Nifekalant Hydrochloride Suppresses Severe Electrical Storm in Patients With Malignant Ventricular Tachyarrhythmias

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Background Some patients with an implantable cardioverter-defibrillator (ICD) suffer from burst of inappropriate multiple discharges (severe electrical storm), and because the current therapeutic options are limited, the effect of nifekalant hydrochloride, a new class III drug, on severe electrical storm was investigated in the present study.

Methods and Results Ninety-one consecutive patients treated with ICD were included in the study (M 70; mean age 58 years; left ventricular ejection fraction 45±15%). Severe electrical storm was defined as more than 10 ICD discharges within 1 h. During a mean follow-up period of 30±13 months, 41/91 (45%) patients had appropriate ICD therapy for arrhythmias and severe electrical storm occurred in 11 of them (12%) at 20±18 months after ICD implantation. The mean number of ICD discharges/h during severe electrical storm was 18±12. In 4 of 10 patients, severe electrical storm was successfully suppressed by a combination of deep sedation and ß-blocking agent; 6 other patients were refractory to this treatment, but severe electrical storm was successfully suppressed by intravenous administration of nifekalant hydrochloride with no adverse effects.

Conclusions Nifekalant hydrochloride is an effective and safe treatment for severe electrical storm. (Circ J 2005; 69: 1508–1513)

Key Words: Implantable cardioverter defibrillator; Nifekalant hydrochloride; Severe electrical storm

A n implantable cardioverter-defibrillator (ICD) effectively terminates ventricular tachycardia (VT) and ventricular fibrillation (VF) and can diminish the incidence of sudden cardiac death in patients with malignant ventricular tachyarrhythmias.1–3 Although the total number of ICD shocks is restricted, some patients experience ‘severe electrical storm’; that is, more than 10 shocks within 1 h. Prior studies have reported a 10–30% incidence of electrical storm defined as 3 shocks per day4–6 Furthermore, recent studies have shown that multiple shocks lead to myocardial injury7 and recurrent episodes of VF are also associated with increased intracellular calcium levels8 that may result in progressive left ventricular dysfunction9 and the induction of tachyarrhythmias8 These findings suggest that severe electrical storm might contribute to mortality5,10 but there are very limited therapeutic options currently available for suppressing severe electrical storm and the current clinical management of these patients is suboptimal.

In recent clinical trials, class III antiarrhythmic drugs were found to be effective in suppressing life-threatening ventricular tachyarrhythmia, so they might be a useful therapy for severe electrical storm. Nifekalant hydrochloride (nifekalant, Nihon Schering K.K., Osaka, Japan), is a new class III antiarrhythmic drug that has recently become available for clinical use11 It is a nonselective K channel blocking agent and does not inhibit either the Na channel or ß-receptors12–14 In an experimental model of previous myocardial infarction nifekalant was effective against ventricular tachyarrhythmias15–18 and moreover, this effect was recently reported in patients with ischemic heart disease19–23 therefore, we investigated the efficacy and safety of nifekalant for the control of severe electrical storm in patients with an ICD.

Methods

Patients This study began in June 2000 when nifekalant was became clinically available. From June 2000 to May 2003, 91 patients received a transvenous ICD (Medtronic, MN, USA) and were included in the present analysis. All devices were capable of storing RR intervals and/or electrograms during ICD discharge. All patients fulfilled the following criteria: (1) clinical documentation of VF, VT or unexplained syncope; (2) induction of VF or VT during an electrophysiological study; and (3) failure of antiarrhythmic drugs to prevent spontaneous and/or induced ventricular tachyarrhythmias. There were 70 men and 21 women with a mean age of 58±15 years (range 13–80 years). Both VT and VF were documented clinically in 12, and VF or VT only was documented in 30 and 46 patients, respectively. The remaining 3 patients had unexplained syncope. The left ventricular ejection fraction (LVEF) ranged from 17% to 73% (mean 45±15%). Underlying conditions included coronary artery disease (n=30), idiopathic dilated cardio-
myopathy (n=13), arrhythmogenic right ventricular cardiomyopathy (n=7), cardiac sarcoidosis (n=6), hypertrophic cardiomyopathy (n=6), and idiopathic VF (n=18) including 13 patients with Brugada syndrome and others.

