Effect of nifekalant on life-threatening ventricular arrhythmias in patients with cardiopulmonary resuscitation or during the perioperative state

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Background: Nifekalant is a unique class III anti-arrhythmic agent with a strong effect on prolonging the myocardial refractoriness, but its clinical effect is still unclear. In this study, we evaluated the effect of nifekalant on life-threatening ventricular arrhythmias and compared the clinical background between the effective and non-effective patients in order to clarify the clinical factors which may have an influence on the efficacy of nifekalant.

Methods: The study population consisted of 47 consecutive patients who underwent nifekalant administration for life-threatening ventricular arrhythmias (VT/VF). Their clinical characteristics and ECG parameters were retrospectively compared between patients with and without an effective result with the nifekalant administration.

Results: Nifekalant was effective for refractory VT/VF in 26/47 patients. There was no significant difference in the age, gender or left ventricular ejection fraction, but the incidence of ischemic heart disease was higher in the effective group (17/26) than non-effective group (9/21, p = 0.004). The incidence of in-hospital events was higher in the effective group than non-effective group (20/26 vs 10/21, p = 0.037). A significant prolongation in the QTc interval was observed in all patients and the degree of QTc prolongation was greater in the effective group than in the non-effective group (0.46 ± 0.04 vs 0.43 ± 0.02 sec, p = 0.026).

Conclusion: Nifekalant was effective in 55% of the patients for refractory VT/VF. It was considered that nifekalant was more effective for patients with ischemic heart disease, during the perioperative period or in those experiencing in-hospital events. The prolongation of the QTc interval might also be useful as an index for the efficacy of nifekalant administration.

Key words: ventricular tachycardia, ventricular fibrillation, nifekalant

Introduction

The incidence of sudden cardiac death (SCD) has been reported to be more than 300,000 annually in the United States, and it commonly appears as a result of life-threatening ventricular arrhythmias due
to acute coronary events. Although the prevalence of ischemic heart disease might differ in Japan, the importance of appropriate therapy for life-threatening ventricular arrhythmias is similar to that of patients in whom nifekalant exhibits dramatic efficacy, the incidence and patient characteristics of nifekalant as a treatment modality remains unclear. In the present study, we evaluated the efficacy of nifekalant on refractory ventricular arrhythmias and also evaluated the clinical characteristics of the patients with effective or non-effective results with nifekalant usage in order to clarify the clinical usefulness of nifekalant in managing refractory arrhythmias.

Methods

The study population consisted of 47 consecutive patients who underwent nifekalant administration for the treatment of lidocaine refractory life-threatening ventricular arrhythmias, i.e., ventricular tachycardia or fibrillation (VT/VF), in Kitasato University Hospital from November 1999 to February 2007. The mean age was 63 ± 6 years, and 13 were female and 34 male. They were retrospectively analyzed for the purpose of this study. The underlying heart disease was diagnosed as ischemic heart disease in 26, idiopathic dilated or hypertrophic cardiomyopathy in 16, and valvular heart disease in 5 patients. The diagnoses were made from the findings in the preceding examinations including the echocardiogram (32/47) and/or cardiac catheterization (24/47), but in the remaining patients (15/47), the diagnoses were made from the findings after or during the treatment for VT/VF.

The lidocaine refractory VT/VF was defined as 1) VT/VF which could not be interrupted by an intravenous lidocaine injection of 50 mg even with direct current defibrillation, or 2) recurrent VT/VF which could not be prevented by an intravenous lidocaine injection of 50 mg even after a successful cardioversion. Nifekalant was used for VT/VF interruption or defibrillation enhancement for continuous VT/VF, and it was used for VT/VF prevention or maintenance of sinus rhythm for recurrent VT/VF. Nifekalant was administered at an initial dose of 0.1–0.4 mg/kg over 5 minutes, and it was followed by a continuous infusion at a dose of 0.4 mg/kg/h when necessary for maintaining sinus rhythm in the patients with effective results. The efficacy of nifekalant was considered as effective when one of the following findings was obtained after the initial infusion of nifekalant, i.e., 1) interruption of lidocaine refractory VT/VF, 2) change in the DC cardioversion results from being non-effective to effective for lidocaine refractory VT/VF, or 3) prevention of any repetitive lidocaine refractory VT/VF. During and after the infusion of nifekalant, the QT interval was continuously monitored and the dose of the nifekalant was decreased when the QTc interval was prolonged by more than 0.60 sec.

