ORIGINAL ARTICLE

Low-Dose Quinidine Effectively Reduced Shocks in Brugada Syndrome Patients with an Implantable Cardioverter Defibrillator: A Chinese Case Series Report

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Background: Only implantable cardioverter defibrillators (ICD) have been proven to prevent sudden cardiac death (SCD) in patients with Brugada syndrome (BrS). However, ICD discharge, whether appropriate or inappropriate, leads to impaired quality of life and even increases rehospitalization. Quinidine might prevent the recurrence of ventricular arrhythmia (VA); however, the effect of low-dose quinidine for preventing spontaneous arrhythmias remains less clear.

Methods: In our cardiology center, 10 confirmed patients with BrS (all men, mean age 38.7 ± 6.72 years) who underwent appropriate ICD shocks due to recurrent VAs were treated with quinidine (≤ 200 mg/day) and followed regularly.

Results: All the patients underwent ICD shocks due to ventricular tachycardia (VT)/ventricular fibrillation (VF) before taking quinidine. A 24-hour distribution of VT/VF demonstrated that most of the events occurred in the sleeping time from 22:00 to 8:00. Quinidine prevented recurrence of VAs in nine patients. The other one patient took quinidine discontinuously because of anxiety suffered from less episodes of VA, and after psychological guidance, he took quinidine 200 mg/day and experienced no VA episodes from then on. In our series, only one patient suffered leukopenia related to quinidine. No other side effect was observed.

Conclusions: Quinidine with a very low dose (≤ 200 mg/day) well controlled VT/VF recurrence for a long-term period in Chinese patients with BrS. Administration (at 21:00) according to the circadian distribution of VT/VF episodes might increase the efficiency and improve the patient's tolerance.

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Brugada syndrome; quinidine; implantable cardioverter defibrillator; ventricular fibrillation

The Brugada syndrome (BrS) is an inherited arrhythmogenic disease associated with a risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF) or fast polymorphic ventricular tachycardia (VT).¹ Recent guidelines claimed that implantable cardioverter defibrillator (ICD) is the only proven effective therapeutic strategy for the prevention of SCD in cardiac arrest survivors with BrS.² Radio-frequency ablation and pharmacotherapy represent future possibilities but

require further investigation. So far, only quinidine has been consistently reported to be beneficial for preventing the recurrence of ventricular arrhythmias (VA) in patients with BrS, and in most studies, the effective dose was 1.0–1.5 g/day.³ After AstraZeneca decided to stop the production of quinidine sulfate, it was difficult to obtain quinidine supplies in many countries including Mainland China.⁴ In order to prevent ICD shocks by VAs in patients with BrS, in view

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of the ethnic difference between the East and West, we tried to explore the response to low doses of quinidine sulfate (200 mg/day, made in Taiwan, China) in Chinese patients with BrS who might have less body weight.

METHODS

Study Population

A total of 10 patients diagnosed with BrS during 2006–2012 were included in our study. The diagnosis of BrS was confirmed if the patient had a type 1 or 2 BrS ECG and one of the following criteria: family history of sudden death (unexplained death before the age of 65 years), syncope, aborted SCD, or recorded VA history. Structural heart diseases were excluded by ECG, transthoracic echocardiography, and cardiac catheterization. All the subjects were implanted with an ICD and received very low doses of quinidine (200 mg/day) after the recurrent shocks of ICD due to VA episodes.

Follow-Up

Clinical follow-up of patients consisted of symptoms, physical examinations, and electrocardiography at least every 6 months. The device was followed up every 6 months. If the patient underwent a shock or any symptoms such as amaurosis or syncope, they would come to our hospital promptly.

Arrhythmic events receiving ICD therapies were predefined according to the cycle lengths of the arrhythmias. The VT zone was programmed to 188–222 beats/min and VF zone higher than 222 beats/min. The circadian distribution of VT/VF events of all the patients was analyzed. All available electrograms of appropriate and inappropriate shocks were analyzed by at least two investigators independently. Electrical storm (ES) was defined by three or more sustained episodes of VT/VF or appropriate ICD shocks within 24 hours.

The following data were collected: (1) demographic characteristics, (2) clinical characteristics and VT/VF events recorded by ICD before and after the use of quinidine, (3) quinidine therapy (formulation, daily dosage, and time on treatment), and (4) side effects (gastrointestinal, neurological, cinchonism, leukopenia, and proarrhythmia).

