

Nifekalant in the treatment of life-threatening ventricular tachyarrhythmias

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effective antiarrhythmic agent for refractory ventricular tachyarrhythmias. Further clinical studies are required before nifekalant is routinely used in the emergency care setting.

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Abstract

The aim of the present study is to review the literature and discuss nifekalant's potential use as a first aid drug in an emergency care setting. The PubMed database was used to identify papers, using keywords nifekalant, MS-551, amiodarone and lidocaine. Nifekalant hydrochloride, formally known as MS-551, is a class III antiarrhythmic agent which acts only by increasing the time course of myocardial repolarization. It was developed and is currently being used only in Japan for the treatment of ventricular tachyarrhythmias. It is a non-selective K⁺ channel blocker without any β -blocking actions. Administration of nifekalant suppressed sustained ventricular tachyarrhythmias in acute coronary syndrome patients, and in cardiac arrest victims as well as during or after cardiac surgery. The major adverse effect of nifekalant is QT interval prolongation and occurrence of torsades de pointes which requires frequent monitoring of the QT interval during nifekalant infusion with adequate dose adjustment. Nifekalant is a possible

INTRODUCTION

Intravenous amiodarone is considered to be the drug of choice for the treatment of ventricular tachycardia/fibrillation (VT/VF) in emergency care medicine^[1]. However, amiodarone does not have a prompt onset of effect; its onset of action is 6-8 h after administration. Furthermore, its intravenous use is occasionally accompanied by adverse effects such as hypotension and bradycardia^[2]. These effects make its use as rescue medication in life-threatening situations difficult.

On the other hand, lidocaine is a class I b antiarrhythmic drug with a modest negative inotropic effect on cardiac function. Although it has been widely used for the treatment of ventricular tachyarrhythmias it was excluded from the list of drugs that can be used to treat such arrhythmias in acute coronary syndrome (ACS) patients because there was no evidence to support its antiarrhythmic effect on sustained VT/VF, according to the guidelines for “the management of patients with ST-elevation myocardial infarction”^[3] or “cardiopulmonary resuscitation and emergency cardiovascular care”^[1].

Recently, researchers have focused on newer class III antiarrhythmic agents such as nifekalant hydrochloride, which act only by increasing the time course of myocardial repolarization. Nifekalant is available only for intravenous injection for the treatment of ventricular tachyarrhythmias and was approved in Japan in June 1999. It was developed and is currently being used only in Japan. The purpose of this paper is to review the literature and discuss its potential use as a first aid drug in an emergency care setting.

LITERATURE SEARCH

The PubMed database was used to identify papers, using keywords: nifekalant hydrochloride, MS-551, amiodarone, lidocaine. Articles published between January 1, 1993 and January 31, 2011 were retrieved. Reference lists of papers were searched to identify relevant publications. Forty-nine articles were found to be relevant and included in this non-systematic review.

NIFEKALANT HYDROCHLORIDE

Nifekalant hydrochloride, which was formerly known as MS-551, is a class III antiarrhythmic agent having a pirimidinedione structure^[4]. It differs from the other class III antiarrhythmic agents such as dofetilide and d-sotalol by having a nitro group instead of a methanesulfonamido group at the 4-para position on the benzene ring. It also differs in that nifekalant blocks the transient outward K⁺ current, the inward rectifier K⁺ current and the adenosine triphosphate (ATP)-sensitive K current in addition to the rapid component of the delayed rectifier K⁺ current, which results in significant prolongation of the duration of the action potential. It affects neither the Na⁺ current nor does it possess β -adrenergic activity^[5-7]. Furthermore, it does not affect the slowly activating delayed rectifier K⁺ channel in rabbit and guinea pig ventricular myocytes^[5,7]. Nifekalant interacts with the cardiac M2 and the peripheral M3 receptors with a Ki value of 27 and 74 mmol/L, respectively. It dose dependently blocks HERG channels with an IC50 value of 7.9 mmol/L, but it does not block minK currents in the *Xenopus* oocyte expression system. It blocks HERG channels mainly in their open state in a frequency dependent manner^[6]. As a pure K⁺ channel blocker, it does not have negative inotropic effects which amiodarone has *via* a β -blocking action and does not af-

fect cardiac conduction. The negative inotropic effect of amiodarone is disadvantageous, particularly when amiodarone is administered rapidly to a failing heart^[8].

