Efficacy of Quinidine in High-Risk Patients With Brugada Syndrome

Bernard Belhassen, MD; Aharon Glick, MD; Sami Viskin, MD

Background—Automatic implantable cardioverter-defibrillator therapy is considered the only effective treatment for high-risk patients with Brugada syndrome. Quinidine depresses $I_{to}$ current, which may play an important role in the arrhythmogenesis of this disease.

Methods and Results—The effects of quinidine bisulfate (mean dose, 1483 ± 240 mg) on the prevention of inducible and spontaneous ventricular fibrillation (VF) were prospectively evaluated in 25 patients (24 men, 1 woman; age, 19 to 80 years) with Brugada syndrome. There were 15 symptomatic patients (including 7 cardiac arrest survivors and 7 patients with unexplained syncope) and 10 asymptomatic patients. All 25 patients had inducible VF at baseline electrophysiological study. Quinidine prevented VF induction in 22 of the 25 patients (88%). After a follow-up period of 6 months to 22.2 years, all patients are alive. Nineteen patients were treated with quinidine for 6 to 219 months (mean ± SD, 56 ± 67 months). None had an arrhythmic event, although 2 had non-arrhythmia-related syncpe. Administration of quinidine was associated with a 36% incidence of side effects that resolved after drug discontinuation.

Conclusions—Quinidine effectively prevents VF induction in patients with Brugada syndrome. Our data suggest that quinidine also suppresses spontaneous arrhythmias and could prove to be a safe alternative to automatic implantable cardioverter-defibrillator therapy for a substantial proportion of patients with Brugada syndrome. Randomized studies comparing these two therapies seem warranted. (Circulation. 2004;110:1731-1737.)

Key Words: antiarrhythmic agents • electrophysiology • tachyarrhythmias

Brugada syndrome is a cardiac disease caused by an inherited ion channelopathy associated with a propensity to develop ventricular fibrillation (VF). Symptomatic patients (cardiac arrest survivors or patients with unexplained syncope) and asymptomatic patients who have inducible VF at electrophysiological (EP) study are considered to be at high risk of sudden death. Consequently, most cardiac electrophysiologists recommend implantation of an automatic cardioverter-defibrillator (ICD) for these patients. ICD therapy, however, is not trivial for this frequently young patient population in which multiple ICD replacements are expected. In addition, for many patients, ICD implantation is not an option because of economic constraints.

For the past 25 years, our group has systematically used EP-guided therapy with quinidine for patients with idiopathic VF with excellent results. When it was later demonstrated that a subgroup of patients with idiopathic VF have Brugada syndrome, we continued using the same approach. In the present study, we report our experience with the use of EP-guided therapy with quinidine in high-risk patients with Brugada syndrome.

Methods

Study Group

Our study cohort consisted of 38 consecutive patients with Brugada syndrome (15 symptomatic, 23 asymptomatic). All patients had the following characteristics: a typical Brugada ECG pattern before or after intravenous administration of flecainide (2 mg/kg over 6 minutes) and no apparent heart disease as judged from normal echocardiogram and normal right and left ventriculography and coronary angiography in cardiac arrest survivors. All patients underwent EP study with programmed ventricular stimulation (PVS), and 11 who had no inducible arrhythmias were excluded. The remaining 27 patients (71%) who had inducible VF were considered for study. Two asymptomatic patients, both with inducible VF, were excluded because of early (<3 days) intolerance to quinidine in one patient and second-degree infranodal block precluding quinidine therapy only in the other patient. The remaining 25 patients (15 symptomatic, 10 asymptomatic) with Brugada syndrome who had inducible VF at baseline EP study and underwent a repeated EP study during oral quinidine therapy constitute the study group.

There were 2 patient groups. Group A was made up of 15 symptomatic patients (14 men, 1 woman; age, 39 ± 19 years): 7 patients resuscitated from VF, 7 with unexplained syncope, and 1 with palpitations and dizziness who had the same symptoms during exercise-induced sustained monomorphic ventricular tachycardia (VT) (200 bpm/min). One patient resuscitated from VF also had exercise-induced monomorphic VT (180 bpm/min). Group B included 10 asymptomatic patients (all men; 39 ± 9 years old) with no documented or suspected spontaneous arrhythmias. One patient had previously documented typical vasovagal syncope. A family history of sudden cardiac death or Brugada syndrome was present in 7 patients (3 from group A, 4 from group B). Seven of the 25 patients are discussed in a previous publication, including 2 originally classified as suffering from idiopathic VF in whom the Brugada ECG pattern appeared during quinidine therapy.
Protocol of EP Studies
The protocol of PVS evolved over the years. From 1979 to 1982, PVS was performed only from the right ventricular apex and with a maximum of 2 extrastimuli. In 1983, pacing from the right ventricular outflow tract was added. Triple extrastimulation was introduced in 1988. In addition, for the past 25 years, our protocol has included repetition (10 times) of double extrastimulation at the shortest coupling intervals that result in ventricular capture. This repetition of double extrastimulation was performed at each pacing site and for each of the cycle lengths tested. This protocol increases the sensitivity of PVS protocols without significantly affecting its specificity. In 1988, repetition (5 times) of triple extrastimulation at the shortest coupling intervals was introduced because we found that it further increases sensitivity of PVS protocols while keeping specificity in satisfactory range (>90%) (unpublished data). The stimulus current intensity was set at 5 times diastolic threshold (but never >3 mA) in all patients.