Statistical Analysis

Continuous variables were presented as mean $\pm$ SD. The chi-square test was used to compare categorical variables. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Totally 10 patients (all men; mean age 38.7 ± 6.72 years; range 25–48 years) received ICDs at our institution from 2006 to 2012 and met the inclusion criteria for this study. All subjects presented with syncope before ICD placement. Spontaneous Brugada type 1 ECG pattern was documented in 6 of 10 patients. All the patients had clinical recurrence of VT/VF shocked by their device before taking quinidine. As a 24-hour distribution of VT/VF shown in Figure 1, all the events were recorded and most of them occurred in the sleeping time from 22:00 to 8:00.

Effects of Quinidine on VT/VF Recurrence

Quinidine was administrated for appropriate ICD shocks, and the results before and after the administration were compared in Figure 2. During the follow-up, no recurrence of VT/VF episodes was observed in nine patients as shown in Figure 2. The other one, patient 5, after 6 months under quinidine without any events, discontinued quinidine because of anxiety and then underwent amaurosis due to VF terminated by direct current (DC) shocks. After psychological guidance, this patient has been followed on quinidine 200 mg/day and has not experienced any VT/VF episodes. There were totally 114 VF episodes terminated by ICD in patient 8 before January 2014. From then on, he began quinidine therapy and no recurrence of VT/VF was recorded (Fig. 3). In July 2015, this patient underwent an ICD replacement, and no VT/VF was recorded until now. About 1 year after implantation, patient 6 suffered from ICD pocket infection and eventually required extraction despite intravenous antibiotic therapy. This subject continued to take quinidine 200 mg/day and was still alive without any symptoms after ICD system extraction. Patient 2 could not afford another ICD after replaced two ICDs,

Figure 1. In all 10 patients, totally 309 VT/VF episodes were recorded by ICD. The 24-hour distribution of VT/VF events significantly increased from 22:00 to 8:00 that was sleeping time for most patients and then gradually decreased from 8:00 to 22:00. ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia; VF = ventricular fibrillation.

Figure 2. The results of follow-up in 10 patients before and after administration of quinidine (one horizontal graph for each patient). To the left of the zero line, each bar shows the number of months without quinidine (blue bars) and number of shocks received during the period (red bars). To the right of the zero line, each bar shows the result on quinidine. For the entire group, the total number of shocks-months was 309 shocks within 289 months of follow-up with no therapy (average of 1.06 shocks per month) versus nine shocks during 409 months on quinidine (0.02 shocks per month).

Figure 3. A total of 114 VF episodes terminated by ICD shocks in patient 8 before taking quinidine 200 mg daily in January 2014. From then on, no recurrence of VT/VF was recorded.

but he continued to take quinidine 200 mg/day and experienced no syncope or SCD until now. Unfortunately, his younger brother died suddenly in his 30s. He neither implanted an ICD nor took any drugs because he had no symptoms before SCD.

Side Effects of Quinidine

Quinidine was stopped in one case because of extracardiac drug intolerance. In patient 2, leukopenia was observed under quinidine 200 mg/day and he reduced the dose to 200 mg every other day. Amazingly, this very low dose of quinidine was effective and could be well tolerated for this subject.

DISCUSSION

Implantable cardioverter-defibrillator implantation is advocated to be the first-line therapy in SCA in BrS survivors.⁵ Unfortunately, an ICD is associated with some device-related complications such as infection and lead fracture. Long-term outcome demonstrated that ICD might have both psychological and social impacts on the patients,⁶ and frequent DC shocks will shorten the longevity of the devices and increase the healthcare utilization.⁷ After Belhassen et al.⁸ firstly reported that VT/VF inducibility could be prevented by quinidine in 1999, the role of quinidine therapy is currently a subject of active interest. Recently, the Expert Consensus Statement on the Diagnosis and Management of Patients with

Inherited Primary Arrhythmia Syndromes recommended quinidine in patients with BrS who experienced arrhythmic storm or in case of supraventricular arrhythmias needing treatment (class IIa) as well as in asymptomatic patients with spontaneous type 1 ECG (class IIb).⁹ Abdel-slam et al. reported that residual inducibility under hydroquinidine is of limited value to predict events during follow-up, maybe due to low rate of events among asymptomatic BrS patients with inducible VF.¹⁰ The value of quinidine in long-term prevention of VT/VF episodes is not well recognized.