Regarding the pharmacokinetics of nifekalant, only the unchanged form is active. It has a prompt onset of action, its half-life is relatively short (1.5-2.1 h) and its volume of distribution is 0.14 L/kg. The urinary excretion ratio for the unchanged form is approximately 30%. The remaining nifekalant undergoes glucuronate conjugation in the liver which may be influenced by the impaired hemodynamics^[9].

The major adverse effect of nifekalant is QT interval prolongation and occurrence of Torsades de pointes (TdP) owing to an increase in transmural dispersion of repolarization^[10].

NIFEKALANT IN ACS PATIENTS

Life-threatening ventricular tachyarrhythmias such as VT or VF are likely to develop during the acute phase of ACS, and the occurrence of these arrhythmias has important effects on the prognosis of these patients^[11].

Nifekalant may be useful for ischemia-induced VT/VF because it inhibits ATP-sensitive potassium channels under ischemic and hypoxic conditions^[6,12]. Ohashi *et al*^[13] evaluated the VT/VF-controlling effect of continuous intravenous infusion of nifekalant in 16 ACS patients with refractory VT/VF and 14 patients with chronic structural heart disease and refractory VT/VF. VT/VF was considered refractory when it appeared in patients pretreated with oral amiodarone or sotalol or when VT/VF did not disappear after intravenous administration of class I a and I b drugs, or was refractory to shock. The mean dose level of nifekalant was 0.19 ± 0.14 mg/kg body weight per hour. Treatment was successful in controlling VT/VF in 12 of the 16 patients (75%) with ACS, and 9 of the 14 patients with chronic structural heart disease. None of these patients experienced worsening of their hemodynamic status. The incidence of TdP after administration of nifekalant occurred in 5 of the 30 patients (17%), but it disappeared soon after nifekalant administration was discontinued, without any additional treatment^[13]. The high incidence of TdP should not be attributed only to the increase in transmural dispersion of repolarization caused by nifekalant, but also to the fact that patients were pretreated with other anti-arrhythmic drugs that enhance QT prolongation^[14].

Another study included 41 ACS patients who presented with sustained VT/VF (refractory to shock) that was producing circulatory failure in the patients. Nineteen of these patients failed to respond to a bolus dose of 1.0 mg/kg followed by a continuous intravenous infusion of 1.0-2.0 mg/kg per hour of lidocaine prior to administration of nifekalant. Nifekalant was given first as an intravenous bolus injection (0.2 mg/kg) and then as a continuous intravenous infusion at a relatively low dose level (0.2 mg/kg per hour) to all patients. Sustained VT/VF was successfully inhibited in 34 patients (83%). In

subgroup analysis, nifekalant achieved VT/VF inhibition in 79% of patients who received lidocaine and in 86% of patients who received only nifekalant. There were no significant changes in systolic blood pressure or heart rate following nifekalant therapy and TdP developed in only 1 patient^[15].

Survival until hospital discharge was significantly higher when nifekalant was administered in 30 patients with ischemic heart disease and VT/VF resistant to first shock. The control group consisted of 33 patients with ischemic heart disease and VT/VF resistant to first shock. The rates of death within 48 h and the rates of cardiac death during hospitalization were significantly lower in the nifekalant group than in the control group (7% *vs* 27% and 40% *vs* 67%, respectively). When a multivariate analysis of all 63 patients was performed, nifekalant administration was a factor that significantly improved mortality rates^[16].

When lidocaine and/or procainamide were unable to control ventricular tachyarrhythmias developing 48-72 h following acute myocardial infarction in patients with single vessel disease for which percutaneous transluminal coronary angioplasty (PTCA) was performed, nifekalant was administered. All patients had severely depressed left ventricular function. Nifekalant was administered in lower doses than usually used (loading dose of 0.05-0.15 mg/kg and a maintenance dose of 0.05-0.20 mg/kg per hour) but effectively suppressed tachyarrhythmias in all patients^[17].

A very interesting case report was that of a 47-year-old man who presented ST segment elevation in leads II, III and lead aVF after being resuscitated from cardiac arrest. Sustained VT appeared immediately after PTCA. Since lidocaine failed to prevent the recurrent VT after electrical cardioversion, a loading dose (0.3 mg/kg every 5 min) followed by maintenance dose (0.4 mg/kg per hour) of nifekalant was administered. Just after the loading injection of nifekalant, the next electrical cardioversion successfully defibrillated the sustained VT which was never again recorded in the ECG monitor in the catheter laboratory^[18].

