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Further Insights into the Effect of Quinidine in Short QT Syndrome Caused by a Mutation in HERG

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Abstract

Introduction—The principal aim of this study was to assess the efficacy of quinidine in suppressing I_{Kr} in vitro and in modulating the rate dependence of the QT interval in the “SQT1” form of the short QT syndrome.

Methods and Results—Graded-intensity bicycle exercise testing was performed off drug in three patients and during oral quinidine in two patients with short QT syndrome and compared to a control group of healthy normal subjects. The in vitro effects of quinidine on currents in patch clamp technique were investigated. Off drugs QT_{pV3} /heart rate correlation is much weaker in patients with short QT syndrome, and QT_{pV3} shortens less with heart rate increase compared to normal subjects. In addition to prolonging the QT interval into the normal range, quinidine restored the heart rate dependence of the QT interval toward a range of adaptation reported for normal subjects. Data from heterologous expression of wild-type and mutant HERG genes indicate the mutation causes a 20-fold increase in IC_{50} of d-sotalol but only a 5.8-fold increase in IC_{50} of quinidine.

Conclusion—Oral quinidine is effective in suppressing the gain of function in I_{Kr} responsible for some cases of short QT syndrome with a mutation in HERG and thus restoring normal rate dependence of the QT interval and rendering ventricular tachycardia/ventricular fibrillation noninducible.

Keywords

short QT syndrome; sudden death; quinidine

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Introduction

A short QT interval with familial atrial fibrillation was first described in 2000 by Gussak et al.¹ Gaita et al.² described a familial short QT interval associated with a high prevalence of sudden death in two unrelated Caucasian families. In this population, constantly short QT interval was documented for all ages. Since the incidence of sudden death in both families was high, non-invasive and invasive diagnostics including programmed electrical stimulation and genetic screening were performed on all available living members. Genetic screening revealed a missense mutation in KCNH2 leading to a gain of function in I_{Kr} ("SQT1").³ Bellocq et al.⁴ reported a mutation in KCNQ1 leading to a short QT syndrome in a patient with aborted sudden death. In their single case, the mutation caused a gain of function in I_{Ks} ("SQT2"). We demonstrated that quinidine effectively prolongs the QT interval on baseline ECG at normal heart rates and prevents inducibility of ventricular tachycardia/ventricular fibrillation (VT/VF).⁵ The present study probes in greater detail the effects of quinidine on QT interval behavior during exercise to assess whether quinidine's effect of normalizing the QT interval persists at faster heart rates. We evaluated in vitro the effectiveness of quinidine on wild-type and N588K mutant HERG channels expressed in TSA201 cells.

Patients and Methods

Patients

Three patients from one family (two female and one male; a 15-year-old adolescent and two adults) with a short QT syndrome carrying a missense mutation resulting in an amino acid change (N588K) in the S5-P loop region of the cardiac I_{Kr} channel HERG (KCNH2) underwent detailed programmed electrical stimulation. The family was described in detail previously.² One patient was symptomatic with syncope, one had atrial fibrillation and frequent ventricular ectopy, and one was asymptomatic. Written informed consent was obtained for each single procedure and drug testing. All patients received a prophylactic implantable cardioverter defibrillator. Two patients with inducible VT/VF at baseline and one patient without inducible VT/VF at baseline underwent serial invasive ($n = 3$ studies) and noninvasive electrophysiologic studies via the implantable cardioverter defibrillator lead ($n = 6$ studies). Three patients underwent exercise testing off drug and two patients on oral quinidine to test for the rate-dependent behavior of the QT interval.

Methods

Drug Administration—Drug treatment was started in-hospital during continuous ECG monitoring beginning with 250 mg quinidine twice daily. The daily dosage was increased over 4 days until a dosage of 1,000 mg/day was reached (Fig. 1). Mean serum concentration of quinidine at the time of investigation was 2.1 ± 0.2 mg/L (therapeutic level 2–5 mg/L).