Although ICDs are effective in treating episodes of VT/VF, they cannot prevent them and do not improve patients quality of life. Therefore, medications should be considered when multiple DC shocks (due to electrical storm or repetitive ventricular tachycardia) are observed. Quinidine, a class IA antiarrhythmic drug, was found to strongly inhibit I_{to} in ventricular epicardial cells, thus restoring electrical homogeneity and abolishing phase II reentry.¹¹ Also, quinidine can prevent spontaneous arrhythmias in high-risk BrS patients and is very effective for terminating VF storms when other drugs fail.¹² Belhassen et al.¹³ recently reported a 38-year-old BrS patient with aborted cardiac arrest who nearly died from VF despite a normally functioning ICD. This patient was fortunate to have his VF episode terminated by the ICD after five unsuccessful discharges (the device has the capability to deliver a maximum of eight shocks). This case raised the question of whether BrS

survivors of cardiac arrest can be safely treated with ICD alone. In our study, low dosage of quinidine (≤ 200 mg/day) was effective in preventing spontaneous VT/VF during the long-term follow-up ranging from 12 to 108 months in all 10 patients with ICD, which was similar to the previous reports.¹⁴ Before the large randomized controlled clinical studies, we still should take low doses of quinidine as a therapy of last resource, and it should be tried only when high doses are not tolerated. The additional use of quinidine in those patients treated with ICD might be an important policy in future.

The much longer survival of patients with BrS (who are young and free of heart disease) inevitably places them at increased risk for ICD-related complications in the long term because the repeated need for ICD replacements significantly increases the risk of device-related infection. Of note, a previous study showed that complications among children with BrS undergoing ICD implantation affected up to 33%.¹⁵ In this particularly active category of patients, electrode fractures can more frequently occur and their long life expectancy might increase rate of device-related complications which will have a significant impact on the quality of life. Young age, history of atrial arrhythmias, or T-wave oversensing at the time of ICD implantation, all of these factors significantly increase their risk for inappropriate shocks.¹⁶ For those patients with limited symptoms at a young age in whom the family does not want to adopt an active approach, quinidine therapy might be considered as an alternative to prevent arrhythmic death until the child grows sufficiently to safely undergo ICD implantation. According to our results, in BrS patients with arrhythmic risk, quinidine might constitute a useful alternative mode of management for those who cannot afford the expenses of ICD implantation or refuse the ICD option (including cardiac arrest survivors) which is consistent with the conclusion of a recent report by Belhasen.¹⁷ However, for now, low doses of quinidine should not be accepted as standard therapy, particularly in patients without ICD.

The action of quinidine depends not only on dosage but also on tissue-plasma distribution. Previous experimental studies suggested that high doses of quinidine (1.0–1.5 g/day) must be prescribed in order to obtain I_{to} block. However, when relatively high doses were used, a third of

the patients had to discontinue quinidine because of its dose-dependent side effects, mainly diarrhea and hepatotoxicity. Present studies reported¹⁴ that the effectiveness of low doses of quinidine (≤ 600 mg/day) was 85% and lower doses were associated with a good long-term tolerability. Lower dose quinidine prevented VT/VF recurrence in all 10 patients in our series, and most of our patients took quinidine 200 mg/day. In our study, the VT/VF events mostly occurred between 22:00 and 8:00 (Fig. 1) and might depend on slow heart rate. Nightly vagus excited can prolong the conduction delay between the anterior wall of the right ventricular outflow tract (RVOT) and septal area, which may explain why the patients with BrS prone to VF during the night. Quinidine can not only significantly disrupt current I_{to} but also inhibit the stimulation of vagus. As the half-time of quinidine is 6–8 hours and it took 1–3 hours to reach the peak, oral administration of quinidine 200 mg nightly at 21:00 could significantly improve the intensive distribution of VT/VF during 22:00 to 4:00 (Fig. 1). This lower dose could reduce the side effects of quinidine, and thereby enhances the tolerance of patients. Our study also supports the report that low doses of quinidine ≤ 200 mg/day may be an option when adverse events occur with recommended high conventional doses.

Unfortunately, however, quinidine is unavailable in areas such as Southeast Asia including Mainland China, where the BrS and sudden unexplained nocturnal death syndrome (SUNDS) are particularly endemic, maybe due to low profit for production companies.¹⁸ In these areas, patients with BrS may take lower dose of quinidine continuously.

We acknowledge some limitations. (1) Our study was not designed as a randomized control trial and was, therefore, limited by the absence of the control group. (2) The population was very small. First, not every patient with BrS who needs an ICD would accept one. So the number of implanted patients was small. Second, quinidine is not available in Mainland China. If a patient needs to take quinidine, he has to get the medicine in Taiwan, China, or Hong Kong, China. We did not detect the drug concentration due to absence of testing methods. (3) Patients without symptoms would not accept another invasive electrophysiological examination to verify the effectiveness of quinidine.

Quinidine with a very low dose (≤ 200 mg/day) well controlled VT/VF recurrence for a long-term period in Chinese patients with BrS. Low-dose quinidine might be an adjunctive therapy for the Chinese BrS patients with frequent ICD shocks when high doses are not tolerated. Administration (at 21:00) according to the circadian distribution of VT/VF episodes might increase the efficiency and improve the patients tolerance.

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