NIFEKALANT AND PERI-OPERATIVE VENTRICULAR TACHYARRHYTHMIAS

Ventricular tachyarrhythmias are potentially fatal or serious complications occurring during or after cardiac surgery. Usually they are treated with class I antiarrhythmic agents, but these drugs often induce heart failure due to their negative inotropic effect. As nifekalant prolongs the refractory period without having a negative inotropic effect, researchers hypothesized that it would be safer to administer nifekalant in such patients.

In fact, when 5 patients with peri-operative VT and 2 patients with peri-operative VF were treated with nifekalant, the recurrence of these arrhythmias was inhibited in 3 of the 5 cases with VT and in both cases with VF. None of the patients exhibited changes in heart rate, cardiac output or QTc interval and no TdP was observed^[19].

Intravenous administration of nifekalant in a dose of 0.3 mg/kg, was also effective against peri-operative VT in two patients with impaired left ventricular function (left ventricular ejection fraction: 26.9% and 16%, respectively)^[20].

Furthermore, in 2 patients with pre-operatively decreased cardiac function due to old myocardial infarction, who presented with sustained VT/VF after coronary artery bypass grafting, nifekalant ceased the life-threatening arrhythmias without producing hypotension. Previous infusion of lidocaine was totally ineffective in controlling the arrhythmias^[21].

Moreover, in a 52-year-old male with ischemic cardiomyopathy and severe ventricular dysfunction who presented with incessant VT early after he underwent coronary artery bypass grafting and left ventricular reconstruction, nifekalant at a loading dose (0.3 mg/kg every 5 min), followed by an intravenous infusion (0.4 mg/kg per hour), controlled the arrhythmia^[22].

Nifekalant completely suppressed VT and ventricular premature contractions in a patient with 3-vessel coronary artery disease and left ventricular aneurysm who underwent coronary artery bypass grafting combined with the Dor approach. Class I b antiarrhythmics, like lidocaine and mexiletine, were unable to control VT^[23].

NIFEKALANT IN CARDIOPULMONARY RESUSCITATION

Cardiac arrest patients, both in- and out-of-hospital, have a poor prognosis for survival. When a rhythm check reveals VT or VF, prompt electrical defibrillation is most effective for terminating these arrhythmias during cardiopulmonary resuscitation. If life-threatening VT or VF persists despite repeated defibrillation attempts, an additional antiarrhythmic drug is required.

The "2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" of the American Heart Association and the International Liaison Committee on Resuscitation, recommend antiarrhythmic drugs such as amiodarone and lidocaine as "acceptable" and "probably helpful" in the treatment of VT/VF that persists after three or more external defibrillation shocks^[1,24].

Researchers in Japan performed a lot of studies in order to compare nifekalant with lidocaine and amiodarone in cardiac arrest victims with persistent VT/VF (Table 1).

In a study that involved 32 out-of-hospital cardiac arrest victims with refractory VT/VF, 11 patients were treated with nifekalant 0.15-0.3 mg/kg followed by intravenous infusion of 0.3-0.4 mg/kg per hour as antiarrhythmic therapy. VT/VF was considered refractory when it appeared in patients pretreated with high dose epinephrine infusion, a bolus dose of lidocaine (1-2 mg/kg) and was refractory to direct current shocks. The remaining 21 patients were treated with one more dose of lidocaine (1-2 mg/kg). Sinus rhythm was restored in 9 patients (82%) treated with nifekalant and only 4 patients (19%) treated with lidocaine. QT interval was not prolonged

Table 1 Efficacy of antiarrhythmic drugs in cardiac arrest victims with persistent ventricular tachycardia/fibrillation

