Quinidine Revisited
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ABSTRACT
One of the earliest antiarrhythmic drugs developed, quinidine had a significant role in the treatment of many arrhythmias. After concerns for increased risk of ventricular arrhythmia and death with quinidine emerged, the use of quinidine fell dramatically in favor of newer antiarrhythmic medications. However, recent trials have generated renewed interest in the use of quinidine. In particular, quinidine appears to be safe and efficacious in combination with verapamil for the treatment of atrial fibrillation. Quinidine has also been used successfully to treat idiopathic ventricular fibrillation, Brugada syndrome, and Short QT syndrome. Although it is one of the oldest drugs in our armamentarium, quinidine continues to have a role in modern cardiology.

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First described in 1848 by Van Heymingen and named by Pasteur in 1853, quinidine has a long history as an antiarrhythmic. An alkaloid that may be derived from the cinchona tree bark and also prepared from quinine, quinidine prolongs the effective refractory period and reduces automaticity in the heart. It is, therefore, useful in the treatment of a wide variety of arrhythmias. The therapeutic qualities of quinidine, a class IA antiarrhythmic, do not come without hazards, however. The phenomenon termed “quinidine syncope” was first described in the 1950s, and it was later realized that quinidine could predispose patients to ventricular fibrillation. Subsequently, its use in the treatment of atrial fibrillation has dramatically decreased. However, there has been growing evidence to support its use in conditions such as idiopathic ventricular fibrillation, Brugada syndrome, and short QT syndrome. In addition, there is renewed interest in the combination of verapamil and quinidine for the treatment of atrial fibrillation.

ATRIAL FIBRILLATION
Quinidine is moderately efficacious in the acute conversion of atrial fibrillation to normal sinus rhythm.\(^1,3\) In addition, it is comparable to disopyramide, flecainide, propafenone, and sotalol in maintaining sinus rhythm.\(^2\) In comparison with placebo, class IA drugs had a favorable treatment difference of 21.5% compared with placebo, class IC drugs had a treatment difference of 33.1%, and class III drugs had a treatment difference of 17.4%.\(^4\) There was no mortality difference found between the drug classes, although most of the studies in this analysis had short follow-up periods.

CONCERNS OF QUINIDINE
The most common side effects of quinidine are gastrointestinal. Infrequently, quinidine can cause thrombocytopenia and agranulocytosis. In 1964, Selzer and Wray\(^5\) described a phenomenon that they coined “quinidine syncope.” They described patients who syncopized secondary to ventricular arrhythmias. The most characteristic feature of the attacks of ventricular fibrillation was their paroxysmal and repetitive nature. These attacks usually occurred within 1 to 3 hours after the last dose of quinidine and were usually sudden and seldom preceded by a warning prodrome.

Further concern about the use of quinidine for atrial fibrillation developed in the early 1990s. Coplen et al\(^6\) pooled data from 6 trials between 1970 and 1984 and

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constructed life table estimates of control groups and the patients still in sinus rhythm at 3, 6, and 12 months after cardioversion for quinidine. The pooled rate difference between the quinidine and control groups was 23% to 24% ($P < .001$ at all 3 time intervals), indicating that quinidine was more effective than no antiarrhythmic therapy in suppressing recurrences of atrial fibrillation. However, the odds of dying in the quinidine-treated group were 3 times higher than in the control group (odds ratio [OR] = 2.98, $P < .05$).

Southworth and colleagues’ meta-analysis in 1999 reiterated doubts about the safety of quinidine. Sotalol and quinidine were comparable in their ability to maintain sinus rhythm at 6 months (~50%), and both are superior to control (34%). However, there was a trend for both agents to increase mortality with long-term therapy. Mortality estimates were 2.2% for sotalol, 3.0% for quinidine, and 1.1% for control.

Most recently, the Cochrane Database pooled 45 studies to analyze the outcomes of antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. At 1 year of follow-up, class IA drugs (disopyramide, quinidine) were associated with increased mortality compared with controls (OR 2.39; 95% confidence interval [CI], 1.03-5.59, $P = .04$) and increased proarrhythmia. Quinidine alone demonstrated a nonsignificant but clear trend to increase mortality (OR 2.26; 95% CI, 0.93-5.45, $P = .07$). When missing patients were counted as deaths, the trend became significant (OR 2.29; 95% CI, 1.05-5.01, $P = .04$).