Exercise testing and ECG analysis—Exercise testing to determine QT behavior at increased heart rates was performed using a graded-intensity bicycle exercise test. ECGs were recorded at rest and at steady heart rate for each workload step. Recordings were obtained for a period of 10 seconds at a paper speed of 50 mm/sec. $QT_{peak(p)}$ and QT_{end} were measured. QT_{end} for each lead was defined as the time from QRS onset and T wave offset. QT_p , which was used because QT_{end} often is difficult to determine during exercise, was defined as the time from QRS onset to the peak of the T wave. QT_p was determined in lead V_3 because lead V_3 permitted the most reliable annotation of the peak of T wave because of its large amplitude. U wave was excluded from analysis. QT measurements were performed by two physicians blinded to the subject being evaluated. Results of the two patients with a short QT syndrome were compared to a control group of 10 normal healthy female subjects.

In vitro transcription and mammalian cell transfection—KCNH2 was a kind gift from Dr. A.M. Brown (Metro-Health Campus, Case Western Reserve University, Cleveland, OH, USA). KCNH2 gene construct was recloned from its original vector into pcDNA3.1 (Invitrogen, Carlsbad, CA, USA). Modified human embryonic kidney cells (TSA201) were cotransfected with the same amounts of pcDNA-KCNH 2 and pcDNA-N588K complex using the calcium phosphate precipitation method, as previously described.⁶ Cells were grown on polylysine-coated 35-mm culture dishes and placed in a temperature-controlled chamber for electrophysiologic study (Medical Systems, Greenvale, NY, USA) 2 days after transfection.

Electrophysiology—Standard whole cell, patch clamp techniques were used to measure currents in transfected TSA201 cells. All recordings were made at room temperature using a MultiClamp 700A amplifier (Axon Instruments Union City, CA, USA). Cells were superfused with HEPES-buffered solution containing (in mmol/L): 130 NaCl, 5 KCl, 1.8 CaCl₂, 1.0 MgCl₂, 2.8 Na acetate, and 10 HEPES, pH 7.3 with NaOH/HCl. Patch pipettes were pulled from borosilicate (7740) or flint glass (1161) (PP89, Narahige, Japan) to resistances between 2 and 4 MΩ when filled with a solution containing (in mmol/L): 20 KCl, 120 KF, 1.0 MgCl₂, 10 HEPES, and EGTA, pH 7.2 (KOH/HCl). Currents were filtered with a four-pole Bessel filter at 1 to 2 kHz, digitized at 4 kHz, and stored on the hard disk of an IBM-compatible computer. All data acquisition and analysis was performed using the suite of pCLAMP programs version 8 (Axon Instruments).

Statistical Analysis

All parameters are expressed as mean $\pm$ SD. QT_{pV3}/heart rate relationship was evaluated using linear regression techniques (version 11; SPSS Inc., Chicago, IL, USA).

Results

QT as a Function of Heart Rate

Three patients underwent exercise testing off drugs. Two of these three patients were taking oral quinidine 1,000 mg/day. Off drugs, QT_{pV3} in all three patients shortened less with increasing heart rate, and the QT_{pV3}/heart rate correlation was much weaker than in the control group of healthy normal subjects. After quinidine treatment, QT_{pV3} decrease with increasing heart rate in the two patients was steeper and more strongly linearly correlated.

In the patient who was tested only off drug, the slope was -0.22 msec/beat/min. Linear regression for the other two patients yielded slopes of -0.59 and -0.39 msec/beat/min and R^2 values of 0.60 and 0.56 off drugs (Fig. 2). Maximal QT_{pV3} intervals in these two patients were 190 and 210 msec at rates of 70 and 60 beats/min, and minimal QT_{pV3} intervals were 170 and 180 msec at rates of 120 and 125 beats/min, respectively. On quinidine, a linear relationship was observed with slopes of -0.75 and -0.56 msec/beat/min and R^2 of 0.93 and 0.94 (Fig. 2). Maximal QT_{pV3} intervals in the two patients were 240 and 240 msec at a rate of 70 beats/min, and minimal QT_{pV3} intervals were 180 and 200 msec at rates of 150 and 140 beats/min, respectively. In the control group of 10 normal healthy female subjects, there was a linear relationship between QT_{pV3} and heart rate expressed by a mean R^2 of 0.91 ± 0.07 with a mean slope of -1.29 ± 0.33 msec/beat/min.

