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Antiarrhythmic Effect of Nifekalant on Atrial Tachyarrhythmia in Four Patients With Severe Heart Failure

Tsuyoshi SHIGA, MD
Naoki MATSUDA, MD
Yuji FUDA, MD
Shoji HARUTA, MD
Nobuhisa HAGIWARA, MD
Hiroshi KASANUKI, MD, FJCC

Abstract

Objectives. Nifekalant is a class III antiarrhythmic drug, which prolongs the refractory period of the atrial and ventricular myocardium, without negative inotropic action. Intravenous nifekalant was administered in four patients with atrial tachyarrhythmia and severe heart failure to terminate or prevent atrial tachyarrhythmia.

Methods and Results. Two of three episodes of atrial tachyarrhythmia were terminated by intravenous nifekalant (0.22 to 0.30 mg/kg) administration. Continuous intravenous infusion of nifekalant (0.15 to 0.40 mg/kg/hr) during six episodes to maintain the sinus rhythm, prevented recurrence of atrial tachyarrhythmia in five episodes in which prolongation of the QTc interval was observed to more than 450 msec. None of the patients showed worsening of the hemodynamics during treatment. One patient developed polymorphic ventricular tachycardia, which deteriorated into ventricular fibrillation.

Conclusions. Nifekalant may be effective for treating atrial tachyarrhythmia in patients with severe heart failure. Further clinical studies are needed to confirm these findings.

Key Words
■Antiarrhythmic agents (nifekalant) ■Atrial fibrillation ■Atrial flutter
■QT interval ■Heart failure

INTRODUCTION

Atrial tachyarrhythmia such as atrial fibrillation and flutter often occur as complications of heart failure. Uncontrolled atrial fibrillation reduces the ventricular filling time, worsens the heart failure, and provokes "tachycardiomyopathy"[1]. The absence of atrial contraction and irregularity of the ventricular rhythm also contribute to worsening of heart failure[1]. Therefore, prevention or conversion of atrial tachyarrhythmia to sinus rhythm is important in the management of heart failure. Many class I antiarrhythmic agents can convert atrial fibrillation and maintain sinus rhythm by slowing the conduction velocity. However, these agents may also worsen heart failure because they have significant negative inotropic effects[2]. In contrast, class III antiarrhythmic drugs prolong the action potential duration and increase the myocardial refractory period without negative inotropic effects[2], and are useful for the treatment of atrial fibrillation and flutter[3–7]. Therefore, class III antiarrhythmic drugs are also expected to be useful for converting atrial fibrillation and flutter to sinus rhythm and maintaining the sinus rhythm in patients with heart failure.

東京女子医科大学附属日本心臓血圧研究所 循環器内科: 〒162–8666 東京都新宿区河田町8–1
Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo
Address for correspondence: SHIGA T, MD, Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Kawada-cho 8–1, Shinjuku-ku, Tokyo 162–8666
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Table 1 Clinical characteristics of four patients with severe heart failure and atrial tachyarrhythmia

Case	Age (yr)	Sex	Underlying heart disease	Arrhythmia	NYHA	Plasma BNP (pg/ml)	LVEF (%)
1	81	Female	AMI	AT, AF, sVT	IV	Not performed	34
2	83	Female	AMI	Af, sVT	IV	1,831	30
3	42	Male	DCM	Af, AF, sVT	IV	533	18
4	67	Female	DCM	AF, nsVT	III	866	19

NYHA=New York Heart Association functional class; BNP=brain natriuretic peptide; LVEF=left ventricular ejection fraction; AMI=acute myocardial infarction; DCM=idiopathic dilated cardiomyopathy; Af=atrial fibrillation; AF=atrial flutter; AT=atrial tachycardia; sVT=sustained ventricular tachycardia; nsVT=non-sustained ventricular tachycardia.