In these patients, the clinical background including the age, gender, underlying heart disease, left ventricular ejection fraction (LVEF), type of targeted arrhythmia, purpose of nifekalant usage, conditions at the onset of the arrhythmic events and relationship to the operative procedure were examined. In patients with in-hospital events, the time interval from the event onset to the start of nifekalant therapy was evaluated. We obtained the ECG parameters and LVEF data from the echocardiogram during sinus rhythm, but in cases in which no stable sinus rhythm could be achieved (n = 11), those parameters were excluded from the evaluation in this study. The levels of the serum creatinine, potassium, and brain natriuretic peptide were examined at the time of the VT/VF event. The patients were divided into two groups in accordance with the effect of the initial injection of nifekalant on the refractory VT/VF, and the parameters described above were compared between the two groups. Similar comparison of the parameter was also performed in subgroup of different purpose of nifekalant therapy, i.e., VT/VF interruption and VT/VF prevention. All evaluations were performed after obtaining informed consent from patient or patient’s family and with the approval of the Committee of Clinical Ethics at Kitasato University Hospital.

Statistics

The data were expressed as the mean ± SD. A one way ANOVA was used for the continuous values and the Mann-Whitney U test was used for comparisons between groups of discrete variables, and P < 0.05 was considered as significant. All mathematical
computations and statistical procedures were performed using the JMP software (SAS Institute Inc.).

**Results**

Nifekalant was used for the purpose of VT/VF interruption in 19/47 and for VT/VF prevention in 28/47 patients. In 19 patients with therapy for VT/VF interruption, VT/VF interruption during nifekalant infusion was observed in 5, and defibrillation enhancing effect\(^4\) was observed in the other 5 patients. In 28 patients with therapy for VT/VF prevention, sinus rhythm was maintained in 16 patients. In total, nifekalant was effective in 26/47 patients who were classified as the nifekalant effective group, and the remaining 21 patients were defined as the non-effective group. In 16/21 patients with non-effective results, a stable sinus rhythm could not be achieved and percutaneous cardiopulmonary support (PCPS) was later applied. Table 1 exhibits the clinical characteristics of the two groups. There were no significant differences in the age, gender, targeted arrhythmia, LVEF or the level of serum creatinine, potassium or BNP between the two groups. In regard to the underlying heart disease, the incidence of acute ischemic heart disease was higher in the effective group and that of cardiomyopathy was higher in the non-effective group (\(p = 0.005\)). Of the 47 patients, the place of event onset was outside the hospital in 17 and inside the hospital in 30 patients. The incidence of in-hospital events was higher in the effective group (20/26) than in the non-effective group (10/21, \(p = 0.037\)). There were 25/47 patients with a perioperative (cardiac surgery and coronary angioplasty) onset of the event, including during percutaneous coronary intervention. The incidence of onset during a perioperative event was also higher in the effective group (18/26) than in the non-effective group (7/21, \(p = 0.014\)). In patients with an in-hospital event, the time from event onset to nifekalant therapy tended to be shorter in the effective group than in the non-effective group, but the difference was not significant. The survival rate of patients was higher in the effective group, as none of the non-effective group patients survived (\(p = 0.0003\)).

Tables 2 and 3 compare the characteristics of patients in the subgroups according to the purpose of the nifekalant therapy. Although data showed a trend similar to that for all patients, a significant

### Table 1 Clinical characteristics of all patients

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Nifekalant effective</th>
<th>Nifekalant non-effective</th>
<th>(p) value</th>
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<tbody>
<tr>
<td>Number (n)</td>
<td>47</td>
<td>26</td>
<td>21</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>63 ± 6</td>
<td>64 ± 5</td>
<td>61 ± 6</td>
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<tr>
<td>Gender (F:M)</td>
<td>13:34</td>
<td>8:18</td>
<td>5:16</td>
<td>0.595</td>
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<tr>
<td>Basic heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A&amp;OIHD/OIHD/CM/others)</td>
<td>7/19/16/5</td>
<td>6/11/4/5</td>
<td>1/8/12/0</td>
<td>0.005*</td>
</tr>
<tr>
<td>Perioperative state (n)</td>
<td>25/47</td>
<td>18/26</td>
<td>7/21</td>
<td>0.014*</td>
</tr>
<tr>
<td>In-hospital event (n)</td>
<td>30/47</td>
<td>20/26</td>
<td>10/21</td>
<td>0.037*</td>
</tr>
<tr>
<td>Time to nifekalant therapy (min)(^\dagger)</td>
<td>26 ± 8</td>
<td>23 ± 8</td>
<td>29 ± 10</td>
<td>0.0891</td>
</tr>
<tr>
<td>Discharge alive (n)</td>
<td>12/47</td>
<td>12/26</td>
<td>0/21</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Targeted arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(VF/poly VT/VT)</td>
<td>19/23/5</td>
<td>7/16/3</td>
<td>12/7/2</td>
<td>0.102</td>
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<td>Purpose of Therapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(interruption, prevention)</td>
<td>19/28</td>
<td>10/16</td>
<td>9/12</td>
<td>0.761</td>
</tr>
<tr>
<td>Initial dose of nifekalant (mg)</td>
<td>23.9 ± 3.5</td>
<td>24.2 ± 3.3</td>
<td>23.4 ± 3.7</td>
<td>0.529</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36 ± 5</td>
<td>37 ± 5</td>
<td>35 ± 4</td>
<td>0.095</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5 ± 0.5</td>
<td>1.4 ± 0.5</td>
<td>1.6 ± 0.5</td>
<td>0.112</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>4.4 ± 0.4</td>
<td>0.332</td>
</tr>
<tr>
<td>BNP (ng/dl)</td>
<td>826 ± 494</td>
<td>932 ± 498</td>
<td>782 ± 488</td>
<td>0.307</td>
</tr>
</tbody>
</table>