In Vitro Electrophysiologic Effects of Quinidine

Previous expression studies of the N588K mutant HERG gene associated with the short QT syndrome in these families showed a dramatic gain of function in the rapidly activating delayed rectifier current I_{Kr} due to failure of the HERG channel to inactivate at positive voltages.³ Loss of inactivation was accompanied by marked reduction in the sensitivity of the channel to block by d-sotalol. d-Sotalol 100 μ M reduced wild-type HERG and N588K currents by an average

of 48% and 9.0%, respectively, when expressed in TSA201 cells. Sensitivity of I_{Kr} to d-sotalol was reduced 20-fold ($IC_{50} = 0.137$ mM for wild-type and 2.34 mM for N588K), accounting for the lack of effectiveness of d-sotalol in the clinic. The sensitivity of the N588K current to quinidine, a less selective but more potent I_{Kr} blocker, was reduced to a much lesser extent. Figure 3 shows that exposure of the TSA201 cells transfected with wild-type HERG to 5 μ M quinidine inhibited approximately 80% of the current (panel A), whereas in cells transfected with the N588K mutant, 5 μ M quinidine inhibited approximately 50% of the current. The mutation caused an only 5.8-fold decrease in sensitivity of I_{Kr} to quinidine ($IC_{50} = 0.75$ for wild-type and 4.35 μ M for N588K).

Discussion

Clinical Effect of Oral Quinidine

Patients with the congenital short QT interval display short atrial and ventricular effective refractory periods. We demonstrated that, in contrast to sotalol and ibutilide, quinidine can normalize the QT interval at resting heart rate and render VF noninducible.⁵ As reported, quinidine prolonged the ventricular effective refractory period in five patients. In serial testing, oral quinidine rendered VT/VF noninducible in two patients in whom *two* separate baseline electrophysiologic studies off drug demonstrated reproducible induction of VF. Among the interesting characteristics of the short QT syndrome is the lack of dependence of QT interval on heart rate under baseline conditions. In addition to prolonging the QT interval into the normal range, quinidine restored the heart rate dependence of the QT interval toward a range of adaptation reported for normal subjects.⁷ Thus, quinidine restores the effective refractory period, QT interval, and restitution properties of ventricular myocardium toward normal limits. The persistent effect of the drug during exercise is significant because sudden death, in at least one case (the father of the 15-year-old boy), occurred during strenuous exercise. These actions of quinidine have been demonstrated in “SQT1” patients, and whether the drug will be effective in “SQT2,” which involves a gain of function in the I_{Ks} channel, is not known.⁴

Interpretation of Quinidine Effects

The basis for the greater effectiveness of quinidine compared to d-sotalol is not fully understood but may be due to differences in the interaction of the two I_{Kr} blockers with the various states of the HERG channel. The affinity of most drugs for ion channels depends on the channel state. d-Sotalol and quinidine interact with the open state of the HERG channel, and drug-receptor interaction is believed to be stabilized by inactivation of the channel.^{8–10} The increased affinity for the inactivated state accounts for reduced effectiveness of these agents when inactivation is eliminated or reduced, as with the N588K mutation. Quinidine’s greater affinity for the open state of the channel may account for the smaller reduction in its effectiveness as a consequence of loss of inactivation.¹⁰ A second factor responsible for the greater effectiveness of quinidine may be its ability to block the slowly activating delayed rectifier current I_{Ks} , which contributes to repolarization of the action potential.^{11–13} These actions of quinidine serve to reduce the markedly augmented repolarizing forces, thus prolonging the QT interval. Quinidine’s effect in reducing inducibility most likely is due to its actions in restoring homogeneity and increasing the wavelength for reentry.

Inhibition of I_{to} may contribute to prolongation of the QT interval, because quinidine has I_{to} -blocking properties. However, inhibition of I_{to} in the setting of an abbreviated action potential tends to further abbreviate the action potential duration.

Study Limitations

Although the sample size used in the present study is smaller than what we are generally accustomed to when arriving at clinical decisions on pharmacologic treatment, the reality of

the situation is that only a few well-defined patients with the short QT syndrome have been identified worldwide. As with other apparently very rare syndromes, wide recognition of the phenotype may provide us with a much larger study population in future years. The explanation for the differences of drug effects is incomplete and partly speculative but consistent with the available data. We must rely on the available data, as limited as they may be, with the recognition that our conclusions may need to be fine-tuned as additional data become available.

