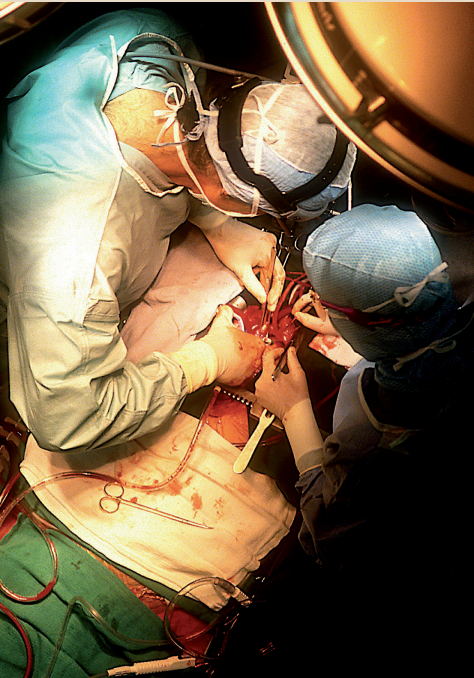


Inadvertent treatment with a pure IKr blocker in LQT2 syndrome



Mohsen Hosseinkhani^{1,*}, MD, PhD, Fahimeh Saboor², MD

Abstract

Long QT syndrome (LQTS) results from structural abnormalities in the potassium channels of the heart, which predispose affected persons to an accelerated heart rhythm (arrhythmia). Nifekalant, a new class III antiarrhythmic agent developed in US, blocks selectively a rapidly-activating component of the delayed rectifier potassium channel (IKr) in cardiac myocytes, and causes dose-dependent increase in atrial and ventricular refractory periods and repolarization. We report a case of congenital long QT syndrome (LQTS) with recurrent ventricular fibrillation inadvertently treated with intravenous nifekalant. Treatment neither modified the rate-corrected QT interval nor induced torsades de points. Subsequent genotyping of the patient revealed a missense mutation in the extracellular loop between S5 and the pore region of HERG (K595E). Since HERG encodes the IKr channel, LQT2 patient may be more tolerant of pure IKr blockers than other LQTS genotypes.

Key Words: Long QT syndrome, torsades de points, Nifekalant, genotype, missense mutation

Introduction:

The long QT syndrome (LQTS) is a rare congenital heart condition with delayed repolarization following depolarization (excitation) of the heart, associated with syncope (fainting) due to ventricular arrhythmias, possibly of type torsade de pointes, which can deteriorate into ventricular fibrillation and ultimately sudden death. Individuals with LQTS have a prolongation of the QT interval on the ECG. The QRS complex corresponds to ventricular depolarization while the T wave corresponds to ventricular

repolarization. The QT interval is measured from the Q point to the end of the T wave. While many individuals with LQTS have persistent prolongation of the QT interval, some individuals do not always show the QT prolongation; in these individuals, the QT interval may prolong with the administration of certain medications.

Genetic LQTS can arise from mutation of one of several genes. These mutations tend to prolong the duration of the ventricular action potential (APD), thus lengthening the QT interval. LQTS can be inherited in an autosomal dominant or an autosomal recessive fashion. The LQT2 type is the second most common gene location that is affected in long QT syndrome, making up about 25 to 30 percent of all cases. This form of long QT syndrome most likely involves mutations of the human ether-a-go-go related gene (HERG) on chromosome 7. The HERG gene (also known as KCNH2) is part of the rapid component of the potassium rectifying current (IKr). (The IKr current is mainly responsible for the termination of the cardiac action potential, and therefore the length of the QT interval.) The normally functioning HERG gene allows protection against early after depolarizations (EADs). In patients with a confirmed or suspected clinical diagnosis of LQTS, genetic diagnosis could have important implications for both management decisions and family members. Therefore, identification of a specific genotype may result in modifications of treatment.

Most drugs that cause long QT syndrome do so by blocking the IKr current via the HERG gene. These include erythromycin, terfenadine, and ketoconazole. The HERG channel is very sensitive to unintended drug binding due to two aromatic amino acids, the tyrosine at position 652 and the phenylalanine at position 656. These

1- Cardiovascular Research Center, Mount Sinai School of Medicine, NY, USA

2- Islamic Azad University, Tehran, Iran

*Address of correspondence and reprints:

Mohsen Hosseinkhani, MD, PhD, Cardiovascular Research Center Mount Sinai School of Medicine 1 Gustave L. Levy Place Box 1030, New York, NY 10029 Tel: 212-241-9177 Fax: 212-241-5510 - Mohsen.hosseinkhani@mssm.edu

amino acid residues are poised so a drug binding to them will block the channel from conducting current. Other potassium channels do not have these residues in these positions and are therefore not as prone to blockage.

