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Original Article

QT prolongation and torsades de pointes during emergency treatment with nifekalant for refractory ventricular tachyarrhythmias: Post-hoc analysis from a large-scale multicenter post-marketing survey in Japan

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ABSTRACT

Background: Nifekalant, a first-line drug for the treatment of ventricular tachycardia/ventricular fibrillation (VT/VF) in Japan, has been known to prolong the QT interval; however, the incidence of excess QT/QTc prolongation and subsequent torsades de pointes (TdP) has not yet been reported.
Methods: The QT/QTc interval and occurrence of TdP during nifekalant therapy were evaluated in 1402 emergency patients with VT/VF.
Results: Thirty-five cases (2.5%) of QT/QTc prolongation and 54 cases (3.9%) of TdP were reported. High nifekalant doses and long QTc intervals were associated with frequent TdP. The incidence of TdP was 1.4% for QTc intervals <0.43, 3.9% for those 0.44–0.49, 5.3% for those 0.50–0.55, 7.3% for those 0.56–0.61, 11.1% for those 0.62–0.67, and 12.5% for those ≥ 0.68. The odds ratio for TdP was elevated in women (2.48); in patients with any heart disease (4.68), New York Heart Association (NYHA) III or IV (1.81), Forrester subset 2 or worse (2.13), depressed cardiac function (1.86), or liver dysfunction (2.06); and in patients who were receiving concomitant drugs (2.67). In 42 patients (77.8%), TdP required treatment with direct current shock or a second drug.
Conclusion: Nifekalant was effective for refractory VT/VF, although careful observation of the QT/QTc interval and possible occurrence of TdP is required, especially in high-risk patients.

1. Introduction

Nifekalant hydrochloride was first approved by the Japanese Ministry of Health, Labour and Welfare in 1999 and is now used as a first-line antiarrhythmic drug for refractory ventricular tachyarrhythmias in the country [1]. Nifekalant is a class III antiarrhythmic agent; thus, it highly selectively blocks the IKr channel and increases the duration of the action potential in myocardial cells, which prolongs the effective refractory period and exerts strong antiarrhythmic effects[2–4]. In recent clinical studies, nifekalant was reported to be safe [5] and effective for terminating arrhythmia attacks and preventing the recurrence of life-threatening refractory ventricular arrhythmia [6–8]. In addition, it suppressed the induction of ventricular tachycardia (VT) and ventricular fibrillation (VF) induced by programmed electrical stimulation [9,10]. Moreover, it improved the rate of return of spontaneous circulation in patients with shock-resistant in-hospital [11] or out-of-hospital cardiac arrest [12]).

However, it is well known that nifekalant prolongs the QT/QTc interval on electrocardiograms (ECGs) due to its pharmacological properties and that it sometimes induces a form of polymorphic ventricular tachycardia – torsades de pointes (TdP) – due to excess QT prolongation. In fact, cases of TdP were reported in the above-mentioned clinical studies.

To determine the safe and effective use of nifekalant in the clinical setting, it is necessary to investigate the incidence of TdP during nifekalant therapy. Thus, the purpose of the present study was to examine the incidence of TdP and its relationship with QT/QTc prolongation in a large Japanese population. In addition, we attempted to identify the risk factors associated with TdP during nifekalant therapy.

2. Materials and methods

2.1. Subjects

In this post-marketing clinical survey, we investigated 1402 consecutive patients who received nifekalant at 301 institutions

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in Japan between September 1999 and March 2005. The survey was conducted by Nihon Schering Co. Ltd. (now Bayer Pharmaceutical Co. Ltd., Osaka, Japan).

All patients had a medical condition for which nifekalant was indicated. Patients were eligible for study inclusion if they met any of the following criteria: (1) unsuccessful use of another antiarrhythmic agent before nifekalant to treat acute ventricular arrhythmia; (2) use of another antiarrhythmic agent that was effective but resulted in an adverse reaction; (3) use of another antiarrhythmic agent that was effective and did not result in an adverse reaction but could not be continued due to hemodynamic deterioration; or (4) the use of no other antiarrhythmic agent before nifekalant.

A total of 1399 patients were enrolled in the safety evaluation, which included QT/QTc interval measurements. Three patients with duplicate records were excluded.

2.2. ECG monitoring and QT/QTc interval measurement

Surface ECG was continuously monitored throughout the nifekalant administration, usually with a bipolar chest lead. TdP was defined as ≥ 3 consecutive polymorphic wide QRS complexes that showed the characteristic twist around the isoelectric baseline. The QT/QTc interval immediately before the TdP onset was measured in patients who developed a TdP episode. When TdP occurred repeatedly during the nifekalant therapy, the first episode was used in the assessment. When TdP did not occur during nifekalant administration, the maximum QT/QTc interval during the study period was used as the representative value.

