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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.

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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

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'[7] 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[8] 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[9] put an end to the use of class IC agents in patients with ventricular arrhythmias post-myocardial infarction, Moosvi et al[10] 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[11] 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.[12]

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.

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.[13-16] 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.[17,18]

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.[19] 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.[20] 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.[21]

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[6] were conducted before a quinidine–digoxin interaction was reported in 1978.[22] It is now