Editorial Comment

Quinidine
Worse Than Adverse?

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In this issue of Circulation, Morganroth and Goin\(^1\) present a meta-analysis that indicates a higher mortality and proarrhythmic rate for patients on quinidine than on four other antiarrhythmic drugs considered as a group, of which one (flecainide) has been proven to have and one (mexiletine) has been strongly suspected of having a higher mortality rate than placebo therapy when used for the suppression of premature ventricular contractions.

See p 1977

Background

Quinidine

Quinidine is the oldest class I antiarrhythmic drug available. Its current indications are “the prevention and/or treatment of ... premature atrial contractions, ... AV junctional premature complexes, ... premature ventricular contractions, ... paroxysmal atrial tachycardia, ... atrial fibrillation, ... atrial flutter, ... paroxysmal junctional tachycardia, ... and ventricular tachycardia.”\(^2\) The proarrhythmic potential of quinidine has been known for years.\(^3\)–\(^5\) Sometimes called “quinidine syncope,” this proarrhythmia has been recognized to be due to a potentially fatal polymorphic form of ventricular tachycardia: torsades de pointes. Reports of the occurrence of proarrhythmia from quinidine led some to recommend that the QT interval be carefully observed when initiating quinidine even though the QT prolongation does not always correlate with the incidence of proarrhythmia\(^4\) and that treatment be initiated in the hospital even though proarrhythmia on quinidine is not dose related and can occur more than a few days after starting therapy.\(^3\)–\(^5\) Thus, even when observing these guidelines for treatment, it is likely that outpatient proarrhythmic events will occur. Despite the proarrhythmic potential of quinidine and the problem of detecting patients with this side effect, the use of quinidine has remained high. As emphasized by Morganroth and Goin, quinidine has been the leading antiarrhythmic drug in the United States for the last 5 years, accounting for 44% of antiarrhythmic drug prescriptions between June 1989 and June 1990.

Other Class I Antiarrhythmic Drugs

The class Ic drugs have the most serious questions related to their safety. In 1989, a report from the Cardiac Arrhythmia Suppression Trial (CAST) announced the withdrawal of encaïnide and flecainide from the study because of the increased mortality rate of patients on these drugs compared with double-blind, randomized placebo therapy (relative risk, 3.6; \(p=0.0003\)) when used for nonsustained ventricular arrhythmia after myocardial infarction.\(^6\) Of note, CAST was designed as a treatment trial rather than a specific antiarrhythmic drug trial; provisions were made in the original protocol design for the substitution of new drugs if the original drugs were withdrawn. In 1989, extensive discussions regarding substitute therapies occurred at the steering committee meetings of CAST. Although quinidine was the leading candidate for substitution by the steering committee, the drug was not added to the trial. The conversations of the steering committee regarding quinidine were quite revealing, the group being passionately divided between those strongly opposed to including quinidine because of its proarrhythmic potential and those strongly in favor of including quinidine because of its high-volume usage (personal observations).

In addition to CAST, there have been a number of other randomized antiarrhythmic drug trials for treatment of nonsustained ventricular arrhythmia, as compiled by Furberg and presented in a recent review by Anderson.\(^7\) Overall, class Ic drugs have been administered to over 1,200 patients with a comparable number on placebo: The overall odds ratio for mortality is 1.33 (\(p=0.09\)) in favor of death on active therapy.

The class Ib agents have also been called into question by Furberg’s summary. Over 6,100 patients have been randomized to Ib active therapy and a comparable number to blinded placebo. Again, the odds ratio for death on active therapy is 1.29 (\(p=0.02\)).

However, there is no apparent trend in Furberg’s summary for class Ia antiarrhythmic drugs, although...
over 1,600 patients received active therapy and a similar number received placebo. These trials result in an odds ratio of 1.04 \((p=0.78)\). Most of the trials of class Ia antiarrhythmic drugs were small, older, and used different enrollment criteria than more recent trials. Even so, at best, there is no benefit from Ia drug therapy for nonsustained ventricular arrhythmia.

An overall meta-analysis of long-term class I antiarrhythmic therapy after myocardial infarction was done by Hine et al.\(^8\) This meta-analysis of 10 randomized trials showed a significant adverse effect for antiarrhythmic therapy with a risk difference of 1.38 \((p<0.05)\). Moosvi et al\(^9\) performed a retrospective study of 209 patients treated at their hospital after successful resuscitation from out-of-hospital cardiac arrest in the years before electrophysiological study \((1975–1982)\). The 2-year survival rates for quinidine, procainamide, and untreated patients were 61%, 57%, and 71%, respectively \((p<0.05)\), suggesting an increased frequency of death (and sudden death, \(p<0.01)\) for patients on antiarrhythmic therapy. Recently, the BASIS study, a randomized trial of patients with nonsustained ventricular arrhythmia after myocardial infarction, compared individualized antiarrhythmic therapy (class I drugs for 95% of the group), low-dose amiodarone and placebo: Mortality rate for patients on class I drugs was similar to that of placebo, whereas mortality rate for patients treated with amiodarone showed a significant reduction \((p<0.01)\).\(^10\)

At this point, it is unlikely that new randomized mortality trials will be done in low- to intermediate-risk patients with nonsustained ventricular arrhythmia, leaving some uncertainty regarding the safety of some class I drugs. However, the above meta-analyses provide growing evidence that extrapolation from the CAST findings should be widely applied.