Nifekalant is a new, pure class III antiarrhythmic drug, 1-8 which prolongs the action potential duration mainly by blocking a rapidly-activating component of the delayed rectifier potassium channel (IKr).^{2,3,5} In animal experiments, it decreased the incidence of ventricular arrhythmias,⁵ and improves electrical defibrillation efficacy.⁹ In the clinical setting, it has been shown to prevent recurrent ventricular tachycardia and fibrillation (VF).^{6-8,10} However, since it may induce torsades de points (TdP), nifekalant is contraindicated in LQTS.

We observed a patient with LQTS and recurrent fibrillation who was inadvertently treated with intravenous nifekalant. Our observations may provide insight into the genotype-dependent sensitivity of LQTS to class III drug.

Results:

A 35-year-old woman with a history of syncope due to LQTS had been successfully treated with propranolol, 60 mg daily since age 17. However, she discontinued her treatment and, 6 months later, developed seizure-like manifestations witnessed by her roommate, who called an ambulance. The paramedics found her drowsy and transported her to the emergency department of Mount Sinai Hospital. She received several transthoracic DC shocks for recurrent episodes of ventricular tachyarrhythmias in the ambulance. On arrival, the patient had been successfully reanimated and had a Glasgow Coma Scale Score of 14 out of 15. Her blood pressure, pulse and respiration rates were 100/80 mmHg, 95 beats per min, and 18 breaths per min, respectively.

She received nifekalant in an initial dose of 0.4 mg/kg over 5 min for prevention of VF recurrences. An attending physician recognized Tdp-like ventricular tachycardia on the electrocardiogram recorded in the ambulance [Fig 1], and cancelled the continuous infusion of nifekalant, which was being prepared. The patient remained in stable sinus rhythm, and her heart rate decreased from 97 to 90 bpm.

Serum potassium and magnesium concentrations were 4.1 mEq/L and 3.6 mEq/L, respectively. Neither Tdp nor VF recurred despite a modest lengthening of the QT interval from 0.417 sec to 0.430 sec [Fig 2]. A 3 mg/min continuous infusion of magnesium sulfate, temporary cardiac pacing at a rate of 100 bpm, and propranolol, 60 mg/day, were started, and the patient left the intensive care unit 3 days later, after an uneventful recovery and no further episode of Tdp or VF. Subsequent review of the 12-lead electrocardiogram recorded 6 months earlier revealed the presence of QT and QTc intervals of 0.521 sec and 0.527 sec, respectively. Over a long-term follow up of 12 months, she has continued to remain symptom-free.

Genotyping of the patient and her family was later performed by a conventional PCR-SSCP and sequencing method. A missense mutation (A1849G) in HERG was identified in the patient and her mother, responsible for an alteration of amino acid from lysine to glutamine at codon 595 [Fig 3], located in the outer loop between s5 and P domains. Since this mutation reverses polarity from basic to acid and is near the pore region of the HERG channel, it was assumed to cause important changes in channel function.

Discussion:

The accidental administration of the IKr blockade, nifekalant, to a patient suffering from the LQT2 syndrome neither significantly increased the QT interval nor induced Tdp. The safety and efficacy of nifekalant have been examined in several studies of patients with premature ventricular complex,^{4,6,11} including intravenously in high (0.4mg/kg), intermediate (0.3mg/kg), or low (0.2mg/kg) doses for 5 min.¹¹ In a dose of 0.3mg/kg, nifekalant decreased the number of premature ventricular complexes and increased QT and QTc intervals by $15.4 \pm 1.7\%$ and $17.1 \pm 1.4\%$ respectively.⁴ In contrast, the administration of high dose of nifekalant to our patient with the LQT2 syndrome caused an increase in QT interval of only $3 \pm 0.9\%$, and a $9.4 \pm 1.8\%$ decrease in QTc.

