Available online at www.sciencedirect.com

ScienceDirect

Journal of Electrocardiology 50 (2017) 277 – 281

JOURNAL OF Electrocardiology

www.jecgonline.com

The effects of pure potassium channel blocker nifekalant and sodium channel blocker mexiletine on malignant ventricular tachyarrhythmias ☆

Sou Otuki, MD,* Kanae Hasegawa, MD, Hiroshi Watanabe, MD, Goro Katsuumi, MD, Nobue Yagihara, MD, Kenichi Iijima, MD, Akinori Sato, MD, Daisuke Izumi, MD, Hiroshi Furushima, MD, Masaomi Chinushi, MD, Yoshifusa Aizawa, MD, Tohru Minamino, MD

Department of Cardiovascular Biology and Medicine, Niigata University School of Medical and Dental Sciences, Niigata, Japan

Abstract

Background: Patients with repetitive ventricular tachyarrhythmias — so-called electrical storm — frequently require antiarrhythmic drugs. Amiodarone is widely used for the treatment of electrical storm but is ineffective in some patients. Therefore, we investigated the efficacy of stepwise administration of nifekalant, a pure potassium channel blocker, and mexiletine for electrical storm.
Methods: This study included 44 patients with repetitive ventricular tachyarrhythmias who received stepwise therapy with nifekalant and mexiletine for electrical storm. Nifekalant was initially administered, and mexiletine was subsequently added if nifekalant failed to control ventricular tachyarrhythmias.
Results: Nifekalant completely suppressed recurrences of ventricular arrhythmias in 28 patients (64%), including 6 patients in whom oral amiodarone failed to control arrhythmias. In 9 of 16 patients in whom nifekalant was partially effective but failed to suppress ventricular arrhythmias, mexiletine was added. The addition of mexiletine prevented recurrences of ventricular tachyarrhythmias in 5 of these 9 patients (56%). There was no death associated with electrical storm. In total, the stepwise treatment with nifekalant and mexiletine was effective in preventing ventricular tachyarrhythmias in 33 of 44 patients (75%). There was no difference in cycle length of the ventricular tachycardia, QRS interval, QT interval, or left ventricular ejection fraction between patients who responded to antiarrhythmic drugs and those who did not. During follow-up, 8 patients had repetitive ventricular tachyarrhythmia recurrences, and the stepwise treatment was effective in 6 of these 8 patients (75%).
Conclusions: The stepwise treatment with nifekalant and mexiletine was highly effective in the suppression of electrical storm.

Keywords: Arrhythmias; Drugs; Sudden death; Electrical storm; Heart diseases

Introduction

An implantable cardioverter–defibrillator (ICD) is the first line treatment to prevent sudden cardiac death from ventricular tachyarrhythmias. More than half of patients with an ICD for secondary prevention of sudden cardiac death receive appropriate ICD therapy, but up to 23% of patients have repetitive episodes of ventricular tachyarrhythmias: so-called electrical storm [1–3].

Electrical storm is a life-threatening emergency and is associated with increased mortality. Therefore, antiarrhythmic drugs to suppress ventricular tachyarrhythmias are usually required when patients develop electrical storm. However, evidence showing the efficacy of antiarrhythmic drugs for frequent episodes of ventricular tachyarrhythmias or electrical storm is limited. Among the antiarrhythmic drugs, amiodarone, which affects various ion channels including potassium, sodium, and calcium channels, is one of the most effective drugs for ventricular tachyarrhythmias and is widely used to control electrical storm [4]. However, amiodarone is ineffective in some patients and is associated with increased risk of drug-related adverse effects compared with other antiarrhythmic drugs [5,6]. Nifekalant is a pure potassium channel blocker, which mainly inhibits the rapid

☆ Disclosures: None declared.

* Corresponding author at: Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Niigata, Japan ZIP: 951-8510.
E-mail address: tallmoca@mte.biglobe.ne.jp

http://dx.doi.org/10.1016/j.jelectrocard.2016.09.005
0022-0736/

components of the delayed rectifier potassium current, and only intravenous formation is commercially available. Nifekalant has been effective in a limited number of patients with a severe form of electrical storm in prior studies and can be an alternative therapy [7–9]. Therefore, we investigated the efficacy of stepwise administration of nifekalant and the addition of the sodium channel blocker mexiletine when nifekalant alone failed to control ventricular tachyarrhythmias as an emergency treatment to control electrical storm.