\(\text{A&OIHD: acute and old ischemic heart disease, CM: cardiomyopathy,}
\VF: ventricular fibrillation, poly VT: polymorphic VT, VT: monomorphic VT
\text{LVEF: left ventricular ejection fraction, BNP: brain natriuretic peptide}
\(\text{\(^\dagger\text{Calculated in 20 effective and 10 non-effective patients with in-hospital event.}}\)
\(*\text{indicates statistical significance.}\)
difference was observed only in patient survival in patients with nifekalant therapy for VT/VF interruption (Table 2). In patients with nifekelant therapy for VT/VF prevention, on the other hand, the incidence of cardiomyopathy was higher in the non-effective group than the effective group
(\(p = 0.038\)) and the time from event onset to nifekalant therapy was significantly shorter in the effective group than the non-effective group \((p = 0.024)\), in addition to the difference in patient survival \((p = 0.017)\).

**Figure** exhibits the changes in the electrocardiographic parameters caused by the initial administration of nifekalant. There was no difference between the data before and after the nifekalant administration in terms of the heart rate or QRS width. The QTc interval was significantly prolonged in both groups, and the degree of the prolongation was greater in the effective group than in the non-effective group.

Table 4 exhibits the comparison of the data of the
patients with in-hospital and out-of-hospital events. Because all perioperative events were observed as in-hospital events, the incidence of perioperative events was significantly different between the patients who had in-hospital versus those who had out-of-hospital events. The population of underlying heart disease was different between the in-hospital and out-of-hospital event patients, and the incidence of acute and old ischemic heart disease was higher in in-hospital event patients and that of cardiomyopathy was higher in out-of-hospital event patients \((p = 0.012)\). There was no difference in patient survival between the two groups.

Adverse effects such as appearance of torsades de pointes, bradycardia \((<50\text{ bpm})\), or abnormal QT prolongation \((\text{QTc} > 0.6\text{ sec}^{1/2})\) was not observed in this study after the initial administration of nifekalant.\(^4,8\) Later appearance of abnormal QTc prolongation was observed in 2/22 patients with continuous infusion of nifekalant and the dose of nifekalant was reduced in such patients.

Discussion

Clinical effects of nifekalant and patient characteristics

In this study, the effect of nifekalant on lidocaine-refractory VT/VF was evaluated in 47 consecutive patients. Although the population included clinically severe patients who underwent circulatory pulmonary resuscitation procedures, nifekalant was effective in suppressing VT/VF in 26/47 patients which closely matched the VT/VF results of earlier studies\(^4,7\) and was much better than that reported for CPA patients.\(^9\) Because the population in this study was selected as “lidocaine-refractory” VT/VF, the arrhythmogenic substrate might be different from that of the total population. The main effects of lidocaine are conduction block due to sodium channel blocking, and the suppression of triggered activity due to the shortening of action potential duration. Therefore the selection of the patients with “lidocaine-refractory” VT/VF might have resulted in the selection of VT/VF with more chaotic and functional reentrant circuits which is not strongly dependent on the presence of triggered activity. Nifekalant is a pure Ikr channel blocker and it exhibits a prolongation of the myocardial refractoriness and enlargement of the central line of block in spiral or leading circle reentry.\(^10,11\) It also leads to exaggeration and irregular meandering of spiral waves and may result in the interruption of tachycardia by the collision of the central core to anatomical obstacles.\(^11–13\) This effect of nifekalant