EP Study at Baseline and on Quinidine Bisulfate
The first EP study was performed in the absence of antiarrhythmic medications for all but 2 patients, who were receiving amiodarone (1200 mg/d for 10 days and 200 mg/d for 10 months) after their index spontaneous VF. Quinidine bisulfate (Quinidurane, Teva) was then given at a dose of 1500 mg/d (500 mg tid) to all 25 patients under close monitoring. The quinidine dose in one patient was increased to 2000 mg/d because of low quinidine serum level; the dose in a second patient was decreased to 750 mg because of diarrhea. The second EP study was then performed after 3 to 7 days of treatment with 1500 mg (23 patients), 2000 mg (1 patient), and 750 mg (1 patient) bisulfate 3 to 6 hours after the last dose administration. Three patients who had no sustained arrhythmias induced on a dose of 1500 mg quinidine agreed to undergo a third EP study on a lower dose (1000 mg). Finally, during long-term quinidine therapy, 4 patients consented to undergo a repeated EP study to confirm long-term drug efficacy. One of these patients underwent an additional EP study during quinidine therapy after he suffered from a syncopal episode. Serum blood levels of quinidine were determined at each EP study.

Definitions
VF was defined as a ventricular tachyarrhythmia manifesting a continuously varying morphology with a mean cycle length <200 ms that required cardioversion for termination. Nonsustained VT was a VT of ≥6 complexes that was <30 seconds in duration and was not associated with loss of consciousness. Arrhythmias were nonsignificant when <6 repetitive ventricular complexes were induced. Patients were defined as EP responders when quinidine prevented VF induction.

Follow-Up
Patients were discharged with the medication regimen that prevented induction of VF and were followed up as outpatients every 6 to 12 months. Attention was given to gastrointestinal disorders, platelet count number, liver function tests, serum potassium levels, and QTc values. Drug serum levels were checked every 6 months, and the quinidine dosage was modified if necessary to achieve serum levels similar to those found during the negative EP study. Patients who developed drug intolerance were advised to undergo implantation of an ICD. Recently, we tested the administration of cholestyramine in a patient with diarrhea. In addition, the potential risks and benefits of drug discontinuation and ICD implantation were discussed with each patient at least once yearly.

Patient compliance with medications was estimated during each follow-up as previously defined. Notes about estimated drug compliance were made prospectively in the patients’ charts.

Patients with ICD were followed up at 3- to 4-month intervals. At each visit, they were questioned about the presence of syncope or device discharges, and their ICD was interrogated. All patients underwent repeated echocardiogram every 5 years. No patients were lost to follow-up.

Statistical Analysis
All values are expressed as mean ± SD or percentages as appropriate. Paired Student t test was performed to compare QTc values before and after administration of quinidine. A value of P < 0.05 was considered statistically significant.

Results
Diagnosis of Brugada Syndrome
The ECGs (leads V1 to V3) of the 25 study patients are shown in Figure 1. The first study patient had spontaneous VF documented in November 1981. Although the Brugada ECG pattern was present at that time, it was recognized 11 years later. Two other patients who had spontaneous VF in 1984 and 1986 had normal ECGs at presentation, and the Brugada ECG pattern became evident after 16.5 and 15 years, respectively, during quinidine therapy (Figure 2). In all other patients, the diagnosis of Brugada syndrome was made at the time of initial patient evaluation and EP study.

The diagnosis of Brugada syndrome was revealed after administration of intravenous flecainide in 7 patients (4 in group A, 3 in group B) (Figures 1 and 3).