Methods

Patients

This was a retrospective study, which included patients who developed electrical storm and received nifekalant therapy in order to treat electrical storm between January 1, 2006 and January 1, 2013 in our institution. Nifekalant was administered as a loading infusion of 0.1 to 0.3 mg/kg for 5 min followed by a maintenance dose of 0.05 to 0.4 mg/kg/h. If the QT or corrected QT interval was prolonged to more than 600 ms, the dose of nifekalant was decreased. The corrected QT interval was calculated using Bazett's formula. If ventricular tachyarrhythmias recurred despite nifekalant administration, mexiletine was subsequently added intravenously or nifekalant was discontinued by the decisions of the treating cardiologists. Electrical storm was defined as 3 or more episodes of ventricular tachycardia and/or ventricular fibrillation within 24 h. Suppression of electrical storm was defined as no ventricular arrhythmia recurrence during the 24 h after the initiation of the therapy. Continuous electrocardiography monitoring was performed during hospitalization in all patients.

Data analysis

All values are presented as the mean ± SD, unless otherwise specified. Data were compared using paired or unpaired Student's t-tests, or Fisher's exact test. A two-sided $P < 0.05$ was considered statistically significant. The authors have full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

This study included 44 patients who received nifekalant due to electrical storm (Table 1). The patients included 34 men (77%), aged 61 ± 15 years (range, 15 to 86 years). The left ventricular ejection fraction was 41 ± 16% (range, 9% to 73%). Nine patients (20%) had prior myocardial infarction, and 27 patients (61%) had cardiomyopathy. When electrical storm developed, 24 of 44 patients (55%) had received antiarrhythmic drugs, including 6 patients (14%) had received oral amiodarone at a dose of 142 ± 61 mg/day during 14 ± 14 months. There were 9 patients (20%) who received sedation combined with nifekalant therapy. There was no patient who received intravenous amiodarone therapy prior to nifekalant to control electrical storm.

Table 1
Baseline characteristics of patients (N = 44).

Male gender, N (%)	34 (77%)
Age, years	61 ± 15
Underlying cardiac disease, N (%)	
Myocardial infarction	9 (20%)
Sarcoidosis	9 (20%)
Dilated cardiomyopathy	6 (14%)
Hypertrophic cardiomyopathy	7 (16%)
ARVC	3 (7%)
Post atrial valve replacement	3 (7%)
Idiopathic ventricular aneurysm	2 (5%)
Others*	5 (11%)
Left ventricular ejection fraction	0.41 ± 0.16
ICD/CRT, N (%)	29 (66%)
Primary prevention for sudden death	24 (55%)
Secondary prevention for sudden death	5 (11%)
Antiarrhythmic drugs at electrical storm, N (%)	
β blockers	28 (64%)
Amiodarone	6 (14%)
Sotalol	11 (25%)
Class I drugs	3 (7%)
Ventricular tachyarrhythmias at electrical storm	
Ventricular tachycardia	44 (89%)
Ventricular fibrillation	0 (0%)
Both	5 (11%)

* Others include Fabry disease (N = 1), tetralogy of Fallot (N = 1), idiopathic ventricular tachycardia (N = 1), cardiac tumor (N = 1), and muscular dystrophy (N = 1). Five patients with sarcoidosis and no patient with ARVC had heart failure. ARVC denotes arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronized therapy.

Nifekalant prolonged the QT and corrected QT intervals from 403 ± 37 ms to 464 ± 46 ms and from 444 ± 50 to 488 ± 63 ms, respectively, while it did not change the heart rate or QRS duration. In all patients, nifekalant decreased the number of episodes of ventricular arrhythmias from 11.7 ± 12.8/day/patient to 5.3 ± 9.5/day/patient. Nifekalant completely suppressed recurrences of ventricular tachyarrhythmias during the initial 24 h in 34 patients (77%) (Fig. 1). Among these patients, there was no arrhythmia recurrence during admission in 28 patients (nifekalant responders), including 5 patients who developed electrical storm despite prior oral amiodarone therapy, while arrhythmias recurred after 24 h of nifekalant administration in the remaining 6 patients. Nifekalant failed to suppress ventricular arrhythmias (non-responders) in 16 patients, including 10 patients who did not respond to nifekalant during the initial 24 h and 6 patients who responded to nifekalant during the initial 24 h but had arrhythmia recurrences thereafter. When comparing nifekalant responders and non-responders, there were no differences in clinical characteristics such as underlying heart disease, left ventricular ejection fraction, cycle length of ventricular tachycardia, electrocardiographic measurements at baseline, and dose of nifekalant (Table 2). Furthermore, nifekalant similarly prolonged the QT and corrected QT intervals between responders and non-responders.