All patients were seen routinely in our out-patient clinic at 3-month intervals or as soon as possible after ICD discharge for device interrogation and retrieval of stored ECGs. An ICD discharge was considered inappropriate when stored ECGs demonstrated a rhythm other than sustained VT or VF.

Definition of Severe Electrical Storm and Therapeutic Regimen

Electrical storm was defined as the occurrence of 3 or more episodes of VT/VF within a 24-h period. ICD discharges included anti-tachycardia pacing, low energy shock and high energy shocks. Severe electrical storm was defined as the occurrence of 10 or more episodes of VT/VF within 1 h (Fig 1). For each arrhythmia, the appropriateness of the ICD therapy was assessed by device interrogation.

Patients who had severe electrical storm were treated according to the following therapeutic regimen. Deep sedation (thiamylal 100–150 mg iv or propofol 0.2 mg/kg iv) and the a β-blocker agent was administered. Intravenous administration of nifekalant was commenced if the severe electrical storm was not suppressed by this treatment. Nifekalant was administered as a loading infusion of 0.1–0.3 mg/kg for 5 min with a maintenance dose of 0.2–0.4 mg·kg⁻¹·h⁻¹.

Statistical Analysis

All values are presented as the mean±SD, unless otherwise specified. A p-value of <0.05 was considered statistically significant.

Results

Electrical Storm

During a mean follow-up period of 30±13 months, 41/91 (45%) patients had ≥1 appropriate ICD therapy for VT/VF. Electrical storm and severe electrical storm occurred in 19 and 11 patients at 15±13 and 20±18 months, respectively, following ICD implantation. Analysis of stored electrograms showed that severe electrical storm consisted of repeated episodes of VT in 9 patients and both VT and VF in 2 patients. The mean number of ICD discharges for severe electrical storm was 18±12/h (range 10–50) per patient. The stored electrograms showed no evidence of device malfunction or inappropriate discharge for supraventricular tachyarrhythmias. The clinical characteristics of these 11 patients are shown in Tables 1 and 2. One patient died just after severe electrical storm because of electromechanical dissociation; 3 patients experienced near syncope during the episodes, and the remaining 7 patients had palpitations or light-headedness. One of the patients experienced progressive left ventricular dysfunction during the severe electrical storm and in 3 patients, severe electrical storm was the first episode of ICD discharge after implantation, but the other 8 patients had experienced prior episodes of ventricular tachyarrhythmias that were terminated by single ICD discharge.

Shocks only were used to treat 9 of the 11 patients during the initial severe electrical storm episodes with anti-tachycardia pacing being added in the remaining 2 patients. Precipitating factors for severe electrical storm could be identified in only 3 patients and included hypokalemia (<3.5 mmol/L), a pneumonic illness with a high fever, and congestive heart failure. There was no apparent precipitating factor evident in the remaining 8 patients.

