi Washizuka, MD**; Hirotaka Sugiura, MD**; Takashi Hirono, MD**; Yoshiyasu Aizawa, MD**; Satoru Komura, MD**; Yukio Hosaka, MD**; Yasutaka Tanabe, MD**; Hiroshi Furushima, MD**; Yoshifusa Aizawa, MD**

Background  Suppression of implantable defibrillator discharges associated with ventricular tachyarrhythmia (VTA) has been reported for sotalol. This study aimed to investigate the efficacy of intravenous nifekalant hydrochloride in predicting the effects of oral sotalol.

Methods and Results  The present study included 14 patients who had sustained VTA associated with structural heart disease. All patients also had inducible VTA. To compare the effects of nifekalant and sotalol, programmed electrical stimulation was performed, in the basal state, after nifekalant administration, and after sotalol administration. Nifekalant and sotalol similarly prolonged the corrected QT interval and ventricular effective refractory periods, but the heart rate was slowed by sotalol only. In 4 of 5 patients whose VTA became non-inducible by nifekalant, subsequent treatment with sotalol also suppressed the inducible VTA. In all of the 9 patients non-responding to nifekalant, VTA remained inducible during sotalol treatment. Nifekalant accurately predicted the response to sotalol during electrophysiologic study in 13 of 14 patients. Of 11 patients who remained on sotalol, VTA recurred in 3 non-responders during a follow-up of 46±11 months.

Conclusions  Nifekalant and sotalol had similar effects on inducible VTA. The response of inducible VTA to nifekalant may predict the clinical efficacy of sotalol. (Circ J 2006; 70: 583–587)

Key Words: Electrophysiological study; Nifekalant; Programmed electrical stimulation; Sotalol; Ventricular tachyarrhythmia

Implantable cardioverter defibrillators (ICD) are effective for terminating ventricular tachyarrhythmias (VTA), and have decreased the risk of sudden cardiac death. However, there are some cases in which VTA cannot be terminated by appropriate ICD therapy, and so the ICD cannot offer full protection against fatal VTA. Therefore, optimized pharmacological therapy is required to improve the prognosis in some patients. Furthermore, patients with ICD often need supplementary therapy to lower the incidence of shock delivery and improve their quality of life.

Since the publication of the results of the Cardiac Arrhythmia Suppression Trial, class III drugs, mainly amiodarone and sotalol, have been considered to be more effective than class I antiarrhythmic drugs in the prevention of life-threatening VTA. Furthermore, sotalol has been shown to decrease ICD shocks in patients with life-threatening VTA. Therefore, a method of predicting the efficacy of sotalol is desired. The aim of the present study was comparing the efficacy of intravenous nifekalant hydrochloride, a pure class III agent, for inducible VTA with that of sotalol for inducible VTA and VTA recurrence.

Methods

Patients  We enrolled 14 of 57 consecutive patients admitted to hospital from 2000 to 2002 for ICD implantation because of symptomatic, sustained VTA. Inclusion criteria were (1) frequent VTA episodes (≥3 episodes/week) and (2) inducible VTA by programmed electrical stimulation without administration of any antiarrhythmic drugs. Four patients (29%) were female. The mean age was 55±14 years and the mean left ventricular ejection fraction was 46±14%.

Methods  Programmed electrical stimulation was performed, in the basal state, after nifekalant administration, and after sotalol administration. Nifekalant and sotalol similarly prolonged the corrected QT interval and ventricular effective refractory periods, but the heart rate was slowed by sotalol only. In 4 of 5 patients whose VTA became non-inducible by nifekalant, subsequent treatment with sotalol also suppressed the inducible VTA. In all of the 9 patients non-responding to nifekalant, VTA remained inducible during sotalol treatment. Nifekalant accurately predicted the response to sotalol during electrophysiologic study in 13 of 14 patients. Of 11 patients who remained on sotalol, VTA recurred in 3 non-responders during a follow-up of 46±11 months.

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Electrophysiologic Study  After obtaining written informed consent, electrophysiologic studies (EPS) were performed twice in all patients in the non-sedated, post-absorptive state. The first EPS was performed after discontinuation of all antiarrhythmic drugs for more than 5 half-life periods. None of the patients had previously been treated with amiodarone. Induction of
VTA was attempted with programmed ventricular stimulation, as previously described. Briefly, 1–3 extra-stimuli at twice the end-diastolic threshold were delivered following ventricular pacing at 2 different cycle lengths, first at the right ventricular apex, then at the right ventricular outflow tract. If VTA was not induced, the same protocol without 3 extra-stimuli was repeated during intravenous administration of isoproterenol at a dose of 20 μg/h. If VTA was not induced from the right ventricle, programmed stimulation was attempted in the left ventricle. The endpoint of the stimulation was induction of a sustained VTA (≥30 s) or completion of the protocol.