Among the 16 patients with arrhythmia recurrences despite nifekalant therapy, mexiletine was added to nifekalant in 9 patients, while nifekalant was discontinued in the remaining 7 patients, per the treating physicians'

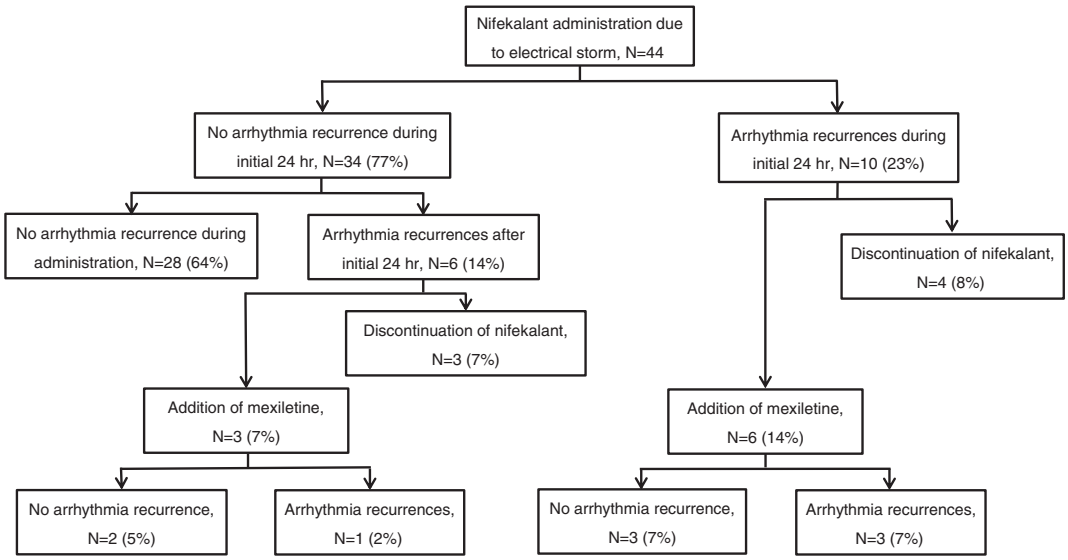

Fig. 1. Efficacy of stepwise administration of nifekalant and additional mexiletine. Nifekalant completely suppressed recurrences of ventricular arrhythmias in 28 patients (64%). The stepwise treatment was effective in preventing ventricular tachyarrhythmias in 33 of 44 patients (75%).

decisions. The addition of mexiletine did not change the heart rate, QRS duration, QT interval, or corrected QT interval (Table 3). Mexiletine prevented recurrences of ventricular arrhythmias in 5 of 9 patients. There was no difference in clinical characteristics, left ventricular ejection fraction, cycle length of ventricular tachycardia, dose of nifekalant and mexiletine, or electrocardiographic measurements before and after mexiletine administration between mexiletine responders and non-responders.

In total, the stepwise treatment with nifekalant and mexiletine was effective in preventing ventricular tachyarrhythmias during administration in 33 out of 44 patients (75%). Nifekalant was administered during 17 ± 14 days and was not discontinued due to complications such as hypotension, heart failure, or torsades de pointes in any of the patients. Mexiletine was discontinued in one patient because of a neurological side effect. Among the 33 patients, 17 patients (52%) received catheter ablation. At discharge, 20 patients (61%) received sotalol, 5 patients (16%) received bepridil, 3 patients (9%) received amiodarone, and 1 patient (3%) received mexiletine. β blockers were initiated in 15 patients and the dose with β blockers was increased in 7 patients who had received β blockers at the admission.

In this study, there were 9 patients with prior myocardial infarction and 6 patients with dilated cardiomyopathy. The stepwise treatment with nifekalant and mexiletine was effective in 6 out of 9 patients (67%) with myocardial infarction and 4 out of 6 patients (67%) with dilated cardiomyopathy. The efficacy of the treatment was similarly high in patients with myocardial infarction or dilated cardiomyopathy compared with those with other heart diseases (P = 0.34).