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References

1. Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, Bjerregaard P. Idiopathic short QT interval: A new clinical syndrome? *Cardiology* 2000;94:99–102. [PubMed: 11173780]
2. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: A familial cause of sudden death. *Circulation* 2003;108:965–970. [PubMed: 12925462]
3. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A, Bianchi F, Giustetto C, Schimpf R, Brugada P, Antzelevitch C. Sudden death associated with short QT Syndrome linked to mutations in HERG. *Circulation* 2004;109:r151–r156.
4. Bellocq C, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM, Baro I, Wilde AA. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004;109:2394–2397. [PubMed: 15159330]
5. Gaita F, Giustetto C, Bianchi F, Schimpf R, Haissaguerre M, Calo L, Brugada R, Antzelevitch C, Borggrefe M, Wolpert C. Short QT syndrome: Pharmacological treatment. *J Am Coll Cardiol* 2004;43:1494–1499. [PubMed: 15093889]
6. Bezzina CR, Verkerk AO, Busjahn A, Jeron A, Erdmann J, Koopmann TT, Bhuiyan ZA, Wilders R, Mannens MM, Tan HL, Luft FC, Schunkert H, Wilde AA. A common polymorphism in KCNH2 (HERG) hastens cardiac repolarization. *Cardiovasc Res* 2003;59:27–36. [PubMed: 12829173]
7. Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on QT interval in normal subjects. *J Am Coll Cardiol* 2002;39:1820–1826. [PubMed: 12039498]
8. Numaguchi H, Mullins FM, Johnson JP Jr, Johns DC, Po SS, Yang IC, Tomaselli GF, Balser JR. Probing the interaction between inactivation gating and d-sotalol block of HERG. *Circ Res* 2000;87:1012–1018. [PubMed: 11090546]
9. Balser JR, Bennett PB, Hondeghem LM, Roden DM. Suppression of time-dependent outward current in guinea-pig ventricular myocytes. Actions of quinidine and amiodarone. *Circ Res* 1991;69:519–529. [PubMed: 1860189]
10. Kang J, Chen XL, Wang L, Rampe D. Interactions of the anti-malarial drug mefloquine with the human cardiac potassium channels KvLQT1/minK and HERG. *J Pharmacol Exp Ther* 2001;299:290–296. [PubMed: 11561091]
11. Balser JR, Hondeghem LM, Roden DM. Quinidine block of IK accumulates at negative potentials. *Circulation* 1987;76:149.
12. Lai L, Su M, Tseng Y, Lien W. Sensitivity of the slow component of the delayed rectifier potassium current (IKs) to potassium channel blockers: Implications for clinical reverse use-dependent effects. *J Biomed Sci* 1999;6:251–259. [PubMed: 10420082]
13. Slawsky MT, Castle NA. K⁺ channel blocking actions of flecainide compared with those of propafenone and quinidine in adult rat ventricular myocytes. *J Pharmacol Exp Ther* 1994;269:66–74. [PubMed: 8169853]

Figure 1.

(Top) Twelve-lead surface ECG at baseline (upper panel). The QT and QTc intervals are 240 and 268 msec, respectively. (Bottom) ECG recorded with patient taking quinidine 1,000 mg/day. QT and QTc intervals are prolonged to 360 and 402 msec, respectively.

Figure 2.

Heart rate-QTpV3 relationship in a healthy female subject from the control group and a short QT patient off drugs and taking 1000 mg of oral quinidine. There is a linear relationship between the QTpV3 and increasing heart rate in the normal proband. There is no linear relationship ($R^2 = 0.56$) and a less steeper slope of QTpV3 increase than in the control group. The heart rate/QTpV3 relationship in the same patient with a short QT syndrome on oral quinidine exhibits a restored linear relationship between QTpV3 and heart rate ($R^2 = 0.93$). The decrease of QTpV3 with increasing heart rate and the increase of QTpV3 at decreasing heart rate, respectively, are more pronounced than before quinidine.

Figure 3.

Wild-type (WT) HERG (A) and N588K (B) currents in TSA201 cells elicited by 800-msec depolarizing pulses to +20 mV from a holding potential of -80 mV. A large, slowly deactivating inward tail current is observed upon repolarization to -80 mV in HERG. Application of quinidine 5 μM inhibited approximately 80% of the current (A). Mutation N588K increased the size of the activation current and significantly accelerated the tail current decay (B). Quinidine 5 μM inhibited about 50% of the N588K current.