**Nifekalant Administration**

After VTA was induced during the first EPS, the effects of nifekalant hydrochloride were studied. Nifekalant was administered at an initial dose of 0.3 mg·kg⁻¹·(5 min)⁻¹, followed by infusion at 0.4 mg·kg⁻¹·h⁻¹ with careful ECG monitoring because of the risk of torsade de pointes. Programmed electrical stimulation was repeated with the same protocol and endpoint as described before. Patients in whom VTA became non-inducible were defined as responders to nifekalant.

**Sotalol Treatment**

After VTA was induced during the first EPS, the effects of sotalol were studied. Sotalol was administered at an initial dose of 80 mg/day, and then increased up to 240 mg/day in increments of 40–80 mg/5 days, as tolerated. A 12-lead ECG was recorded before each increase in dose during the upward drug titration. The maximum tolerated dose was defined by intolerant hypotension, marked bradycardia, or prolongation of the QT interval and/or corrected QT (QTc) interval >550 ms. The EPS was repeated at least 5 days after administration of the final dose. The stimulation protocol and endpoints of the follow-up EPS were identical to those of the first study.

Patients in whom VTA was not inducible during the second EPS were considered to be drug responders and were changed to long-term sotalol treatment. If sustained VTA was induced during the second EPS, the patient was considered a non-responder. In non-responders who needed further treatment for uncontrolled VTA, sotalol was exchanged for another drug. Non-responders without any complications or VTA recurrence also continued with sotalol. Patients who discontinued sotalol therapy were excluded from the analysis of long-term sotalol therapy.

**Follow-up**

Patients were followed monthly in the outpatient clinic. ICD data was checked every 3 months and at the time of any ICD discharge.

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**Table 1 Electrophysiological Effects of Nifekalant and Sotalol**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Nifekalant</th>
<th>Sotalol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>72±13</td>
<td>72±7</td>
<td>57±5*</td>
</tr>
<tr>
<td><strong>QT (ms)</strong></td>
<td>424±49</td>
<td>490±47†</td>
<td>531±46†</td>
</tr>
<tr>
<td><strong>QTc (ms)</strong></td>
<td>460±56</td>
<td>535±40†</td>
<td>515±42*</td>
</tr>
<tr>
<td><strong>ERP (ms)</strong></td>
<td>250±22</td>
<td>281±31*</td>
<td>285±23†</td>
</tr>
</tbody>
</table>

QTc, corrected QT interval; ERP, effective refractory period measured at a basic cycle length of 600 ms.

*p<0.05 vs baseline, †p<0.01 vs baseline value.

**Data Analysis**

We compared the efficacy of nifekalant and sotalol for inducible VTA. We also studied whether the effects of nifekalant in inducible VTA could predict the clinical effects of sotalol. All values are presented as means±SD. Paired or unpaired values were compared by appropriate Student’s t-test or 1-way analysis of variance. Time-to-event curves describing the proportion of patients who remained event-free were constructed using the Kaplan-Meier method and compared using the log-rank test. A p-value <0.05 was considered statistically significant.

**Results**

**Electrophysiologic Effects**

The electrophysiological effects of nifekalant and sotalol are shown in Table 1. The heart rate was slowed by sotalol but not by nifekalant. The QT interval, QTc interval, and effective refractory period (ERP) at the right ventricular apex were prolonged similarly by nifekalant and sotalol (p=NS for nifekalant vs sotalol).