During a follow-up of 48 ± 32 months after discharge from our hospital, 8 patients had recurrences of electrical storm. The stepwise treatment of nifekalant and mexiletine suppressed ventricular tachyarrhythmias in 6 of these 8 patients (75%); nifekalant alone successfully controlled arrhythmias in 4 patients, and mexiletine as an adjunctive therapy to nifekalant controlled arrhythmias in other 2

Table 2
Effects of nifekalant and clinical characteristics.

	Nifekalant responder, N = 28	Nifekalant non-responder, N = 16	P value
Women, N (%)	8 (29%)	2 (13%)	0.28
Age, years	62 ± 14	59 ± 17	0.57
Underlying cardiac disease, N (%)			0.90
Myocardial infarction	5 (18%)	4 (25%)	
Cardiomyopathy	18 (64%)	9 (56%)	
Others	5 (18%)	3 (19%)	
Left ventricular ejection fraction	0.37 ± 0.14	0.46 ± 0.17	0.07
VT cycle length, ms	379 ± 72	347 ± 55	0.22
Nifekalant dosage, mg/kg/h	0.22 ± 0.08	0.25 ± 0.10	0.28
ECG findings at baseline			
Heart rate, beats/min	75 ± 14	75 ± 12	0.96
QT interval, ms	400 ± 42	409 ± 29	0.53
Corrected QT interval, ms	440 ± 57	452 ± 39	0.52
QRS duration, ms	112 ± 28	118 ± 31	0.55
ECG findings during nifekalant administration			
Heart rate, beats/min	66 ± 14	71 ± 12	0.29
QT interval, ms	467 ± 44	453 ± 40	0.39
Corrected QT interval, ms	482 ± 60	485 ± 46	0.88
QRS duration, ms	111 ± 25	111 ± 23	0.99
ΔQTinterval by nifekanalt, ms	67 ± 40	44 ± 50	0.17
ΔCorrected QT interval by nifekalant, ms	42 ± 56	33 ± 62	0.68

VT denotes ventricular tachycardia; ECG, electrocardiography.

Table 3
Effects of mexiletine in addition to nifekalant.

ECG findings	Nifekalant	Mexiletine and nifekalant	P value
Heart rate, beats/min	68 ± 9	66 ± 8	0.79
QRS duration, ms	112 ± 30	108 ± 16	0.82
QT interval, ms	464 ± 41	440 ± 36	0.40
Corrected QT interval, ms	483 ± 46	463 ± 49	0.58

patients. In the 8 patients, the stepwise treatment decreased the number of episodes of ventricular arrhythmias from 19.9 ± 17.3/patient to 8.7 ± 17.1/patient.

Discussion

In this study, we demonstrated that the stepwise therapy of nifekalant and mexiletine was highly effective in the suppression of electrical storm. Furthermore, the stepwise therapy was also effective in patients who had electrical storm despite oral amiodarone therapy and in those who had recurrence of electrical storm during follow-up.

Efficacy of nifekalant for electrical storm

Nifekalant is a potassium channel blocker that mainly blocks the rapid component of the delayed rectifier potassium current without affecting sodium current, calcium current or β-adrenergic activity [7]. In our prior study, nifekalant was effective in patients with a severe form of electrical storm defined as 10 or more episodes of ventricular tachyarrhythmias within one hour [8]. In this study, nifekalant was effective in the suppression of electrical storm in 64% of patients.

Potassium channel blockers, such as amiodarone and sotalol, are first-line treatments for ventricular tachyarrhythmias [4]. However, amiodarone and sotalol have side effects including hypotension and heart failure and thus are sometimes difficult to use in patients with severe left ventricular dysfunction or significant heart failure, even though these patients are at high risk for the development of electrical storm [10–13]. Intravenous administration of amiodarone can cause hypotension in up to 26% of patients as well as heart failure and sinus bradycardia [5,14,15]. In this and previous studies, no patient had worsening heart failure because of nifekalant [16]. Furthermore, 6 patients developed electrical storm despite oral amiodarone therapy, and nifekalant completely suppressed the recurrences of ventricular arrhythmias in 5 of these patients. Taken together, these results show that nifekalant can be used as an alternative therapy in patients with electrical storm, especially in those who have severe heart failure.