The QT interval was measured as the length from the onset of the Q wave to the end of the T wave. The end of the T wave was manually determined as the point at which the T wave deflection returned to the baseline level. QTc was calculated using Bazett's correction ($QTc = QT/RR^{1/2}$).

2.3. Nifekalant protocol

The approved protocol for nifekalant administration was an initial single bolus injection of 0.3 mg/kg followed by continuous intravenous infusion of 0.4 mg/kg/h; however, in the clinical setting, physicians were permitted to adjust this regimen according to each patient's condition [13].

2.4. Statistical analysis

All data are expressed as mean $\pm$ standard deviation. The chi-square test was used to compare TdP incidences. P values < 0.05 were considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for several putative risk factors for TdP.

3. Results

3.1. Patient backgrounds

Mean age was 65.1 ± 14.7 years, and 1048 (74.8%) patients were male. A total of 1287 (92.0%) patients had underlying heart disease, including 831 with ischemic heart disease, 227 with cardiomyopathy, and 229 with other organic heart diseases; 73.7% had depressed left ventricular function, i.e., an ejection fraction (EF) $< 40\%$. A total of 339 patients had liver dysfunction, while 581 patients had renal dysfunction. A total of 1271 (90.9%) patients were prescribed more than 1 concomitant drug, including class I and III antiarrhythmic drugs, β-blockers, catecholamines, human atrial natriuretic peptide (hANP), nicorandil, nitroglycerin, and loop diuretics.

3.2. Nifekalant administration

Nifekalant was administered as a single bolus injection in 277 (19.8%) patients, as a single bolus injection followed by continuous infusion in 751 (53.7%) patients, and as a continuous infusion only without a single bolus injection in 369 (26.4%) patients. The single bolus dose was 0.25–0.35 mg/kg in 766 (74.6%) of 1027 patients. Among the 1122 patients who received a continuous infusion, the starting dose was 0.15–0.24 mg/kg/h in 292 (26.0%), 0.25–0.34 mg/kg/h in 240 (21.4%), 0.35–0.44 mg/kg/h in 430 (38.3%), and ≥ 0.45 mg/kg/h in 28 (2.5%) patients.

3.3. Arrhythmia control

The efficacy of antiarrhythmics in suppressing ventricular arrhythmias and the prophylaxis of arrhythmia recurrence was evaluated in 620 and 964 patients, respectively. The rate of effectiveness in suppressing ventricular arrhythmias was 69.2% when nifekalant was used as a first-line therapy and 63.9% in cases that were refractory to treatment with other drugs. The prophylaxis of acute arrhythmia recurrence by continuous nifekalant infusion was successful in 84.8% of cases in which it was used as a first-line therapy and in 82.1% of cases that were refractory to treatment with other drugs.

3.4. Occurrence of TdP and QT/QTc prolongation

Fifty-four patients (3.86%) had 1 or more episodes of TdP. In 8 patients, TdP occurred during the single bolus administration of nifekalant; in the remaining 46 patients, it occurred during continuous infusion of the drug. Thirty-five patients (2.50%) had QT/QTc prolongation that was not associated with TdP. Twenty-three patients required direct current (DC) shock to terminate TdP, while 13 patients required additional pharmacological therapy to manage TdP, including magnesium and lidocaine.

3.4.1. Relationship between QTc and TdP

Fig. 1 shows the number of patients with and without QTc-induced TdP episodes immediately before TdP or maximum QTc among 669 patients from whom ECG data were collected. As Fig. 1 illustrates, long QTc intervals were associated with a high proportion of patients with TdP episodes. The proportion of patients with TdP steadily rose as the QTc interval increased (Fig. 2): 1 of 72 (1.4%) for a QTc < 0.43, 7 of 181 (3.9%) for a QTc of 0.44–0.49,

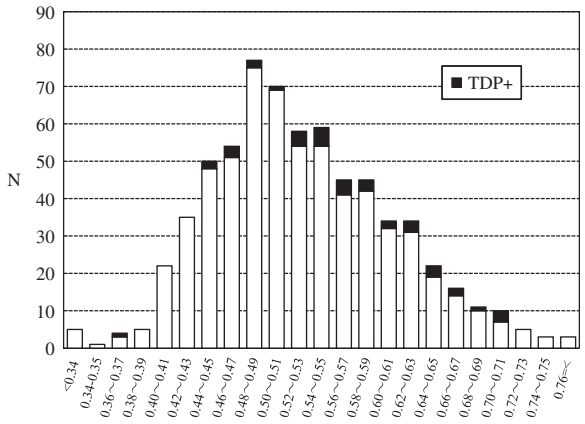

Fig. 1. Relationship between QTc and torsades de pointes (TdP). Ordinate, no., abscissa, QTc.