First author	Type of study	n	Drug used	Termination of arrhythmia	Other complications	TdP	Survival
Human studies							
Amino <i>et al</i> ^[25]	Out of hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine	32	11 nifekalant 21 lidocaine	9 (82%) 4 (19%)		0 0	2 (18%) 0
Yoshioka <i>et al</i> ^[26]	Out of hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine	36	12 nifekalant 24 lidocaine and magnesium and procainamide if necessary	9 (75%) 4 (17%)	4 sinus suppression (sinus bradycardia and sinus pause)	0	2 (17%) (24 h)
	In hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine	29	9 nifekalant 20 lidocaine and magnesium and procainamide if necessary	8 (89%) 15 (75%)	0 sinus suppression (sinus bradycardia and sinus pause)	1	4 (44%) (24 h)
Tahara <i>et al</i> ^[27]	Out of hospital cardiac arrest with refractory VF to epinephrine	120	55 nifekalant 65 lidocaine			0 0	37 (67%) (hospital admission) 29 (53%) (24 h) 24 (37%) (hospital admission) 20 (31%) (24 h)
Igarashi <i>et al</i> ^[28]	Out of hospital cardiac arrest (VF)	22	8 nifekalant 14 lidocaine	5 (61.5%) 2 (14.3%)			
Yasuda <i>et al</i> ^[29]	Out of hospital cardiac arrest with refractory VT/VF to epinephrine	14	14 nifekalant	12 (86%)		1	11 (79%) (hospital admission)
Shiga <i>et al</i> ^[30]	In hospital cardiac arrest with refractory VT/VF	55	27 nifekalant 28 lidocaine	22 (81%) 15 (54%)	0 Asystole 2 PEA 1 QT>0.55 7 Asystole 1 PEA 0 QT>0.55	0 0	13 (48%) (1-mo survival) 12 (44%) (survival to discharge) 9 (32%) (1-mo survival) 8 (29%) (survival to discharge)
Amino <i>et al</i> ^[31]	Out of hospital cardiac arrest with refractory VF	30	15 nifekalant 15 amiodarone	7 (47%) 10 (67%)	0 Thyroid dysfunction 1 Thyroid dysfunction	0 0	7 (47%) (hospital admission) 4 (27%) (survival to discharge) 10 (67%) (hospital admission) 8 (53%) (survival to discharge)
Animal studies							
Ji <i>et al</i> ^[32]	4 min of untreated VF	36	12 saline 12 nifekalant 12 amiodarone	7 (58.3%) ROSC 12 (100%) ROSC 12 (100%) ROSC		0 1 0	2 (17%) (24 h) 8 (67%) (24 h) 9 (75%) (24 h)

VT/VF: Ventricular tachycardia/fibrillation; TdP: Torsades de pointes.

and no TdP was observed. Two patients finally survived in the nifekalant group, while no patient survived in the lidocaine group. Interestingly, most patients in the nifekalant group died from sinus arrest in comparison with the lidocaine group in which most patients died from persistent VT/VF^[25].

The authors concluded that one of the reasons for the sinus arrest was the acidotic condition of the patients. Therefore, another study investigated the differences in the effect of nifekalant in out-of-hospital cardiac arrest patients with acidosis ($n = 36$) and in-hospital cardiac arrest patients without acidosis ($n = 29$). According to the

protocol patients with persistent or recurrent VT/VF after administration of epinephrine (1 mg iv), lidocaine (1 mg/kg iv) and direct current defibrillation attempts were divided in two groups: a lidocaine group, in which additional lidocaine up to 3 mg/kg plus magnesium sulfate and procainamide were administered if necessary; and a nifekalant group in which 0.15 mg/kg of nifekalant was slowly injected in combination with direct current shocks. Additional nifekalant was administered for persistent or recurrent VT/VF as needed. Sinus rhythm was restored in 43% (19/44) of the lidocaine group and 81% (17/21) of the nifekalant group. The successful defibril-

lation rate of out-of-hospital cardiac arrest patients was significantly lower than that of in-hospital cardiac arrest patients ($P < 0.05$) in the lidocaine group. On the other hand, in the nifekalant group, the successful defibrillation rate was more than 75% in both out-of-hospital and in-hospital cardiac arrest patients. This means that the VT/VF-controlling effect of nifekalant was maintained even with acidosis. However, sinus bradycardia in out-of-hospital cardiac arrest patients and TdP in in-hospital cardiac arrest patients were occasionally observed^[26].

A bigger study which included 120 out-of-hospital cardiac arrest victims with VF persistent to shocks from an external defibrillator and intravenous epinephrine, found that patients treated with nifekalant had significantly higher rates of survival to hospital admission. They also had a significantly higher 24 h survival^[27].

Nifekalant's efficacy was also studied in 8 out-of-hospital cardiac arrest victims who presented to the hospital with VF. Sinus rhythm returned in 5 of 8 patients in comparison with only 2 out of 14 patients treated with lidocaine (control group) ($P < 0.05$)^[28].