Nifekalant (MS-551) is a new pure K channel blocker developed in Japan, which selectively inhibits the rapid component of the delayed rectifier potassium current (Ikr), as well as prolonging the refractory period of the atrial and ventricular myocardium[8,9]. The pharmacokinetic characteristics of nifekalant are as follows: Urinary excretion ratio of the unchanged drug is approximately 30%, most of the drug promptly undergoes glucuronate conjugation in the liver, the elimination half-life of the unchanged drug is short at 1.5 hr, and the volume of distribution is small at 0.14 *l*/kg[10]. Therefore, nifekalant is used as an intravenous administration and adjustment of the dose is relatively easy. To obtain a constant blood concentration, nifekalant must be administered at a constant rate by continuous intravenous infusion.

We studied the intravenous use of nifekalant in four patients with heart failure and worsened hemodynamics due to complicating atrial tachyarrhythmia.

SUBJECTS AND METHODS

The subjects were four patients with severe heart failure in New York Heart Association (NYHA) functional class III or IV with atrial fibrillation or flutter or tachycardia (**Table 1**). All patients had ventricular tachycardia with structural heart disease, and the atrial fibrillation or flutter or tachycardia occurred during treatment for the heart failure. Termination and prevention of atrial tachyarrhythmia were required for treatment of refractory heart failure. Termination of three episodes of atrial fibrillation, flutter or tachycardia was attempted by a bolus injection of nifekalant in two patients (Cases 1 and 2). Nifekalant was administered by continuous intravenous infusion for the prevention of recurrence of atrial fibrillation, flutter or tachycardia in six episodes in all patients.

RESULTS

Two of three episodes of atrial tachyarrhythmia in Cases 1 and 2 were terminated following intravenous administration of nifekalant, bolus of 0.22 to 0.30 mg/kg over 5 to 10 min (**Fig. 1**). The other episode of atrial flutter in Case 1 required electrical cardioversion for termination (**Fig. 2**, **Table 2**). Continuous intravenous infusion of nifekalant was used in six episodes as soon as possible after termination. There were no recurrences of atrial tachyarrhythmia during nifekalant administration except one episode in Case 2, in whom recurrence was seen under a low dose (0.20 mg/kg/hr), but not when the dose was increased from 0.20 to 0.40 mg/kg/hr (**Fig. 2**, **Table 2**). The QTc intervals at sinus rhythm during continuous intravenous infusion were prolonged compared to those in sinus rhythm before the infusion of nifekalant. In the five episodes in which the recurrence of atrial tachyarrhythmia was not observed, the QTc interval with nifekalant was prolonged to more than 450 msec or more than 5% increase. In Case 2, the QTc interval with nifekalant was less than 450 msec before the recurrence of atrial fibrillation, but the QTc interval was prolonged to more than 450 msec and recurrence was not observed when the dose of nifekalant was increased (**Fig. 3**). In all patients, no sustained monomorphic ventricular tachycardia occurred during infusion of nifekalant. **Table 3** shows the hemodynamic parameters in sinus rhythm before and during continuous infusion of nifekalant. None of the patients showed worsening of hemodynamic factors during the infusion of nifekalant. Polymorphic ventricular tachycardia which deteriorated into ventricular fibrillation occurred during continuous infusion of nifekalant in Case 4, but no