Baseline EP Studies
All 25 patients had inducible VF at baseline EP study. VF was induced with single, double, and triple ventricular extra-
stimulation in 1, 19, and 5 patients, respectively (Figure 4A). Inductions of VF occurred during repetition of double extrastimulation in 6 patients and during repetition of triple extrastimulation in 2. VF was induced from the right ventricular apex in 18 patients and the right ventricular outflow tract in 7. Reproducibility of VF induction was assessed in 11 patients (5 from group A, 6 from group B) and showed reproducible VF induction in all patients. In the 2 patients who had associated exercise-induced monomorphic VT, the latter could not be induced with either atrial or ventricular stimulation.

**Early EP Testing on Quinidine Bisulfate**
Quinidine (mean dose, 1483 ± 240 mg) prevented reinduction of VF in 22 of the 25 patients (88%) (Figure 4B). The efficacy rates were 87% and 90% in groups A and B, respectively. In 8 of the 22 responders, asymptomatic non-sustained polymorphic VT (1.5 to 17 seconds; mean ± SD, 6 ± 5 seconds) was induced, whereas in the remaining 14 patients, no significant ventricular arrhythmias were observed. The effective quinidine serum blood levels ranged from 1.29 to 5.2 mg/L (mean ± SD, 2.65 ± 0.99 mg/L). In the 3 nonresponders, quinidine serum levels were 1.5, 3.0, and 8.0 mg/L. In 1 of 3 patients who responded to 1500 mg quinidine, a lower dose of quinidine (1000 mg) was similarly effective in preventing VF reinduction.

**Late EP Testing on Quinidine Bisulfate**
Four group A patients agreed to undergo an additional EP study after several years of quinidine therapy (2 patients after 5 years, 1 patient after 11 years, and 1 patient after 17 years). In all patients, results were similar to initial results despite the use of more aggressive protocols of PVS in 2 patients (Figure 5). One patient underwent an additional EP study on quinidine 3 years later after he suffered a syncopal episode. This study showed a persistent preventive effect of quinidine on VF reinduction.

**ECG Effects of Quinidine**
During quinidine therapy in 23 patients not previously treated with amiodarone, QTc intervals significantly increased by a mean of 15.8% (from 410 ± 24 to 475 ± 32 ms; P < 0.0001). In the 2 patients under amiodarone, QTc also increased (from 0.47 to 0.56 seconds and from 0.46 to 0.56 seconds). Quinidine markedly attenuated the Brugada ECG pattern in 3 patients (12%).

---

**Figure 2.** Patient A2. ECG leads V1 through V3 recorded after cardiac arrest on no antiarrhythmic therapy in 1984 (A) and 18 years later in September 2002 during quinidine therapy (B). Brugada pattern is suspected in B but not in A.

**Figure 3.** Patient A2. In October 2002, after discontinuation of quinidine, administration of intravenous flecainide results in Brugada ECG pattern (V1 through V3) associated with ventricular extrasystoles originating from right ventricular outflow tract.
Long-Term Follow-Up
All patients are alive after 6 months to 22.2 years of follow-up. Repeated echocardiograms performed at 5-year intervals showed normal findings in all patients. Of the 25 study patients undergoing EP testing with quinidine, 16 were subsequently treated with quinidine (6 months), 6 received ICD therapy, and the remaining 3 were treated with both quinidine (6 months) and ICD.

Quinidine Therapy
Among the 19 patients treated with quinidine for 6 months, induction of VF was prevented by quinidine in 18; the remaining patient (from group B) was a nonresponder who refused ICD therapy and opted for quinidine therapy.

Eleven group A patients received quinidine for 82±77 months (range, 6 to 219 months), whereas 8 group B patients received this medication for 20±19 months (range, 6 to 58 months). In one of the 2 patients who underwent baseline EP study on amiodarone, a low dose of this medication (200 mg) was continued with quinidine therapy (see below). None of the 19 patients had an arrhythmic event documented while receiving quinidine for 6 to 219 months (mean±SD, 56±67 months), including 5 patients with aborted cardiac arrest who were treated during periods ranging from 7.2 to 18.2 years. However, 2 patients had syncope. The first patient originally presented in 1994 with recurrent syncope and documented VF. He remained asymptomatic for 8 years on 1500 mg quinidine (which was found to be effective at 2 EP studies) but later had unexplained syncope that prompted a third EP study on quinidine. Although this study showed only the induction of a 4-second episode of nonsustained VT, an ICD was implanted without discontinuation of quinidine therapy. Three months later, the patient had

Figure 4. A, Patient A2. At baseline EP study (EPS; 1985), VF requiring DC shock is easily induced with single ventricular extrastimulus (and possibly facilitated by bundle-branch reentry beat). B, Same patient. After administration of quinidine bisulfate (1500 mg), only nonsustained polymorphic VT is induced with double ventricular extrastimulation.
recurrent syncope, and ICD interrogation failed to reveal any arrhythmia. The second patient originally presented with syncope that was so typical of vasovagal syncope that he was categorized into group B. He was treated with quinidine, which prevented VF induction. During follow-up, he had recurrent vasovagal syncopes that were identical to those present before treatment. Of note, the only female study patient had 2 uneventful pregnancies and normal childbirth during quinidine therapy.