Fig 1. Example of severe electrical storm in a 63-year-old patient with dilated cardiomyopathy and ventricular tachyarrhythmias (Case 4). Arrhythmic cluster was observed during a short time. Each tachycardia was successfully terminated by cardioversion from the implantable cardioverter-defibrillator.
Ten of the 11 patients with severe electrical storm required hospitalization for pharmacological therapy (patient No. 11 died). These 10 patients were treated according to the therapeutic regimen described earlier. The combined therapy of deep sedation and β-blockade suppressed severe electrical storm in 4 patients and in the remaining 6 patients were stabilized by intravenous administration of nifekalant. In 1 of these 6 patients, VT ceased during the administration of the loading dose of nifekalant. Fig 2 shows the ECG recordings from case 8, a 57-year-old male with hypertrophic cardiomyopathy and severe electrical storm. The sustained monomorphic VT at a rate of 180 beats/min recurred immediately after successful cardioversion by ICD before nifekalant administration, despite the deep sedation and β-blockade (Fig 2A). In this patient, we also used overdrive pacing (120 beats/min) to diminish the trigger ventricular premature contractin, but VT recurred. The VT stopped during the administration of the loading dose of nifekalant (0.15 mg/kg) and did not recur (Fig 2B). In the other 5 patients, the frequency of ICD discharges was markedly reduced after nifekalant administration. No hemodynamic deterioration was evident during the administration of nifekalant in these 6 patients. Although the heart rate and QRS width did not change, QT and corrected QT intervals were significantly prolonged from 425±66 to 463±73 ms and from 499±72 to 538±80 ms, respectively, by the administration of nifekalant (Fig 3). No pro-arrhythmic events occurred and nifekalant was continued for 16±10 days (range 4–30 days). In one of the 6 patients, severe electrical storm recurred despite treatment with nifekalant and an infusion of mexiletine was required to suppress it. After the nifekalant therapy, 3 patients were given a combination of amiodarone and a β-blocking agent and the other 3 patients were given dl-sotalol.

### Discussion

In the present study, 11/91 (12%) patients experienced severe electrical storm as a relatively late phenomenon after ICD implantation. The trigger was evident only in 3 of the 11 patient. Intravenous nifekalant was an effective and safe treatment for severe electrical storm that was refractory to deep sedation and administration of a β-blocking agent. These findings suggest that nifekalant could be a therapeutic option for the treatment of severe electrical storm.

The definition of severe electrical storm has not been standardized, although a working definition of electrical storm is more than 3 episodes of recurrent VT or VF during a 24-h period. Credner et al. studied the incidence and prognosis of electrical storm in 136 consecutive patients with ICD. During a mean follow up of 403±242 days, 10% of patients experienced electrical storm and the cumulative probability of survival in these patients was not worse than that of patients without electrical storm. However, Exner et al. assessed the prognostic significance of electrical storm in 457 patients registered in the AVID trial and of them 20% experienced electrical storm, which was considered to be a significant risk factor for subsequent cardiac death. It has been suggested that frequent shocks increases the cardiac troponin level, which indicates myocardial injury, whereas myocardial fibrosis and acute cellular injury may occur in patients who had recent shocks from ICD. Moreover, recurrent episodes of VT/VF are also associated with...
increased intracellular calcium levels, which may lead to progressive left ventricular dysfunction, apoptosis of cardiac cells and facilitation of arrhythmias. In the present study, 1 patient experienced progressive left ventricular dysfunction during a severe electrical storm, so it is very important to control this phenomenon. However, the current therapeutic options are antiarrhythmic drugs or radiofrequency current ablation. Moreover, in patients with left ventricular dysfunction that is refractory to either of these treatments, mechanical circulatory support is needed.

With the exception of intravenous amiodarone, antiarrhythmic therapy has yielded frustrating results in patients with severe electrical storm. Credner et al recently reported that combined therapy with intravenous amiodarone and a ┐-

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**Fig 2.** Effect of nifekalant administration on severe electrical storm in a patient with hypertrophic cardiomyopathy and a cluster of ventricular tachycardia (VT). Prior to nifekalant administration VT immediately recurred a few beats after successful cardioversion, but during nifekalant administration it ceased and did not recur.

**Fig 3.** Change in the ECG parameters QT interval, corrected QT interval, heart rate (HR) and QRS width before and after nifekalant administration. QT and corrected QT interval were significantly prolonged after nifekalant administration, although HR and QRS width did not change.
blocking agent was effective in 6 patients who were refractory to class I drugs. Intravenous amiodarone has also been shown to decrease the frequency of unstable VT/VF. At the current time, intravenous amiodarone is the only effective antiarrhythmic drug for suppressing severe electrical storm, but it has some extracardiac side effects and is no longer able to be used in Japan. Thus, another intravenous antiarrhythmic drug is needed and we have demonstrated the efficacy of nifekalant, a new class III drug, in the acute management of severe electrical storm.