Addition of mexiletine to potassium channel blocker

Monotherapy with a sodium channel blocker is currently indicated in limited situations in patients with ventricular tachyarrhythmias. In a previous study of electrical storm, sodium channel blockers were efficacious in only 33% of patients [17]. Furthermore, sodium channel blockers have severe proarrhythmic effects [4,18]. However, sodium channel blockers in combination with potassium channel blockers have been effective for ventricular tachyarrhythmias [19–23]. A combination treatment of amiodarone and mexiletine was effective for repetitive episodes of drug-refractory ventricular tachycardia in 3 patients [19]. Furthermore, mexiletine, when added to amiodarone, decreased the number of ventricular tachyarrhythmia episodes in 20 patients [22]. In this study, additional mexiletine was effective in 56% of patients who had arrhythmia recurrences despite nifekalant. The addition of mexiletine to potassium channel blockers may be considered when potassium channel blockers are ineffective in elimination of electrical storm.

In a previous study, the addition of another sodium channel blocker flecainide to class III drugs has been effective in 10 patients in whom amiodarone or sotalol failed to control electrical storm, but the combination treatment resulted in significant prolongation of the QRS duration in 2 patients [21]. However, the addition of mexiletine at doses that suppressed ventricular tachyarrhythmias did not result in marked conduction delay in this and previous studies [22].

Treatment with antiarrhythmic drugs for electrical storm

Electrical storm is an emergency medical condition, and appropriate treatment to suppress ventricular tachyarrhythmias is immediately required. Although the causes triggering arrhythmias, such as electrolyte disturbances, ischemia and heart failure should be treated initially, most patients do not have correctable factors and thus need treatment with antiarrhythmic drugs. However, few studies have systematically investigated the efficacy of antiarrhythmic drugs for the suppression of electrical storm. Amiodarone is widely used for electrical storm because of its high efficacy against the recurrence of ventricular tachyarrhythmias [4,6,24]. Amiodarone has previously been effective in 59% of patients with frequent recurrences of ventricular tachyarrhythmias [5], and nifekalant was similarly effective in suppressing electrical storm in 64% of patients in this study. If monotherapy with potassium channel blockers fails to control electrical storm, combinations of antiarrhythmic drugs, usually a potassium channel blocker and a sodium channel blocker, may be considered. In this study, our stepwise treatment with nifekalant and adjunctive mexiletine when nifekalant alone failed to control arrhythmias successfully suppressed electrical storm in 75% of patients.

Study limitations

This study has several limitations. The number of patients was not large and further studies are needed. The efficacy of stepwise treatment with nifekalant and mexiletine was studied retrospectively in a single center and was not compared with other therapies such as intravenous amiodarone. Intravenous β blockers were not commercially available at the study period in Japan, and the efficacy of β blockers were not studied. Although surgical sympathetic denervation is used for severe forms of ventricular tachyarrhythmias, the treatment was not available in our institution at the study period [25,26]. Similar to previous Japanese studies, the frequency of ischemic heart disease was not high and the clinical characteristics of patients in this study may be different from those in western countries [27,28]. However, the efficacy of stepwise treatment with nifekalant and mexiletine was similarly high in patients with myocardial infarction or dilated cardiomyopathy compared with those with other heart diseases. Further studies to compare the efficacy of the treatment with nifekalant and mexiletine and other treatments such as intravenous

amiodarone and β blockers are needed. Despite these limitations, this study indicates that the stepwise treatment is effective in controlling severe electrical storm.

References

[1] Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation 2000;102:742–7.

[2] Hohnloser SH, Al-Khalidi HR, Pratt CM, Brum JM, Tatla DS, Tchou P, et al. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. Eur Heart J 2006;27:3027–32.

[3] Exner DV, Pinski SL, Wyse DG, Renfroe EG, Follmann D, Gold M, et al. Electrical storm presages nonsudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial. Circulation 2001;103:2066–71.

[4] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force and the European Society of Cardiology Committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European heart rhythm association and the Heart Rhythm Society. Circulation 2006;114:e385–484.

[5] Helmy I, Herre JM, Gee G, Sharkey H, Malone P, Sauve MJ, et al. Use of intravenous amiodarone for emergency treatment of life-threatening ventricular arrhythmias. J Am Coll Cardiol 1988;12:1015–22.

[6] Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. JAMA 2006;295:165–71.