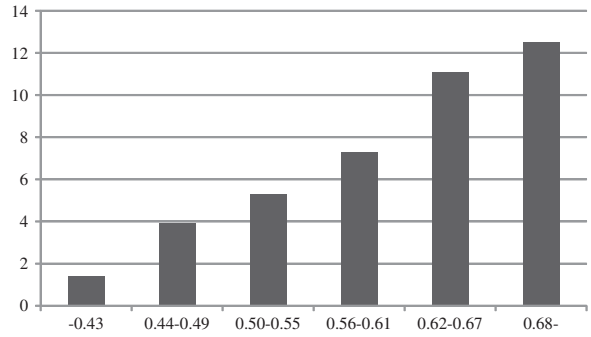

Fig. 2. Incidence of torsades de pointes. Ordinate, %; abscissa, QTc.

Table 1
Incidence of torsades de pointes (TdP) during single bolus injection.

Dose	No.	TdP+	Incidence of TdP (%)
≤0.14 mg/kg	34	0	0.00
0.15–0.24 mg/kg	121	1	0.83
0.25–0.34 mg/kg	766	5	0.65
0.35–0.44 mg/kg	62	0	0.00
≥0.45 mg/kg	37	2	5.41
Total	1020	8	0.78

Table 2
Incidence of torsades de pointes (TdP) during continuous infusion.

Dose	No.	TdP+	Incidence of TdP (%)
≤0.14 mg/kg	131	3	2.29
0.15–0.24 mg/kg	292	9	3.08
0.25–0.34 mg/kg	240	11	4.58
0.35–0.44 mg/kg	430	21	4.88
≥0.45 mg/kg	28	2	7.14
Total	1121	46	4.10

10 of 187 (5.3%) for a QTc of 0.50–0.55, 9 of 124 (7.3%) for a QTc of 0.56–0.61, 8 of 72 (11.1%) for a QTc of 0.62–0.67, and 4 of 32 (12.5%) for a QTc ≥0.68.

3.4.2. Relationship between nifekalant dose and TdP

As shown in Tables 1 and 2, the overall incidence of TdP was higher during continuous infusion than during single injection. In addition, high nifekalant doses, whether given as a single bolus injection or continuous infusion, were associated with high TdP incidence.

3.4.3. Patient characteristics and the incidence of TdP

As shown in Table 3, the incidence of TdP during nifekalant therapy was high (>5%) in women; in patients with cardiomyopathy, NYHA functional class III disease, Forrester subset 2 or 3 disease, or liver dysfunction; and in those using β-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), loop diuretics, or magnesium. ORs for the occurrence of TdP are shown in Fig. 3. Elevated ORs were observed for the female sex (OR, 2.48; 95% CI, 1.43–4.30), any heart disease (4.68; 0.64–34.18), NYHA functional class III or IV disease (1.81; 0.96–3.42), Forrester subset 2 or worse disease (2.13; 0.87–5.25), depressed cardiac function (1.86; 0.87–3.97), liver dysfunction (2.06; 1.17–3.60), use of concomitant drugs (2.67; 0.64–11.08), and use of loop diuretics (1.74; 1.01–3.00).

3.5. Suppression of TdP

In 42 of 54 patients (77.8%), treatments, including DC shock and a second IV antiarrhythmic drug, were required to suppress TdP. DC cardioversion was performed in 23 patients and a second antiarrhythmic drug, including magnesium and lidocaine, was effective in 13 patients. In 6 patients, TdP was terminated by a precordial thump or right ventricular overdrive pacing. In 8 patients, TdP resolved spontaneously and quickly without the need for additional treatment.

3.6. Other adverse reactions

Mild bradyarrhythmias, including sinus bradycardia, sinoatrial block, and atrioventricular block, occurred in 20 of 1,121 patients (1.78%) during nifekalant infusion. The incidence of other adverse reactions was low, including those for liver dysfunction (0.64%), renal dysfunction (0.5%), and hypotension (0.07%).