A recent multicenter study enrolled 14 patients with out-of-hospital VF refractory to 3 or more precordial shocks and intravenous epinephrine. Nifekalant was intravenously administered at a dose of 0.15-0.30 mg/kg body weight and then an additional shock was delivered. If VF persisted, an additional dose of nifekalant was administered. The rate of return of spontaneous circulation was 86% and the rate of survival to hospital admission was 79%. Only one patient developed TdP^[29].

When 55 patients with in-hospital VT/VF resistant to at least two defibrillation attempts were treated with either lidocaine or nifekalant, nifekalant was more effective in terminating the arrhythmias. Half of the patients treated with nifekalant showed termination of VT/VF after intravenous infusion alone. Patients with nifekalant were more likely to achieve return of spontaneous circulation but no difference was observed in 1-mo survival or survival to hospital discharge between the two groups. No Tdp was observed^[30].

The only human study to compare nifekalant with amiodarone, in 30 patients with first defibrillation failure or VF recurrence, treated half with amiodarone and the rest with nifekalant. Defibrillation success was achieved in 67% of patients treated with amiodarone and 47% of patients treated with nifekalant. The hospital discharge survival rate was 53% in the amiodarone and 27% in the nifekalant group ($P = 0.06$). Compared to the amiodarone group, patients treated with nifekalant achieved faster defibrillation success. This may be the reason that all 4 survivors in the nifekalant group could take up normal daily life, in comparison with only 2 patients from the 11 survivors in the amiodarone group^[31].

These results were further supported by a porcine model of VF treated with either amiodarone or nifekalant. Restoration of spontaneous circulation and 24 h survival rate were comparable for nifekalant and amiodarone^[32].

A very interesting study by Amino *et al.*^[33] demonstrated that the combination of intravenous nifekalant and left stellate ganglion block can be useful for patients with VT/VF resistant to lidocaine and nifekalant. In fact sinus rhythm was restored in 7 out of 11 patients refractory to lidocaine and nifekalant VT/VF when left stellate ganglion block was performed.

NIFEKALANT IN PATIENTS WITH IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Electrical storm defined as 3 shocks per day is reported in 10%-30% of patients with an implantable cardioverter-defibrillator (ICD)^[34]. Recurrent episodes of VF are associated with intracellular calcium overload^[35] which results in progressive left ventricular dysfunction^[36] and re-initiation of VF^[35]. In addition, multiple shocks from ICD increase cardiac troponin levels and thus lead to myocardial injury^[37,38].

When 10 patients with a mean number of 18 ± 12 ICD discharges/h were treated with a combination of deep sedation (thiamylal or propofol) and β -blockade, the electrical storm was treated in 4 patients while the remaining 6 patients were stabilized after intravenous administration of nifekalant. In 1 of these 6 patients, VT ceased during the administration of the loading dose of nifekalant and did not re-occur. No hemodynamic deterioration was evident during the administration of nifekalant in these 6 patients although 4 of them had left ventricular ejection fraction < 0.40 ^[39].

COMPARISON OF NIFEKALANT WITH OTHER ANTIARRHYTHMIC DRUGS

A study that compared the effects of nifekalant to sotalol in humans showed that both drugs had similar effects on inducible ventricular tachyarrhythmias. The comparison was made with programmed electrical stimulation, in 14 patients with sustained ventricular tachyarrhythmia, after nifekalant and after sotalol administration. The response of inducible ventricular tachyarrhythmia to nifekalant could predict the clinical efficacy of sotalol. In fact, in 4 out of 5 patients whose ventricular tachyarrhythmia became non-inducible by nifekalant, subsequent treatment with sotalol also suppressed the inducible tachyarrhythmias. On the other hand, in all of the 9 patients not responding to nifekalant, tachyarrhythmias remained inducible during sotalol treatment^[40].

A comparison between nifekalant and procainamide was performed by Igawa *et al.*^[41] in 30 patients with inducible sustained VT (programmed ventricular stimulation of up to three extra stimuli). Nifekalant suppressed VT in 4 of 15 patients while procainamide suppressed VT in 6 of 15 patients but the difference was not statistically significant. QT interval was significantly increased in the nifekalant group.

DISCUSSION

Effective control of recurrent ventricular tachyarrhythmias can be expected with an antiarrhythmic drug that has prompt onset of effect and that does not alter hemodynamic status variables such as blood pressure. It is difficult to use a drug that takes time until the onset of its effect, such as amiodarone, in the emergency care of patients suffering frequent episodes of VT/VF.