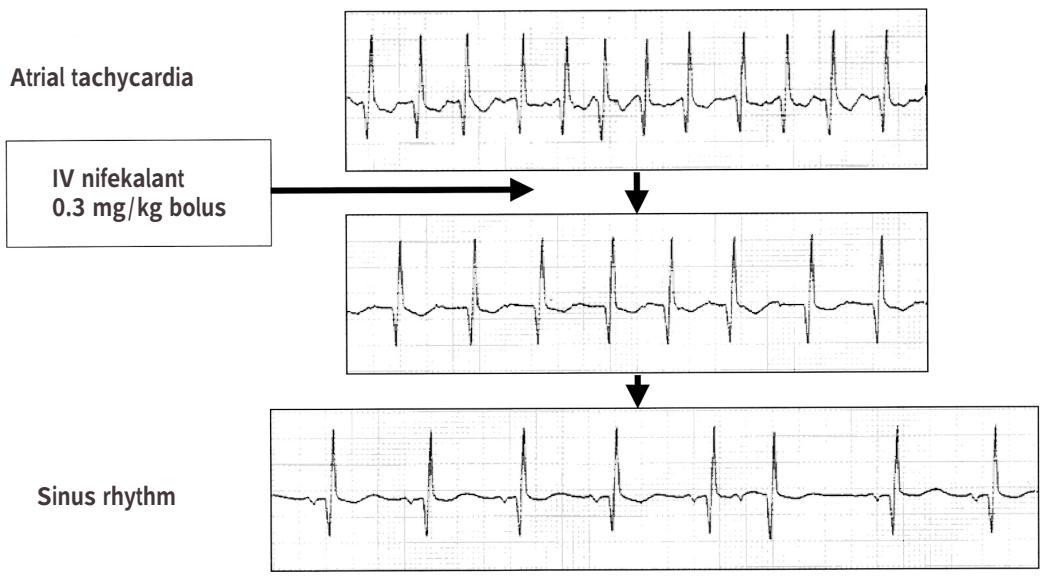

Fig. 1 Termination of atrial tachycardia by nifekalant administration in a patient with congestive heart failure: Case 1
Intravenous nifekalant converted multifocal atrial tachycardia with rapid atrial rate to atrial tachycardia with slow atrial rate, followed by termination.
IV = intravenous.

recurrence of polymorphic ventricular tachycardia or fibrillation was observed after discontinuation of nifekalant.

DISCUSSION

Two mechanisms are considered to underpin the potential clinical benefits of nifekalant in atrial fibrillation or flutter or tachycardia in patients with severe heart failure. First, nifekalant prolongs the repolarization and refractoriness of the atrial and ventricular myocardium[8,9]. Atrial fibrillation causes time-dependent decreases in both the effective refractory period and the conduction velocity, resulting in decreased wavelength, which, together with increased regional heterogeneity, provides the substrate for sustained atrial fibrillation[11–13]. Nifekalant can prolong refractoriness without slowing the conduction velocity and may be effective for termination and prevention of atrial fibrillation and flutter[14–17]. However, experimental and electrophysiological studies have suggested that class Ic antiarrhythmic drugs might be as effective in the termination of atrial fibrillation as nifekalant[16–19]and the efficacy of intravenous nifekalant for conversion of paroxysmal atrial fibrillation or flutter in patients of NYHA functional classes I and II, including lone atrial fibrillation,

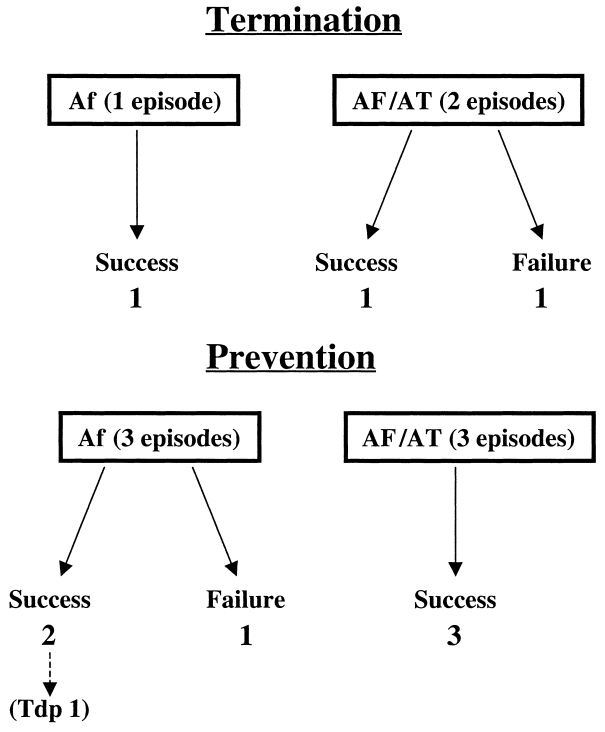

Fig. 2 Efficacy of nifekalant for the termination or prevention of atrial tachyarrhythmia in patients with severe heart failure
Tdp=torsades de pointes. Other abbreviations as in Table 1.