In addition to the concerns regarding the use of quinidine for atrial fibrillation, there was growing evidence of harm with its use in the treatment of ventricular arrhythmias. As the results of the Cardiac Arrhythmia Suppression Trial put an end to the use of class IC agents in patients with ventricular arrhythmias post-myocardial infarction, Moosvi et al demonstrated an increase in mortality with quinidine when used empirically for ventricular arrhythmias in this patient population. Similar concerns were raised in a meta-analysis comparing quinidine with flecainide, mexiletine, tocainide, and propafenone. The combined risk of dying while taking quinidine was significantly higher compared with the other 4 drugs. Proarrhythmia also was reported in 20 patients taking quinidine versus 11 patients taking the other 4 drugs ($P = .09$). Given the negative climate surrounding class I antiarrhythmics, quinidine use decreased dramatically. According to data from the National Ambulatory Medical Care Survey, the use of quinidine for maintenance of sinus rhythm decreased from 5.0% in 1991 and 1992 to 0.0% in 1999 and 2000.

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**REVIVAL OF QUINIDINE: ATRIAL FIBRILLATION**

Experimental and clinical data suggest that verapamil is able to suppress after-depolarizations produced by antiarrhythmic drugs of class I and III, which are likely to lead to torsades de pointes. The addition of verapamil also is desirable to avoid high ventricular rates during arrhythmia recurrences caused by enhanced atrioventricular conduction promoted by the vagolytic effect of quinidine.

The Prevention of Atrial Fibrillation after Cardioversion Trial (PAFAC) examined the fixed combination of quinidine and verapamil in comparison with sotalol and placebo in patients with persistent atrial fibrillation after DC cardioversion. A total of 848 patients with persistent atrial fibrillation who were successfully cardioverted were randomized to sotalol, quinidine plus verapamil, or placebo. After a mean follow-up of 266 days, there was no statistical difference in the recurrence rate between quinidine plus verapamil (65%) versus sotalol (67%). In addition, the recurrence rate for persistent atrial fibrillation was reduced with quinidine plus verapamil versus placebo (38% vs 77%). Adverse events while taking sotalol and quinidine plus verapamil were comparable with the exception that all 10 torsades de pointes episodes occurred while taking sotalol. Notably, 65% of all proarrhythmic and potentially life-threatening adverse events occurred during the first 4 days of treatment. This study suggested that the use of quinidine be reconsidered given the promising synergy with verapamil.

In the Suppression of Paroxysmal Atrial Tachyarrhythmias Trial (SOPAT), a fixed combination of quinidine and verapamil (480/240 mg/d or 320/160 mg/d) was found to be as effective as sotalol (320 mg/d) in reducing the recurrence rate of symptomatic paroxysmal atrial fibrillation. The combination prolonged the time to first recurrence of symptomatic paroxysmal atrial fibrillation and reduced the number of episodes of symptomatic paroxysmal atrial fibrillation compared with placebo.

SOPAT did demonstrate a low but definite risk of severe side effects. There were more deaths, syncope, and ventricular tachycardia events in the antiarrhythmic groups (placebo = 2, high-dose quinidine plus verapamil = 5, low-dose quinidine plus verapamil = 4, sotalol = 7). There were no cases of torsades de pointes reported throughout the trial.

So how does one interpret the data from PAFAC and SOPAT in comparison with the older trials with quinidine? Previous experiences with quinidine often involved the use of digoxin. Four of the 6 trials examined in the meta-analysis by Coplen et al were conducted before a quinidine–digoxin interaction was reported in 1978. It is now

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**CLINICAL SIGNIFICANCE**

- In combination with verapamil, quinidine is a relatively safe and effective alternative to sotalol and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation.
- Quinidine has been shown to prevent tachyarrhythmias and may prevent sudden cardiac death in patients with idiopathic ventricular fibrillation, Brugada syndrome, and short QT syndrome.
Table 1  Quinidine: Drug Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>70% from Gut</td>
</tr>
<tr>
<td>Peak plasma concentration</td>
<td>1-3 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>6-8 h (increased in liver or renal disease); longer with slow-release preparation</td>
</tr>
<tr>
<td>Protein binding</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly by liver via hydroxylation</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (15%-25% as unchanged drug)</td>
</tr>
<tr>
<td>Plasma levels for antiarrhythmic effects</td>
<td>2-5 μg/mL (3.5-5.5 μmol/L)</td>
</tr>
<tr>
<td>Notable drug interactions</td>
<td>Amiodarone, verapamil, and diltiazem may increase quinidine levels. Digoxin, metoprolol, propranolol, mexiletine, and nifedipine levels might be increased by quinidine. Warfarin effects might be increased by quinidine.</td>
</tr>
</tbody>
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recommended that digoxin dosage be reduced by 50% because quinidine significantly reduces the renal tubular secretion of digoxin (Table 1). Some of the arrhythmia-related deaths may have been due to digoxin toxicity.