Nifekalant is a novel class III antiarrhythmic agent that blocks the rapid component of the delayed rectifier K current, the transient outward K current, the inward rectifier K current, and the ATP-sensitive K current without affecting either the Na current or ß-adrenergic activity. As a pure K channel blocker, it does not have negative inotropic effects and does not affect cardiac conduction. In addition, it can be used only intravenously and its half-life is relatively short. Previous studies have shown that nifekalant suppresses ventricular tachyarrhythmias in myocardial ischemia and infarction. More recently, Koizumi et al reported the efficacy of nifekalant hydrochloride in the treatment of life-threatening ventricular tachyarrhythmias during reperfusion for acute myocardial infarction. Takenaka et al also reported the antiarrhythmic efficacy of nifekalant for severe ventricular tachyarrhythmias in 4 patients with acute myocardial infarction and depressed left ventricular function (16±4% fractional shortening). In the present study, nifekalant did not significantly depress cardiac function, as none of the patients who received nifekalant showed hemodynamic deterioration despite the fact that 4 of the 6 patients had left ventricular dysfunction (LVEF <40%).

In the present study, other class III drugs (amiodarone or sotalol) were administered to 5 of the 6 patients with severe electrical storm. However, after nifekalant administration, the QT interval was significantly prolonged even in these patients, so the class III effect of intravenous nifekalant might be superior to other oral class III drugs. We also used a ß-blocking agent with nifekalant administration, because the SWORD trial reported excess mortality with ß-blockade, found to be more effective than 6 other class I drugs in the ESVEM trial. Thus the combination of a pure class III drug and ß-blocking agent appears to be most effective in patients with VTs. However, excessive bradycardia caused by the ß-blocking agent must be avoided, because it would cause marked QT prolongation leading to torsade de pointes (TdP). Moreover, the pacing function of ICD should be used when bradycardia or excessive QT prolongation is observed. Nifekalant has been also reported to decrease the defibrillation threshold (DFT). Murakawa et al reported that nifekalant decreased the DFT in both open- and closed-chest animal models. On the other hand, amiodarone might raise the DFT. This effect of nifekalant is suitable in patients with an ICD, especially those experiencing electrical storm.

The precise mechanism by which nifekalant suppresses severe electrical storm is unknown, but prolonging cardiac repolarization might be it because most of the cases of severe electrical storm in this study comprised monomorphic VT caused by reentry. Prolonging the refractory period narrows the excitable gap of reentry circuit and prevents the VT. However, even small doses of nifekalant have produced marked QT prolongation and TdP, especially in patients with renal dysfunction or severe LV dysfunction. Other precipitating factors for TdP (eg, hypokalemia and bradycardia etc) need to be controlled and close monitoring of the QT interval is needed.

Study Limitations

First, this study was not randomized and the number of patients was small, because the number of patients who experienced severe electrical storm was limited and they needed emergency therapy. Second, we did not compare the effect of nifekalant with that of other antiarrhythmic drugs. Most of the patients with severe electrical storm had left ventricular dysfunction such that the intravenous administration of a class I drug was not favorable, apart from class Ib drugs. In addition, we cannot administer intravenous amiodarone clinically in Japan at the current time, so we used nifekalant. Third, our results do not apply to patients with arrhythmic storms related to VF unrelated to heart disease, such as idiopathic VF or Brugada syndrome. However, despite these limitations, the present study indicates that nifekalant is effective in controlling severe electrical storm in patients with organic heart disease.

Conclusion

Despite the limitation of this study, the results suggest that short-term intravenous administration of nifekalant is an effective and safe treatment for arrhythmic clusters. These findings indicate the therapeutic potential of this new class III antiarrhythmic drug in the treatment of severe electrical storm in patients with ICD.

References