Table 2 Efficacy of nifekalant for the termination or prevention of atrial tachyarrhythmia in patients with severe heart failure

Case	Rhythm	Heart rate (beats/min)	Duration	Dose	Termination	Prevention
1	AT	170	25 min	0.30 mg/kg bolus, then 0.15 mg/kg/hr	+	+
	AF	160	30 min	0.22 mg/kg bolus, then 0.15 mg/kg/hr	−*	+
2	Af	100	30 min	0.23 mg/kg bolus, then 0.20mg/kg/hr	+	−
	Af	100	25 min	0.40 mg/kg/hr	Not performed*	+
3	Af	100	14 days	0.20 mg/kg/hr	Not performed*	+
4	AF	110	19 hr	0.20 mg/kg/hr	Not performed**	+

*Electrical cardioversion or **antitachycardia pacing was required for termination.
+=success; −=failure. Other abbreviations as in Table 1.

Table 3 Hemodynamic parameters in sinus rhythm before and during infusion of nifekalant in patient with severe heart failure and atrial tachyarrhythmia

Case	Episode	Blood pressure (mmHg)		Cardiac index (l/min/m²)		$\bar{m}$PWP (mmHg)	
		Before	During	Before	During	Before	During
1	AT	98/40	90/50	3.0	3.1	20	14
	AF	80/50	96/54	Not performed		Not performed	
2	Af	79/49	94/50	1.3	1.8	28	24
	Af	70/40	92/48	1.3	2.0	17	16
3	Af	84/50	90/50	1.9	2.5	15	13
4	AF	110/60	120/60	Not performed		Not performed	

$\bar{m}$PWP=mean pulmonary wedge pressure. Other abbreviations as in Table 1.

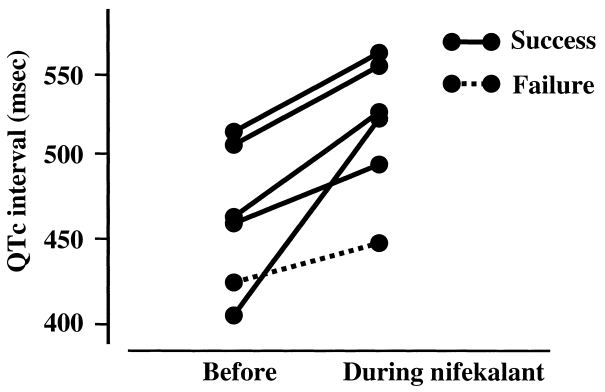

Fig. 3 Change in QTc interval of sinus rhythm before and during continuous intravenous infusion of nifekalant in six episodes to prevent atrial tachyarrhythmia

were observed in only 13(30%)of 44 cases[20]. A recent experimental study using epicardial mapping showed that congestive heart failure, but not rapid atrial pacing, related to atrial fibrillation was often due to macroreentry, with dofetilide, a pure K channel blocker, causing termination by blocking the reentry circuits[21]. Nifekalant would also increase the wavelength and contribute to the termination and prevention of atrial fibrillation or flutter concomitant with heart failure. We found that intravenous nifekalant changed atrial flutter or multifocal atrial tachycardia with a rapid atrial rate to atrial tachycardia of longer cycle length and caused termination in some cases.

Pure K channel blockers have little or no effect for inducing negative inotropic effects[2]. Once heart failure has occurred, atrial fibrillation and flutter can be triggered through an increase in atrial pressure and volume loads[1]. Experimental models show that when the atrial muscle is stretched, atrial tachyarrhythmia is also induced by a reduced atrial refractory period and an increased vulnerability to atrial fibrillation[22]. Nifekalant did not worsen the hemodynamics in all patients, and this benefit may also be involved in the antiarrhythmic effect.