Southworth and colleagues demonstrated a nonsignificant trend for mortality with long-term treatment. Of the 7 studies examined for quinidine, 4 were the same studies examined by Coplen and colleagues, which predated knowledge of the quinidine–digoxin interaction. The majority of deaths (9/15 patients) in the quinidine pool occurred in these older studies. Finally, the Cochrane database examined 7 studies pertaining to quinidine. Three studies were pre-1978, 2 studies were conducted in the 1980s with higher dose quinidine, and 2 studies were the PAFAC and SOPAT. Although one cannot deny that multiple studies have reported a trend for worse outcomes with quinidine, one should recognize that the absolute numbers are small, a number of studies acted as a common denominator in the meta-analyses, and improved knowledge of the drug–drug interactions of quinidine would likely have resulted in improved morbidity and mortality.

Because verapamil may prevent torsades de pointes induced by quinidine, the combination of quinidine with verapamil in PAFAC and SOPAT may account for the improved outcomes in these 2 studies. PAFAC and SOPAT also used lower doses of quinidine (320-480 mg/d vs 800-1800 mg/d) than in older studies. In a systematic review by Lafuente-Lafuente et al, a nonsignificant trend to increased mortality was seen with quinidine (OR = 2.26; 95% CI, 0.93-5.45; P = .07). However, when selectively pooling trials with adequate allocation concealment or those including more than 250 patients, there were only 2 trials that met criteria: PAFAC and SOPAT. Combined data from these 2 trials demonstrated no effect on mortality. Quinidine may therefore have a role as a drug in combination with verapamil in the maintenance of atrial fibrillation.

**IDIOPATHIC VENTRICULAR FIBRILLATION**

Quinidine may have a role in patients with idiopathic ventricular fibrillation with a normal resting electrocardiogram (ECG). Although the natural history of this patient population is not well defined, some studies suggest a high risk of recurrent major arrhythmic events. Among 34 patients with idiopathic ventricular fibrillation (5 of whom had classic ECG criteria for Brugada syndrome), sustained polymorphic ventricular tachycardia or ventricular fibrillation was induced in 27 patients (79%) at the baseline electrophysiologic study. Class IA drugs, primarily quinidine (in 25/27 inducible patients; dosed 1000 to 2000 mg/d), effectively prevented induction of polymorphic ventricular tachycardia or ventricular fibrillation in 26 of 27 patients. During a mean follow-up of 9.1 ± 5.6 years, none of the patients experienced a sustained symptomatic ventricular arrhythmia or sudden death. The mechanism by which quinidine suppresses ventricular tachycardia or ventricular fibrillation in patients with idiopathic ventricular fibrillation with a normal ECG is unknown. However, the fact that ventricular tachycardia and ventricular fibrillation can be induced reproducibly with programmed electrical stimulation in a substantial percentage of patients suggests a reentrant or triggered mechanism.

**BRUGADA SYNDROME**

Brugada syndrome was first described in 1992 and is characterized by a typical electrogram pattern (right bundle branch block and persistent ST-segment elevation in the right precordial leads) with the susceptibility for ventricular fibrillation and sudden cardiac death. It is a primary electrical disorder and may be responsible for up to 12% of all sudden deaths.