The congenital LQTS has been linked with multiple abnormalities in ion channels function caused by a variety of mutation in at least 6 different gene encoding cardiac ion channels or their regulatory subunits.^{12,13} The genotypes of our patient and her mother, revealing a missense mutation in HERG, were consistent with the congenital LQT2 syndrome. Most antiarrhythmic agents, including nifekalant, modify the function of HERG channel, which accelerate repolarization. Since the potential reserve of outward current through HERG channel was probably already reduced, the treatment of our patient with nifekalant produce a smaller than reported change in QT interval, consistent with a genotype-specific effect of the drug on ventricular repolarization. LQT2 is a disease of complexity that depends on various mechanisms including abnormalities in protein processing and trafficking, subunit co-assembly, and channel function that vary from one mutation to the next.¹² Furthermore, a nomogram of QT interval at different heart rates adjusted for sex and age could be used to assess dynamic changes of QT interval of various pathological conditions. For example, patients with IVF had shorter QT interval at slower heart rates suggest of arrhythmogenicity of this specific syndrome at night. Patients with LQT had prolonged QT interval at specific heart rate ranges depending on their genotype. In the range of physiologic heart rates, class III agents could manifest different profiles of rate dependence in their QT-prolonging effect. Although our case did not show Tdp, in LQT1 or

even in patient with other HERG mutations exposure of nifekalant and similar IKr blockers would cause marked QT prolongation or Tdp. Therefore, intravenous nifekalant should be used under monitored conditions only, by clinicians that are skilled in the management of cardiac arrhythmias.

Acknowledgment:

1. Nakaya H, Broth G. Electropharmacology of nifekalant, a new class III antiarrhythmic drug. *Cardiovasc Drug Rev* 2008;16:133-144.
2. Cheng J, Kamiya K, Komada I. Differential effect of MS-551 and E-4031 on action potentials and the delayed rectifier K⁺ current in rabbit ventricular myocytes. *Cardiovas Res* 2008;31:963-974.
3. Ishi M, Kamiya J, Costa K. Cellular electrophysiology effect of MS-551, a new class III antiarrhythmic agent. *Drug Devel Res* 2007;35:61-68.
4. Isomoto S, Konoe A, Centurion OA. Electrophysiological effect of MS-551 in humans: A class III antiarrhythmic agents. *Pacing Clin Electrophysiol* 2006; 18:2022-2027.
5. Kamiya J, Ishii M, Katakami T. Antiarrhythmic effect of MS-551, a new class III antiarrhythmic agent, on canine models of ventricular arrhythmia. *Jpn J Pharmacol* 2007; 58:107-115.
6. Kato K, Atarashi H, Ino T. Phase I study of MS-551 (1): A single intravenous injection study (in USA). *J Clin Ther Med* 2007;13:1659-1674.
7. Kondo K, Hashimoto H, Nishiyama H. Effect of MS-551, a new class III antiarrhythmic drug, on programmed stimulation-induced ventricular arrhythmias, electrophysiology, and hemodynamic in a canine myocardial infarction model. *J Cardiovas Pharmacol* 2007;23:674-680.
8. Onishi, S, Shoda M. Efficacy of intravenous doses of MS-551 for drug-resistant sustained ventricular tachycardia. *J Clin Ther Med* 2008;13:1797-1771.
9. Murakawa Y, Yamashita T, Kanese Y. Can a class III antiarrhythmic drug improve electrical defibrillation efficacy during ventricular fibrillation?. *J Am Coll Cardiol* 2007;29:688-692.
10. Shiga T, Ando T. 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.

11. Kato K, Ogawa S, Iinuma H. Efficacy of intravenous doses of MS-551 for ventricular premature contraction. *J Clin Ther Med* 2007;13:1711-1725.

12. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. *Cell* 2001;104:569-580.

13. Kubota T, Shimizu W, Kamakura S. Hypokalemia-induced long QT syndrome with an underlying novel missense mutation in S4-S5 linker of KCNQ1. *J Cardiovasc Electrophysiol* 2000;11:1048-1054.

Figure legends

Figure 1. Cardioversion for torsades de point-like tachycardia recorded in the ambulance. Bar indicate 1 sec.

Figure 2. Electrocardiogram before and 10 min after the administration of nifekalant. Mean values of QT=average of 5 consecutive beats in lead V3. QTc was calculated by Bazett's formula. (A) leads I, II, V1, V3 and V5. QTc decreased from 0.530 to 0.525 sec. (B) Superimposed lead V3 recorded before (solid line) and 10 min after (dotted line) nifekalant. Bar indicates 0.2 sec.