**Efficacy of Nifekalant for Inducible VTA**

In the first EPS, VTA was inducible before nifekalant administration in all of the 14 patients, and isoproterenol administration was not required for VTA induction in any of them. After nifekalant administration, VTA was not induced in 5 patients (Table 2, patients 1–5), whereas VTA remained inducible without isoproterenol in the remaining 9 patients (patients 6–14). The clinical characteristics of the responders and non-responders to nifekalant did not differ (Table 3). Of the 5 responding patients, 1 had inducible monomorphic VT before administration of nifekalant, 3 had polymorphic VT, and 1 exhibited both types of VT (Table 2). Of the 8 non-responding patients in whom monomorphic VT was induced during nifekalant administration, 7 patients had inducible monomorphic VT before nifekalant, and 1 exhibited both monomorphic and polymorphic VT. In 7 of the 8 patients in whom monomorphic VT was induced during nifekalant administration, the morphology was identical to those induced before the administration, but was different in the remaining patient. Polymorphic VT was induced during nifekalant administration in 1 patient who had polymorphic VT before nifekalant. Nifekalant slowed the rate of monomorphic VT from 209±21 to 196±19 beats/min, but this effect was not significant (p=0.09). The number of extra-stimuli for induction of VT was increased by nifekalant in 4 of the 9 non-responders.

The QT or QTc interval either before or during nifekalant administration did not differ between the patients who responded to nifekalant and those who did not (Table 3). The ERP both before and during nifekalant administration were significantly longer in the non-responders than the
responders (Table 3). However, there was no difference in the prolongation of the ERP between the responders and the non-responders (12±9% vs 7±7%, p= NS).

Efficacy of Sotalol for Inducible VTA

During sotalol therapy at an average maintenance dose of 133±53 mg/day, the second EPS was conducted 35±10 days after the first study. Before the second study, VTA did not recur in any patients. In 4 of the 5 patients responding to nifekalant, sotalol also suppressed the induction of VTA (patients 1–4). In all of the 9 patients who did not respond to nifekalant, VTA was induced during sotalol administration. In 7 of the 9 cases of inducible monomorphic VT during sotalol therapy, the QRS morphology was identical to that induced before nifekalant administration during the first EPS, but was different in the remaining 2 patients. Sotalol did not change the VT rate (from 205±18 to 200±27 beats/min, p=0.55). Of 9 patients in whom VTA was refractory to both nifekalant and sotalol, the inducibility of VTA became more difficult in 3 patients during sotalol administration compared with nifekalant (ie, the number of extra-stimuli needed to induce VTA increased in 1 patient and isoproterenol was needed in 2 patients, whereas VTA became easier to induce in 2 patients). Nifekalant predicted the response of inducible VTA to sotalol during EPS in 13 of 14 patients (93%) (specificity 80%, sensitivity 100%).

Long-Term Sotalol Treatment

Sotalol treatment was continued at a similar dose to that used in the EPS (mean dose 122±45 mg/day), combined with the ICD in 11 patients: 4 responders and 7 non-responders to sotalol. Three non-responders discontinued sotalol because of a change to another drug (patients 6 and 7) or patient disagreement with long-term treatment.
VTA Management

Antiarrhythmic drugs remain necessary in certain ICD recipients, and class III drugs can play a role in this capacity.1–3,18 Although nifekalant is effective in suppressing VTA, it cannot be used for chronic medication in conjunction with ICD because it can only be administered intravenously. Sotalol is a potential candidate for replacement because recent reports have shown that it can suppress ICD shocks for VTA and reduce mortality.10,11

Although an EPS was performed to predict drug efficacy for VTA in this study, the appropriateness of serial drug-testing has been called into question.8,22 The response to programmed stimulation during drug administration may select patients at lower risk of VTA recurrence. However, EPS-guided antiarrhythmic therapy was found to be more effective than the absence of antiarrhythmic therapy in some primary prevention trials and our secondary prevention trial.11,23 In the present study, the efficacy of sotalol for suppressing VTA recurrence was not different between responders and non-responders despite the lack of recurrence in the responders. The small number of patients may have affected the results.

Amiodarone is another candidate to replace nifekalant, but there have been few reports describing its efficacy for reducing ICD shocks. The acute and chronic effects of amiodarone differ, and it is difficult to predict its efficacy.24,25 Therefore, the drug is usually administered empirically.26 Moreover, both sotalol and nifekalant have been reported to decrease the defibrillation threshold, whereas amiodarone may increase it.27–29

The results of this study suggest that in patients in whom VTA is suppressed by nifekalant, sotalol is very likely to be efficacious. Thus, the response of inducible VTA to nifekalant may provide useful information about the clinical efficacy of sotalol treatment.

Study Limitations

The number of patients studied was small and a control group was absent. Assessment of statistical analysis may be difficult because of the small population and the variability of heart disease. The role of EPS in drug selection remains controversial.

References

Nifekalant and Sotalol for VT