4. Discussion

4.1. Patient backgrounds and nifekalant effectiveness

Although the patient characteristics varied (Table 3), most were critically ill from severe underlying cardiac disease. Nifekalant was used emergently to control life-threatening ventricular arrhythmias under these critical conditions. The conditions of >70% of patients were refractory to other antiarrhythmic drugs, including lidocaine, before nifekalant was used. The underlying heart diseases included ischemic heart disease, cardiomyopathy, and other organic heart diseases, and many patients had depressed left ventricular function as indicated by an EF <40%.

This patient population was comparable to those investigated in large-scale randomized trials conducted in North America and Europe, including the participants of the CHF-STAT1 [14], EMIAT [15], CAMIAT [16], and SCD-HeFT [17] trials. In the present critically ill population, nifekalant had a high rate of effectiveness with no severe adverse reactions, except TdP. Nifekalant administration resulted in a success rate of >60% for suppressing refractory VT/VF and a success rate of >80% for preventing the acute recurrence of ventricular arrhythmias. These results are comparable or superior to those reported for other conventional antiarrhythmic drugs, including intravenous lidocaine, procainamide, and amiodarone [18].

4.2. Relationship between QTc and TdP

Prolongation of the QT/QTc interval is a major risk factor for severe ventricular arrhythmias [19,20]. It has long been known that TdP and sudden cardiac death occur frequently in patients with congenital long QT syndrome (LQTS), e.g., those with Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome, and in patients with secondary LQTS, which is induced by a number of drugs [21–23]. QT interval prolongation might result in more frequent TdP; however, the relationship between the degree of prolongation and the exact incidence of TdP has not been comprehensively investigated [24,25]. Patients with longer QT intervals do not always have more TdP episodes than do patients with shorter QT intervals, perhaps because of differences in sensitivity to arrhythmogenicity, which depend on the degree of QT prolongation in each patient. In some cases of congenital LQTS, TdP may be induced by emotional stress or the sudden auditory stimulation of an alarm clock [26–28]. Thus, sensitivity may differ with regard to the pathogenesis of QT prolongation, including the presence of ion-channel gene mutations.

Table 3
Patient characteristics and the incidence of torsades de pointes (TdP).

Characteristics	Category	No.	TdP+	Incidence of TdP (%)	P (χ^2 test)
Sex	Male	1047	30	2.87	< .001
	Female	352	24	6.82	
Age (years)	< 15	11	0	0	0.641
	15–44	92	3	3.26	
	45–64	469	22	4.69	
	≥ 65	827	29	3.51	
Any heart disease	−	110	1	0.91	0.094
	+	1287	53	4.12	
AMI	−	866	33	3.81	0.892
	+	531	21	3.95	
OMI	−	1005	37	3.68	0.568
	+	392	17	4.34	
Angina	−	1267	50	3.95	0.624
	+	130	4	3.08	
Cardiomyopathy	−	1154	41	3.55	0.187
	+	243	13	5.35	
Myocarditis	−	1353	53	3.92	0.578
	+	44	1	2.27	.
Other cardiac diseases	−	1157	46	3.98	0.638
	+	240	8	3.33	
Cardiac surgery	−	1132	44	3.89	0.949
	+	263	10	3.8	
NYHA functional class	I	263	5	1.9	0.092
	II	256	9	3.52	
	III	221	14	6.33	
	IV	470	19	4.04	
Forrester subset	I	264	6	2.27	0.379
	II	138	7	5.07	
	III	73	4	5.48	
	IV	339	15	4.42	
LVEF	< 40%	538	24	4.46	0.857
	40–49%	190	7	3.68	
	≥ 50%	262	10	3.82	
Depressed cardiac function	−	326	8	2.45	0.106
	+	1031	46	4.46	
Any other complication	−	480	10	2.08	0.012
	+	917	44	4.8	
Liver dysfunction	−	1060	33	3.11	0.01
	+	339	21	6.19	
Renal dysfunction	−	818	27	3.3	0.198
	+	581	27	4.65	
Any concomitant drugs	−	127	2	1.57	0.161
	+	1271	52	4.09	
Any antiarrhythmic drugs	−	494	15	3.04	0.236
	+	904	39	4.31	
Lidocaine	−	369	16	4.34	0.582
	+	1029	38	3.69	
β-blocker	−	1135	40	3.52	0.173
	+	263	14	5.32	
Cardiac stimulant	−	531	17	3.2	0.315
	+	867	37	4.27	
Catecholamine	−	652	24	3.68	0.742
	+	746	30	4.02	
Digoxin	−	1277	48	3.76	0.513
	+	121	6	4.96	
PDE-III inhibitor	−	1255	48	3.82	0.827
	+	143	6	4.2	
hANP	−	1243	47	3.78	0.654
	+	155	7	4.52	
Other cardiac stimulant	−	1364	53	3.89	0.778
	+	34	1	2.94	
Vasodilator	−	725	28	3.86	0.999
	+	673	26	3.86	
Nicorandil	−	1207	49	4.06	0.337
	+	191	5	2.62	
ACE-I	−	1261	46	3.65	0.206
	+	137	8	5.84	
ARB	−	1239	50	4.04	0.349
	+	159	4	2.52	
Loop diuretics	−	856	26	3.04	0.044
	+	542	28	5.17	
Spironolactone	−	1228	47	3.83	0.854
	+	170	7	4.12	
Magnesium	−	1258	44	3.5	0.034
	+	140	10	7.14	