[7] Sato R, Koumi S, Hisatome I, Takai H, Aida Y, Oyaizu M, et al. A new class III antiarrhythmic drug, MS-551, blocks the inward rectifier potassium channel in isolated guinea pig ventricular myocytes. J Pharmacol Exp Ther 1995;274:469–74.

[8] Washizuka T, Chinushi M, Watanabe H, Hosaka Y, Komura S, Sugiura H, et al. Nifekalant hydrochloride suppresses severe electrical storm in patients with malignant ventricular tachyarrhythmias. Circ J 2005;69:1508–13.

[9] Kurisu K, Hisahara M, Onitsuka H, Sekiya M, Ikeuchi M, Kozai T, et al. Nifekalant hydrochloride terminated electrical storms after coronary surgery. Ann Thorac Surg 2010;89:1637–9.

[10] Schwartz A, Shen E, Morady F, Gillespie K, Scheinman M, Chatterjee K. Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular function and recurrent ventricular tachycardia. Am Heart J 1983;106:848–56.

[11] Villacastin J, Almendral J, Arenal A, Albertos J, Ormaetxe J, Peinado R, et al. Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators. Circulation 1996;93:753–62.

[12] Pacifico A, Ferlic LL, Cedillo-Salazar FR, Nasir Jr N, Doyle TK, Henry PD. Shocks as predictors of survival in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol 1999;34:204–10.

[13] Sesselberg HW, Moss AJ, McNitt S, Zareba W, Daubert JP, Andrews ML, et al. Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: a MADIT-II substudy. Heart Rhythm 2007;4:1395–402.

[14] Scheinman MM, Levine JH, Cannom DS, Friehling T, Kopelman HA, Chilson DA, et al. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. The intravenous amiodarone multicenter investigators group. Circulation 1995;92:3264–72.

[15] Schutzenberger W, Leisch F, Kerschner K, Harringer W, Herbinger W. Clinical efficacy of intravenous amiodarone in the short term treatment of recurrent sustained ventricular tachycardia and ventricular fibrillation. Br Heart J 1989;62:367–71.

[16] Katoh T, Mitamura H, Matsuda N, Takano T, Ogawa S, Kasanuki H. Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. Circ J 2005;69:1237–43.

[17] Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. J Am Coll Cardiol 1998;32:1909–15.

[18] Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction The cardiac arrhythmia suppression trial (CAST) investigators Med 1989;321:406–12.

[19] Waleffe A, Mary-Rabine L, Legrand V, Demoulin JC, Kulbertus HE. Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia. Am Heart J 1980;100:788–93.

[20] Lee SD, Newman D, Ham M, Dorian P. Electrophysiologic mechanisms of antiarrhythmic efficacy of a sotalol and class Ia drug combination: elimination of reverse use dependence. J Am Coll Cardiol 1997;29:100–5.

[21] Fuchs T, Groysman R, Meilichov I. Use of a combination of class III and class Ic antiarrhythmic agents in patients with electrical storm. Pharmacotherapy 2008;28:14–9.

[22] Gao D, Van Herendael H, Alshengeiti L, Dorian P, Mangat I, Korley V, et al. Mexiletine as an adjunctive therapy to amiodarone reduces the frequency of ventricular tachyarrhythmia events in patients with an implantable defibrillator. J Cardiovasc Pharmacol 2013;62:199–204.

[23] Ermakov S, Hoffmayer KS, Gerstenfeld EP, Scheinman MM. Combination drug therapy for patients with intractable ventricular tachycardia associated with right ventricular cardiomyopathy. Pacing Clin Electrophysiol 2014;37:90–4.

[24] Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation 1997;96:2823–9.

[25] Yousuf O, Chrispin J, Tomaselli GF, Berger RD. Clinical management and prevention of sudden cardiac death. Circ Res 2015;116:2020–40.

[26] Jacobson JT, Iwai S, Aronow W. Management of ventricular arrhythmias in structural heart disease. Postgrad Med 2015;127:549–59.

[27] Satomi K, Kurita T, Takatsuki S, Yokoyama Y, Chinushi M, Tsuboi N, et al. Amiodarone therapy in patients implanted with cardioverter-defibrillator for life-threatening ventricular arrhythmias. Circ J 2006;70:977–84.

[28] Noda T, Kurita T, Nitta T, Abe H, Watanabe S, Furushima H, et al. Appropriate duration of driving restrictions after inappropriate therapy from implantable cardiac shock devices-interim analysis of the Nippon storm study. Circ J 2014;78:1989–91.