Nifekalant prolongs the action potential duration by its K channel blocking action and also prolongs the QT interval, so the effect can be estimated by observing the QT interval. In our four patients, pre-

ventive effect against atrial tachyarrhythmia was observed during five episodes with prolongation of the QTc interval to more than 450 msec or more than 5% increase, although the QT interval did not always reveal the atrial refractoriness. QT interval may be helpful for the assessment of effect. Nifekalant, a pure Ikr channel blocker, exhibits selective prolongation and reverse use-dependent actions on myocardial repolarization and refractoriness, which may predispose the patient to the development of torsade de pointes as a proarrhythmic reaction[2,23]. Monitoring of the QT(QTc)interval is necessary during infusion of nifekalant for safety.

This study consisted of only four cases, so we cannot definitively conclude that nifekalant is useful for the management of atrial tachyarrhythmia in patients with severe heart failure. However, nifekalant apparently acts on the termination and prevention of atrial tachyarrhythmia in patients with severe heart failure. Further clinical studies are needed to confirm these findings.

CONCLUSIONS

Two of three episodes of atrial tachyarrhythmia were terminated and no recurrence was observed in five of six episodes during intravenous nifekalant infusion in four patients with severe heart failure. Nifekalant may be effective in treating atrial tachyarrhythmia in patients with severe heart failure. However, further clinical studies are needed to confirm these findings.

要　　約

重症心不全患者4例に合併した心房頻拍性不整脈に対するニフェカラントの抗不整脈効果

志賀　剛　　松田　直樹　　布田　有司
春田　昭二　　萩原　誠久　　笠　貫　宏

目　的: Ⅲ群抗不整脈薬であるニフェカラントは陰性変力作用を有さず，心房および心室の不応期を延長する．我々は重症心不全に心房頻拍性不整脈を合併した4例に対し，ニフェカラントの静注を行い，心房頻拍性不整脈の停止あるいは予防を試みた．

方法と結果: 心房頻拍性不整脈の持続中にニフェカラントの静注(0.22−0.30 mg/kg)を行ったところ，延べ3回のうち2回に不整脈の停止を認めた．さらに，洞調律維持のため延べ6回のニフェカラントの持続静注(0.15−0.40 mg/kg/hr)を行ったところ，5回の持続静注中には心房頻拍性不整脈の再発を認めず，QTc間隔は450 msec以上に延長していた．また，持続静注中に血行動態が悪化した例はなかった．しかし，1例で持続静注中に多形性心室頻拍が出現し，心室細動に移行した．

結　論: ニフェカラントは重症心不全に合併した心房頻拍性不整脈の治療に有効であるかもしれない．このことを確かめるため，さらに臨床研究が必要である．

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References

1) Crijns HJGM, Van den Berg MP, Van Gelder IC, Van Veldhuisen DJ: Management of atrial fibrillation in the setting of heart failure. Eur Heart J 1997; **18**(Suppl C): C45−C49
2) Singh BN: Current antiarrhythmic drugs: An overview of mechanisms of action and potential clinical utility. J Cardiovasc Electrophysiol 1999; **10**: 283−301
3) Ellenbogen KA, Stambler BS, Wood MA, Sager PT, Wesley RC Jr, Meissner MD, Zoble RG, Wakefield RK, Perry KT, Vanderlugt JT, for the Ibutilide Investigators: Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: A dose-response study. J Am Coll Cardiol 1996; **28**: 130−136
4) Falk RH, Pollak A, Singh SN, Friedrich T, for the Intravenous Dofetilide Investigators: Intravenous dofetilide, a class Ⅲ antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. J Am Coll Cardiol 1997; **29**: 385−390
5) Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gangé P, Nattel S, Thibault B, for the Canadian Trial of Atrial Fibrillation Investigators: Amiodarone to prevent recurrence of atrial fibrillation. N Engl J Med 2000; **342**: 913−920
6) Torp-Pedersen C, Møller M, Bloch-Thomsen PE, Køber L,

Sandøe E, Egstrup K, Agner E, Carlsen J, Videbæk J, Marchant B, Camm AJ, for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group: Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med 1999; **341**: 857−865

7) Pritchett ELC, Page RL, Connolly SJ, Marcello SR, Schnell DJ, Wilkinson WE, and the Azimilide Supraventricular Arrhythmia Program 3 (SVA-3) Investigators: Antiarrhythmic effects of azimilide in atrial fibrillation: Efficacy and dose-response. J Am Coll Cardiol 2000; **36**: 794−802