AMI; OMI; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PDE-III, phosphodiesterase-III; hANP, human atrial natriuretic peptide; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

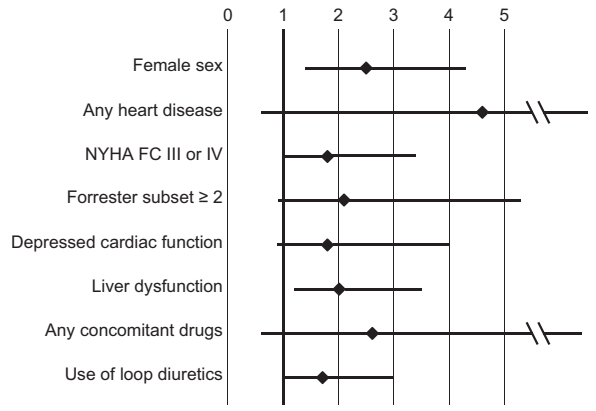

Fig. 3. Odds ratios for torsades de pointes. Diamonds, odds ratios; bars, 95% confidence intervals.

The findings of the present study of nifekalant therapy reveal that greater prolongation of the QT interval resulted in more frequent TdP in critically ill patients with severe underlying cardiac disease. QT/QTc prolongation is clearly the most important marker of TdP risk; however, the threshold QT/QTc interval for TdP may differ substantially among individuals. Our findings indicate that a QTc interval of 0.6 might be a critical value for TdP risk because it was associated with an exponential increase in the rate of TdP (to $\geq$10%) in the patients of the present study.

4.3. Risk factors for TdP occurrence

The results of the present study show that the incidence of TdP during nifekalant therapy was $>$5% in women; in patients with cardiomyopathy, NYHA functional class III disease, Forrester subset 2 or 3 disease, or liver dysfunction; and in patients using β-blockers, ACE-Is, loop diuretics, or magnesium. Because of the critical condition of the patients and the need for emergent therapy, we have no data on the QT/QTc interval before nifekalant administration; thus, we were unable to determine the extent to which QT/QTc was prolonged relative to the period before nifekalant administration.

It is well known that the long QT/QTc interval and high incidence of TdP among women is associated with female sex hormones [29–31] and that heart failure with depressed cardiac function resulting from severe heart disease is a clear risk factor for ventricular arrhythmias [32,33]. The use of β-blockers, ACE-Is, and loop diuretics may be representative of underlying heart failure. Magnesium use can be explained as the treatment for TdP.

Several factors were associated with elevated ORs for TdP in the present study. Female sex, any heart disease, and concomitant drug use were associated with ORs of $\geq$2.0. Therefore, such factors should also be considered important risks for TdP during nifekalant therapy.

4.4. Study limitations

The present study has some limitations. The most important of which is that the study was planned in a retrospective manner as a post-hoc analysis of post-marketing surveillance in Japan. In addition, it lacked positive and negative control groups. Because it was not a randomized prospective trial, the dosage and protocol for nifekalant use were determined by attending physicians according to patient condition. We could not confirm each TdP waveform and determine whether the episode was a true TdP or a recurrence of original ventricular tachyarrhythmia in the real ECG recordings. In addition, the types of the original ventricular tachyarrhythmia, monomorphic or polymorphic, sustained or non-sustained, were not confirmed. The QT measurement method was decided upon and promulgated before the study began, and the QT intervals were measured by the respective attending physicians in the emergency room mainly through the use of monitor ECGs with bipolar chest leads. Because the QT interval measurements were not performed by a central laboratory, some of the measurements may have been inaccurate. In addition, control ECGs (i.e., before nifekalant use) could not be obtained due to the patients' critical conditions.

A future randomized prospective study with a positive control group is needed to clarify the threshold level of QT prolongation for the occurrence of TdP.

Potential conflicts of interests

None.

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