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of patients with in- and outside-hospital events</th>
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<tbody>
<tr>
<td></td>
<td>In-hospital events</td>
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<tr>
<td>Number (n)</td>
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<tr>
<td>Age (years)</td>
<td>63 ± 6</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>7:23</td>
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<tr>
<td>Basic heart disease</td>
<td></td>
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<td>(A/H/O/CM/others)</td>
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<td>Discharge alive (n)</td>
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<tr>
<td>Targeted arrhythmia</td>
<td></td>
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<tr>
<td>(VF/poly VT/VT)</td>
<td>10/16/4</td>
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<tr>
<td>Efficacy of nifekalant</td>
<td></td>
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<tr>
<td>for VT/VF interruption (n)</td>
<td>7/11</td>
</tr>
<tr>
<td>for VT/VF prevention (n)</td>
<td>13/19</td>
</tr>
<tr>
<td>Initial dose of nifekalant (mg)</td>
<td>24.4 ± 3.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37 ± 5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>BNP (ng/dl)</td>
<td>912 ± 472</td>
</tr>
</tbody>
</table>

\(^*\)indicates statistical significance.

A/H/O: acute and old ischemic heart disease, CM: cardiomyopathy, VF: ventricular fibrillation, poly VT: polymorphic VT, VT: monomorphic VT

LVEF: left ventricular ejection fraction, BNP: brain natriuretic peptide

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might make it more effective for the present population than the total population.

In the present study, the incidence of in-hospital events or perioperative events was higher in the nifekalant effective group than in the non-effective group. In a study in CPA patients, Yoshioka et al. have suggested the influence of the difference between in-hospital and out-of-hospital CPA in the levels of acidosis, serum potassium, or preceding use of epinephrine or lidocaine, but there was no significant difference in such factors in this study. The precise mechanisms of those results were unclear, but the time from the event onset to the active treatment seemed to play at least one important role. Because the perioperative patients were usually under intensive monitoring, the interval from the event onset to the time of the treatment should have been the shortest. Although the data was selected in patients with in-hospital events, the time interval from the event onset to nifekelant administration tended to be shorter in the effective group than the non-effective group and the difference was significant in patients with nifekalant therapy for VT/VF prevention. Additionally, the incidence of acute ischemic heart disease was higher in the effective group and cardiomyopathy was more prevalent in the non-effective group. It would be partly explained by the correlation between the underlying heart disease and the place of event onset in the population of the present study (Table 4), but nifekalant might be less effective in cardiomyopathy than in ischemic heart disease. The mechanism of this difference is unclear but it might be explained by the electrical or structural remodeling in chronic heart failure which is characterized by the prolongation in action potential duration and decrease in cell-to-cell connection. Because there might be multiple small anatomical obstacles due to weak cell-to-cell connections, small stable reentry may play a role in such ventricle and therefore class III antiarrhythmic agent might be less effective. In contrast, the shortening of action potential duration and transmural dispersion are considered to play a role in acute ischemia, and the effect of nifekalant in prolonging the action potential and decreasing transmural dispersion would be more effective in such cases.

In the electrocardiographic parameters, the QTc interval was significantly prolonged by nifekelant and the degree of the QTc prolongation was greater in the effective group than in the non-effective group (Figure). That result indicated that the QTc prolongation caused by the nifekalant may vary in individual patients even with the same amount of the drug, and more effective results would be expected in patients with a larger QTc prolongation. Because nifekalant is considered to interrupt the tachycardia by prolonging the action potential duration of the ventricular muscle, the strength of the antiarrhythmic effect of nifekalant could be monitored by the degree of the QTc prolongation.

Effect of nifekalant on patient survival

Reflecting the severe conditions of the patients, the survival rate of the patients was considerably low in our series (12/47). There were no survivors in the nifekalant non-effective group and all the survivors were in the nifekalant effective group. Interestingly, the incidence of survivors in the nifekalant effective patients tended to be higher in the non-operative patients (5/7) than in the perioperative patients (7/18) although the difference was not significant. This probably indicates that the patients’ short-term prognoses was strongly dependant on the success of the initial treatment for life-threatening arrhythmias, but the long-term prognoses would have been determined by the underlying heart diseases themselves.

Limitations

This study evaluating the effect of nifekalant on lidocaine-refractory VT/VF had several limitations. First, the study was designed retrospectively, therefore the basic therapies and backgrounds varied among the patients. Second, the number of patients was limited. Third, because the patients were selected as a lidocaine refractory VT/VF population, the characteristics of patients with lidocaine effective VT/VF are unclear. Finally, the time points for the evaluation of the arrhythmias and clinical parameters were limited, and thus the time course of the changes in those parameters were unclear.

Conclusions

Nifekalant was effective in 24/47 (55%) of the patients for lidocaine refractory VT/VF. It was considered that nifekalant was more effective for patients with ischemic heart disease, during the perioperative period or in those experiencing in-hospital events, and less effective for patients with cardiomyopathy. The prolongation of the QTc interval might also be useful as an index for the efficacy of nifekelant administration.
References