8) Nakaya H, Uemura H: Electropharmacology of nifekalant, a new class III antiarrhythmic drug. Cardiovas Drug Rev 1998; **16**: 133−144

9) Isomoto S, Konoe A, Centurion OA, Hayano M, Kaibara M, Hirata T, Yano K: Electrophysiological effects of MS-551 in humans: A class III antiarrhythmic agent. Pacing Clin Electrophysiol 1995; **18**: 2022−2027

10) Kato T, Tsunoo M, Mitsuhashi T, Atarashi H, Ino T, Kuroki S, Tanaka T, Kamei S, Endo Y, Nomura A, Hayakawa K, Hirata H: Phase I study of MS-551(1): A single intravenous injection study. J Clin Ther Med 1997; **13**: 1659−1674 (in Jpn with Eng abstr)

11) Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ: Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 1988; **62**: 395−410

12) Gaspo R, Bosch RF, Talajic M, Nattel S: Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation 1997; **96**: 4027−4035

13) Kumagai K, Gondo N, Matsuo K, Annoura M, Muroe K, Nakashima Y, Hiroki T, Arakawa K: Wavelength index: A predictor of the response to disopyramide in paroxysmal lone atrial fibrillation. Cardiology 1994; **85**: 184−192

14) Ishii M, Kamiya J, Hashimoto K: Cellular electrophysiological effects of MS-551, a novel class III anti-arrhythmic agent. Drug Dev Res 1995; **35**: 61−68

15) Kunimoto S, Watanabe I, Kojima T, Kanda A, Kondo K, Takahashi Y, Kajita J, Saito S, Ozawa Y, Kanmatsuse K: Electrophysiological effect of a novel class III antiarrhythmic agent, MS-551 on human atrium and ventricle. Jpn J Cardiac Pacing Electrophysiol 1995; **11**: 257−282 (in Jpn with Eng abstr)

16) Watanabe H, Watanabe I, Nakai T, Oshikawa N, Kunimoto S, Masaki R, Kojima T, Saito S, Ozawa Y, Kanmatsuse K: Frequency-dependent electrophysiological effects of flecainide, nifekalant and d,l-sotalol on the human atrium. Jpn Circ J 2001; **65**: 1−6

17) Hayashi H, Fujiki A, Tani M, Usui M, Inoue H: Different effects class Ic and III antiarrhythmic drugs on vagotonic atrial fibrillation in the canine heart. J Cardiovasc Pharmacol 1998; **31**: 101−107

18) Shinagawa K, Mitamura H, Sato T, Kanki H, Takatsuki S, Ogawa S: Effect of Na and K channel blockers on the spatial and temporal dispersion of atrial refractoriness during atrial fibrillation. Jpn J Electrocardiol 1998; **18**: 433−442 (in Japanese)

19) Kanki H, Mitamura H, Takatsuki S, Sueyoshi K, Shinagawa K, Sato T, Ogawa S: Postrepolarization refractoriness as a potential anti-atrial fibrillation mechanism of pilsicainide, a pure sodium channel blocker with slow recovery kinetics. Cardiovasc Drugs Ther 1998; **12**: 475−482

20) Kato K, Inoue H, Iinuma H, Ohe T, Ogawa S, Kasanuki H, Kato T: Efficacy of intravenous doses of MS-551 for paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation or flutter: Phase II study. J Clin Ther Med 1997; **13**: 1745−1758 (in Jpn with Eng abstr)

21) Li D, Benardeau A, Nattel S: Contrasting efficacy of dofetilide in differing experimental models of atrial fibrillation. Circulation 2000; **102**: 104−112

22) Ravelli F, Allessie M: Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation 1997; **96**: 1686−1695

23) Shiga T, Ando S, Suzuki T, Matsuda N, Kasanuki H: Reverse use-dependent QT prolongation during infusion of nifekalant in a case of recurrent ventricular tachycardia with old myocardial infarction. J Electrocardiol 2001; **34**: 77−80