Quinidine therapy was well tolerated in 14 of 22 EP responders (64%) but resulted in side effects in the remaining 8 (36%). These included thrombocytopenia (3 patients), intolerable diarrhea (2 patients), esophagitis (1 patient), allergic reaction (1 patient), and aggravation of sinus node dysfunction (1 patient). These side effects occurred within the first month of quinidine therapy in 5 patients and led to definite drug discontinuation in 7. One patient continued suffering diarrhea on 750 mg quinidine and was given oral cholestyramine (4g BID). This medication suppressed diarrhea without preventing quinidine absorption, as assessed by quinidine blood levels, and without impairing the quinidine EP effects, as assessed by QT intervals and repeated EP study that showed prevention of VF induction. In summary, in 16 study patients (64%), including 15 EP responders and 1 nonresponder, quinidine (in combination with cholestyramine in one patient) could be chronically tolerated with therapeutic effectiveness.

Compliance with medical therapy was excellent in all but 2 patients. One group A patient took amiodarone (200 mg) and quinidine (1500 mg) regularly for 5 years (1981 to 1986) but then discontinued all medications (against medical advice) and remained well for 6 years. He then had repeated EP study in 1992 that showed VF induction off drugs and persistent quinidine efficacy on VF reinduction. Eventually, the patient agreed to renew quinidine only but developed thrombocytopenia after 3 years of treatment. For the past 10.5 years, he has repeatedly refused implantation of ICD but agreed to take amiodarone. The second patient (group B) intermittently took quinidine (because of diarrhea) and declined ICD implantation.

ICD Therapy
Nine study patients (36%), 6 from group A and 3 from group B, eventually underwent ICD implantation (combined with quinidine therapy in one group A patient). Failure of quinidine to prevent VF induction was the reason for ICD implantation in only 2 patients. In the remaining 7 patients, ICD was implanted because of quinidine-related side effects (5 patients), syncope (1 patient), and the patient’s wishes after 17 uneventful years of quinidine therapy (the female patient). Of note, the last patient subsequently developed complications from ICD implantation (see below).

Follow-up after ICD implantation lasted from 6 to 117 months (mean±SD, 41±35 months). One patient exhibited appropriate ICD discharges. This patient was one of the 2 symptomatic patients who had inducible VF on quinidine therapy. Nevertheless, when he developed an arrhythmic storm, quinidine 1500 mg/d (the same dose that had failed at EP study) was given with immediate resolution of the spontaneous arrhythmias. He then remained free of arrhythmias on quinidine for the following 4 years.

Complications related to ICD implantation occurred in 4 patients; 3 had inappropriate shocks, which resulted in severe psychological disturbances in 1 patient. The female patient who opted for ICD therapy eventually required a surgical revision because of oversensing of electrical noise. This revision was complicated by iatrogenic pneumothorax.

Discussion

Main Findings
Our study shows the following. First, quinidine is highly effective (88% success rate) for preventing VF induction in Brugada patients with inducible VF. Second, quinidine also appears to be effective in preventing spontaneous VF, with no arrhythmic events observed during a mean±SD follow-up of 56±67 months. Third, the drug could be chronically tolerated with therapeutic effectiveness in 16 study patients (64%). Fourth, no proarrhythmic event occurred in any treated patient despite QT prolongation. Finally, although quinidine-related side effects were common, they were always transient and invariably resolved after drug discontinuation.

EP Efficacy of Quinidine
After our preliminary report of quinidine efficacy in Brugada syndrome,7 Hermida et al11 conducted a systematic evalua-
tion of quinidine in Brugada syndrome. They administered hydroquinidine chlorhydrate (600 to 900 mg/d; serum levels, 2.7±1.3 μmol/L) to 29 asymptomatic patients with inducible VF. They reported suppression of VF induction in 22 patients (76%). Their study, however, included only patients with asymptomatic Brugada syndrome, whereas we found a somewhat higher efficacy of quinidine in both symptomatic and asymptomatic patients. It remains to be determined whether the different preparations and doses of quinidine used by Hermida et al could explain the higher success rates of quinidine in preventing VF inducibility in our series.