Figure 3. Left: Mutation analysis. DNA sequence analysis of the patient's (top) and her sister's (Bottom) PCR products screened by the PCR/SSCP method. The patient had a heterozygous mutation at position 1849 from A to G, resulting in the amino acid change from lysine to glutamine at position 595. Right: Partial pedigree of patient's family. Affected members are shown in blue and the proband is indicated by arrow.

Figure 1

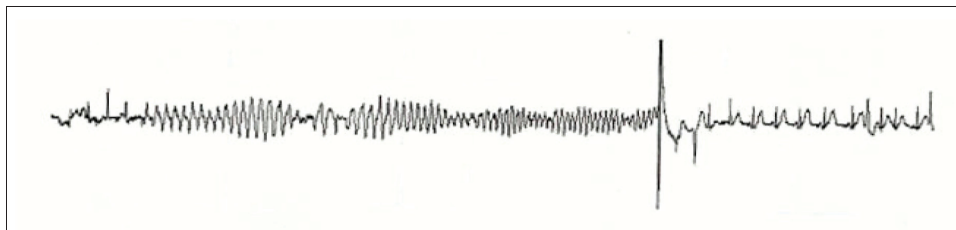


Figure 2

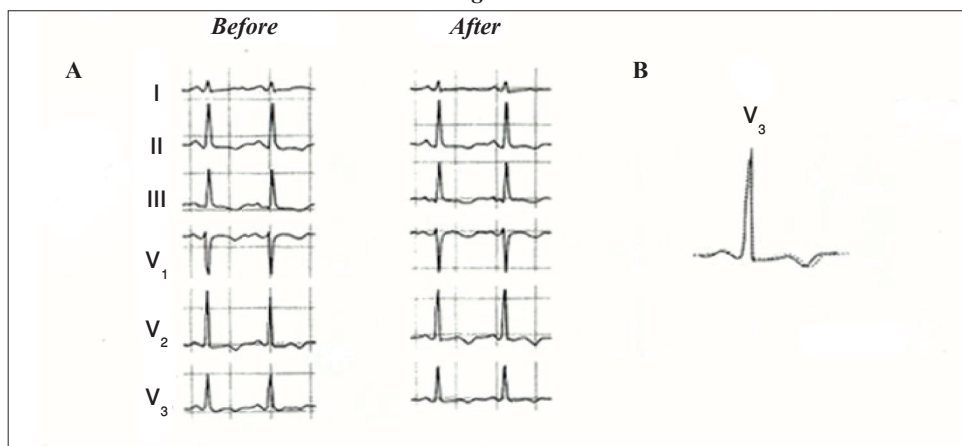


Figure 3

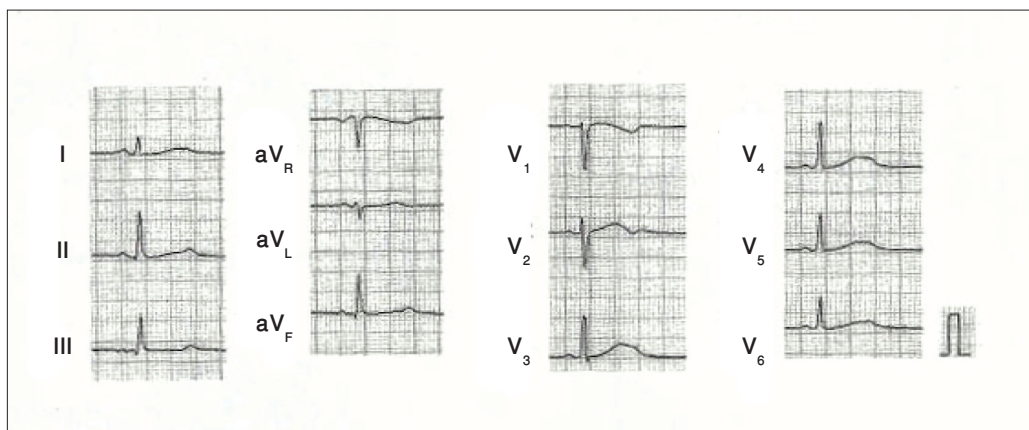


Figure 4