Quinidine is a useful agent in the treatment of Brugada syndrome. The use of quinidine in Brugada syndrome is justified in its action on the potassium currents, including Ito. Antzelevitch showed that the Ito current in the right ventricular epicardium plays a pivotal role in the pathogenesis of Brugada syndrome. The basis of the phase 2 reentry (trigger of the episodes of ventricular fibrillation) in Brugada syndrome is considered to be the loss of the action potential dome in the right ventricular epicardium, where Ito is more prominent. This is caused by an outward shift in the balance of currents, principally Ito and ICa, at the end of phase 1 of the action potential. The loss of this action potential plateau results in marked abbreviation of epicardial action potentials, transmural dispersion of repolarization, and susceptibility to phase 2 reentry. In animal models, agents that inhibit Ito exert an antiarrhythmic effect by restoring the action potential dome in the epicardium. Agents such as 4-aminopyridine, quinidine, and disopyramide inhibit Ito and therefore prevent ventricular tachycar-
dia/ventricular fibrillation by restoring the action potential dome and homogenizing repolarization. As molecular genetic observations have demonstrated mutations in the cardiac sodium channel SCN5A in families with Brugada syndrome, a reduction or loss of sodium channel activity may contribute to the ECG phenotype and susceptibility to ventricular tachycardia/ventricular fibrillation in patients with Brugada syndrome by leaving Ito unopposed, leading to loss of the epicardial action potential dome. Quinidine is the only agent available that has significant Ito-blocking properties.

The literature is increasing on the successful prevention and treatment of ventricular tachycardia/ventricular fibrillation in patients with Brugada syndrome using quinidine. Although quinidine only attenuated the Brugada ECG pattern in 3 of 25 high-risk patients examined by Belhassen et al.,35 quinidine prevented ventricular fibrillation induction at electrophysiologic study in 22 of 25 patients (88%). In addition, no symptomatic ventricular arrhythmias were documented in 19 patients receiving quinidine therapy after a mean follow-up of 56 months. Case reports also have documented successful treatment of ventricular tachycardia/ventricular fibrillation with quinidine in patients with Brugada syndrome.36-39 Last, low doses (300-600 mg/d) of quinidine also might be a useful adjunct for patients with Brugada syndrome with frequent implantable cardioverter defibrillator discharges.40

**SHORT QT SYNDROME**

The short QT syndrome was initially described in 1999 and is an inheritable primary electrical disease of the heart. Characterized by a QT less than 300 ms, patients with the short QT syndrome have increased risk of developing atrial fibrillation and sudden cardiac death. Reentry and life-threatening tachyarrhythmias associated with the syndrome are due to the shortening of the effective refractory period in combination with an increased dispersion of repolarization.

Mutations in the human ether-a-go-go gene have been described where IKr is dramatically increased, leading to heterogenous abbreviation of the action potential duration and refractoriness and rendering the channel relatively unresponsive to IKr blockers, such as sotalol and ibutilide.41 The increase of IKr results in a shortened QT/QTc, and thus an increase in the risk for sudden cardiac death. Kangaroos, who are known to have short QT intervals, are known for their high incidence of sudden cardiac death.42

Although cardioverter defibrillator implantation is the therapy of choice for patients with short QT syndrome, medical therapy is useful and revolves around normalizing the QT interval. In a study examining class IA, IC, and III antiarrhythmic drugs, only hydroxyquinidine produced a significant QT prolongation.41 Hydroxyquinidine produced a QT prolongation from 263 ± 12 ms to 362 ± 25 ms (calculated QT from 290 ± 13 ms to 405 ± 26 ms). Administration of hydroxyquinidine resulted in noninducibility of ventricular fibrillation on programmed ventricular stimulation. In short QT syndrome, quinidine may produce a re-equilibration of ionic currents, particularly via its ability to block the slow component of the delayed rectifier current IKs. Quinidine therefore suppresses the hyperfunctioning IKr responsible for some cases of short QT syndrome with a mutation in the human ether-a-go-go gene. The normal rate dependence of the QT interval is restored by quinidine and ventricular tachycardia, and ventricular fibrillation is rendered noninducible.43

**CONCLUSIONS**

Although the use of quinidine has declined substantially over the last 2 decades, there is cause for renewed interest in its use. In patients with structurally normal hearts and highly symptomatic atrial fibrillation, maintenance of sinus rhythm with quinidine in combination with verapamil is a viable option. Quinidine also has a role in the prevention of tachyarrhythmias and sudden cardiac death in patients with idiopathic ventricular fibrillation, Brugada syndrome, and short QT syndrome. One of the earliest antiarrhythmic drugs, quinidine still has a role in tachyarrhythmias. Used carefully in the appropriate patient populations, quinidine is a reasonably safe and effective antiarrhythmic drug.

**References**