In our study, 87% of our symptomatic Brugada patients and 90% of asymptomatic patients with inducible VF had a negative EP study on quinidine. These results should be appreciated in the setting of the aggressive protocol of PVS used in our study. This protocol uses stimulus currents that are higher than those used in most EP laboratories, allowing us to test the effects of very short coupling intervals. Moreover, short coupling intervals that were found to be more likely to induce VF in Brugada syndrome,12 were repeated (10 times for double extrastimuli, 5 times for triple extrastimuli) at each pacing site and basic cycle length. Another interesting finding of our study was that reproducible noninducibility of VF on quinidine was observed in all 4 patients who underwent repeated EP testing 5 to 17 years after the initial EP studies. This result is important in view of the high reproducibility of VF induction at baseline EP study observed by us and others13 in the absence of therapy.

**Clinical Efficacy of Quinidine**

During a follow-up period ranging from 6 to 219 months (mean±SD, 56±67 months), no arrhythmic events were documented in any of our 19 patients treated with quinidine, including 5 patients with aborted cardiac arrest treated for very long periods. The syncopal episodes in 2 quinidine-treated patients had a nonarrhythmic origin, as suggested by the typical vasovagal picture in one patient and the lack of ICD-stored arrhythmias in the other. In the absence of a control group, however, it is impossible to conclude how much of this arrhythmia prevention is really due to quinidine therapy. It is therefore important to compare our long-term results with those of similar series of patients treated with ICD therapy and no antiarrhythmic medications. By far, the largest series is the multicenter study recently reported by Brugada et al11 in 443 patients. After 35±45 months, 54% of their patients presenting with cardiac arrest, 23% of those presenting with syncope, and 12% of asymptomatic patients with inducible VF eventually had VF documented by implanted ICD. These figures sharply contrast with the nil incidence of arrhythmic events observed in our patients despite similar baseline patient characteristics and longer follow-up. In the study by Hermida et al,11 0 of the 21 asymptomatic high-risk patients treated with quinidine died, and 2 (9.5%) had syncope during 16±15.5 months of follow-up.

**Mechanism of Action of Quinidine in Brugada Syndrome**

Genetic mutations detected so far in the Brugada syndrome result in defective myocardial sodium channels that reduce sodium inflow currents, resulting in shorter-than-normal action potentials.14 Prominent $I_{Na}$ (transient outward) current in the right ventricular epicardium further shortens the action potentials.14 Work by Antzelevitch14 and Yan and Antzelevitch15 suggests that quinidine may exert its beneficial effects in Brugada syndrome by inhibiting $I_{Na}$, thereby restoring electrical homogeneity. In addition, quinidine prolongs ventricular refractoriness. Finally, the anticholinergic effect of quinidine might contribute to its antiarrhythmic efficacy in the Brugada syndrome.15,16 Despite these hypotheses, the basis for quinidine efficacy in this setting remains to be elucidated.

**Quinidine-Related Side Effects**

Side effects were common during quinidine therapy (36% incidence). They usually appeared within the first month and in all instances resolved with drug discontinuation. As expected, diarrhea was an important side effect. In this regard, the resolution of quinidine-induced diarrhea without impairment of its EP effect in one patient after adjunction of cholestyramine is encouraging. The potential for QT prolongation and torsade de pointes has always been a cause for concern during quinidine therapy. The absence of organic heart disease in patients with Brugada syndrome and the predominance of male patients probably translate into lesser risk. Although proarrhythmia was never observed in our patients, close monitoring of the QT interval is warranted during initiation of therapy and periodically thereafter.

**Study Limitations**

The limited number of patients and the absence of a control group preclude definitive conclusions about the beneficial effects of quinidine in Brugada syndrome. However, the same is true for studies recommending ICD implantation. Only one study compared ICD implantation with drug therapy ($\beta$-blockers) in Brugada syndrome and found longer survival in the ICD group.17 However, the selection of $\beta$-blocker agents for the drug arm of the study was unfortunate because these drugs are well known to worsen the ECG features of Brugada syndrome.16

**Clinical Implications**

When the nonresponders and those subjects with intolerable side effects leading to drug cessation are taken into account, the success rate of quinidine may appear less impressive. However, we believe quinidine still deserves consideration as an alternative to ICD therapy in Brugada syndrome. On the basis of the results of the present study, the basic EP data by Antzelevitch,14 and the anecdotal reports of immediate resolution of arrhythmic storms by quinidine in patients with Brugada syndrome,11 randomized clinical trials comparing ICD therapy and quinidine seem warranted. Until such studies become available, we recommend the systematic testing of quinidine in patients with Brugada syndrome and inducible VF so that an informed choice can be made between drug therapy and ICD.

**References**