Amiodarone is a multiple-channel blocker with complex pharmacologic properties, affecting β -adrenergic receptors, calcium channels, sodium channels, and potassium channels. A lot of patients with ACS as well as cardiac arrest victims with refractory to direct current shock tachyarrhythmias, are likely to have cardiac dysfunction. Antiarrhythmic drugs with negative inotropic activity can negatively affect the outcome of such patients.

Nifekalant seems to have some important advantages. It does not have negative inotropic effects^[42,43], it lowers the defibrillation threshold^[44-46] and even if adverse reactions develop, they are transient because nifekalant has a short half-life^[47]. It is clearly demonstrated that nifekalant is also effective against peri-operative ventricular tachyarrhythmias, especially in patients with impaired left ventricular function.

Of course the reviewed articles had some limitations that should be kept in mind. For example, in Tahara's paper^[27], the lidocaine group was a historical control. Shiga's paper^[30] was a prospective multicenter study, but was not randomized and most of the studies were retrospective evaluations in single centers. In addition, in many of the studies included in this review, nifekalant was administered in patients with refractory VT/VF, in which other anti-arrhythmic drugs had already been given. Therefore the possibility of possible cumulative effects needs to be ruled out. However, despite these limitations the results of these studies did not differ from the results of a multicenter cohort post-marketing study^[48] which demonstrated that intravenous administration of nifekalant successfully terminated VT/VF in around 50% of the patients studied and prevented the recurrence of refractory VT/VF in about 60%. Most of the patients for whom nifekalant was effective were refractory to lidocaine or other antiarrhythmic drugs. In patients who failed to terminate VT, even after single administration of nifekalant, their heart rate during VT significantly decreased and of course this property of nifekalant should be considered therapeutically beneficial. It was also demonstrated that nifekalant enhances the defibrillating effect of direct current by lowering the defibrillation threshold of myocardium, in contrast to class I anti-arrhythmic agents which usually increase the defibrillation threshold by blocking sodium channels^[48].

Needless to say that nifekalant may exhibit significant side-effects which may limit its use. Because excretion in the urine is an important pathway for elimination of nifekalant, dosages must be adjusted and it must be administered cautiously in patients with renal failure.

Myoishi *et al.*^[9] demonstrated that in patients with im-

paired left ventricular function and chronic renal failure, half of the dose administered in patients with normal renal function and stable hemodynamics (0.15 mg/kg BW per hour) achieved almost the same therapeutic concentration in the plasma. They also reported that concentration did not change significantly before or after hemodialysis, even under continuous infusion. A possible explanation is that nifekalant binds strongly to protein and it may not be dialyzed.

It has been demonstrated that higher doses of nifekalant have resulted in higher rates of VT termination accompanied by QT dispersion prolongation^[14]. Occurrence of TdP due to the development of QT interval prolongation should always be taken into account. It is considered important to monitor QT interval frequently during nifekalant infusion with adequate dose adjustment. Another important factor that can induce TdP while administering nifekalant is hypokalemia. It has been proposed that serum levels of potassium concentration should be maintained above 4.0 mmol/L^[14].

It is also important to note that nifekalant has a reverse use-dependent blocking action. It causes less action potential prolongation with an increasing heart rate and inversely, action potential prolongation is enhanced with a decreasing heart rate^[47]. Furthermore, it has been reported that the QTc interval shows diurnal variation that is influenced by autonomic activity and that its variation reaches a peak shortly after awakening, which suggests that the action of nifekalant may be weakened not only by an increased heart rate but also by increased sympathetic activity^[49]. Needless to say such considerations may support the usefulness of combination therapy using nifekalant and a β -blocker.

As amiodarone has not yet been approved in Japan, to the best of our knowledge, only one animal study and one human study have compared the effects of nifekalant with those of amiodarone in an emergency care setting^[31]. From these reports, it seems that amiodarone is borderline superior over nifekalant but further studies are needed for extraction of safer conclusions.

On the other hand, lot of studies have demonstrated that nifekalant has a much greater inhibitory effect on ventricular tachyarrhythmias than lidocaine, but again it is difficult for conclusions to be made as nifekalant is not yet available in USA and Europe and no European or American study has ever been conducted.

CONCLUSION

Nifekalant is a possible effective antiarrhythmic agent for refractory ventricular tachyarrhythmias. Further clinical studies are required before nifekalant is used as a first aid drug in the emergency care setting.

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