In support of the widespread applicability of CAST, Coplen et al\(^11\) performed a meta-analysis of quinidine compared with placebo for chronic prevention of atrial fibrillation after an episode of this arrhythmia. In this compilation of 808 patients, quinidine was more effective than placebo for maintaining sinus rhythm but resulted in a threefold increased mortality rate compared with placebo \((\text{odds ratio}, 2.98; p<0.05)\).

### The Morganroth and Goin Study

In this issue of Circulation, Morganroth and Goin provide further evidence that quinidine is associated with a high risk of proarrhythmia.\(^1\) Their study was possible because, over the last decade, quinidine has been used as the reference agent in many new antiarrhythmic drug trials. These investigators, in their literature search, found four parallel-designed, randomized blinded comparison trials of quinidine with new antiarrhythmic drug therapy. The experimental designs of these studies were similar enough to allow combining them. All were treating patients with nonsustained ventricular arrhythmias. In these four studies, the reference agents were flecainide (definitively associated with increased mortality rate compared with placebo in CAST\(^6\)), mexiletine (strongly suspected of having increased mortality rate \(^7,13\)), tocainide (safety suspect by meta-analysis, similarity with mexiletine, and reports of proarrhythmia\(^7,13,14\)), and propafenone (suspect because of its similarity to encainide and flecainide and because of reported proarrhythmia\(^15\)).

Morganroth and Goin found that there were 12 deaths on quinidine and four on the comparison drugs \((p=0.05)\). All the deaths were probably arrhythmic except two: One of the two was classified as myocardial infarction and the other as CAD, a term possibly associated with an episode of sudden death by a coroner. In addition, these investigators found 20 episodes of nonfatal proarrhythmia in patients on quinidine compared with 11 patients on the comparison agents \((p=0.09)\). The risk difference for quinidine versus other drugs was 0.16 and the odds ratio was 3.08 for death for patients on quinidine compared with other drugs.

Other antiarrhythmic drug trials comparing quinidine with other agents were designed as crossover studies. These were appropriately excluded by the investigators. Unfortunately, one of these was a large study comparing encainide with quinidine.\(^16\) A parallel design for that trial might have had substantial influence on the meta-analysis.

Of interest, Morganroth and Goin also looked at events during the placebo periods in the four included trials. During an approximately equal period of exposure, there was one death on placebo, one death on mexiletine, and six on quinidine.

Thus, this meta-analysis indicates that quinidine is more likely to produce fatal and nonfatal proarrhythmia than other drugs that are already known to have a greater risk of proarrhythmia than placebo. Is the most commonly used antiarrhythmic drug in the United States “worse than adverse”?\(^1\)

### Meta-Analysis

The purpose of meta-analysis is to combine similar trials that do not independently show a treatment effect, in an effort to overcome limitations of small sample size. When performing meta-analysis, it is important that the criteria for proper conduct of this technique be maintained.\(^17,18\) Although the study by Morganroth and Goin is atypical in that the comparison is made with other antiarrhythmic drugs rather than with placebo and that the comparison antiarrhythmic drugs differ in the trials, the analysis is otherwise performed by using conventional methodology. One possible flaw in the study design is the exclusion of unpublished data. It is generally known among investigators in this field that other multicenter trials have compared new class I antiarrhythmic agents with quinidine. These unpublished trials in some cases include drugs not currently approved for clinical use. However, access to these data may be feasible by request to the pharmaceutical companies sponsoring these studies. The impact of these trials on the meta-analysis is unknown.
Implications

For the treatment of nonsustained ventricular arrhythmia in patients with structural heart disease (potentially lethal arrhythmias as defined by Morganroth and Bigger19,20), encaidine and flecainide have been clearly proven to be harmful in CAST and are thus contraindicated. There are no controlled trials demonstrating reduction in mortality on any antiarrhythmic drug. Meta-analyses have strongly implicated mexiletine as well as other Ic and Ib drugs. The Morganroth and Goin trial adds further doubt about the class Ia group, of which quinidine is a member. This Ia agent appears to have an even higher proarrhythmic potential than those in classes Ib and Ic. Thus, at this time, class I drugs are either unsafe or have unknown safety: None have been shown to be beneficial. Treatment is not indicated with any class I agent for suppression of nonsustained ventricular arrhythmia.

Can we extrapolate from the studies of suppression of nonsustained ventricular arrhythmia to management of atrial arrhythmias? Coplen’s meta-analysis of quinidine for atrial fibrillation implies that we can and should.11 At this time, a reasonable approach for patients with a first episode of atrial fibrillation in whom restoration of sinus rhythm will be attempted is use class I drugs temporarily to attempt chemical cardioversion in a hospital setting with electrocardiographic monitoring and then to discontinue the drug regardless of whether sinus rhythm is restored. If recurrent atrial fibrillation occurs frequently, the decision to use long-term class I antiarrhythmic drug therapy to suppress recurrent episodes of atrial fibrillation must be made with consideration of the potential risk of fatal ventricular proarrhythmia. If the atrial fibrillation is particularly disabling or life endangering, therapy might have a favorable risk-to-benefit ratio. For infrequent or mildly symptomatic atrial fibrillation, the risk of long-term class I antiarrhythmic drug therapy probably exceeds the potential benefit. Consideration of other approaches for control of atrial fibrillation should be made, including amiodarone, ablation of the atrioventricular node, and surgical techniques for interruption of atrial fibrillation.

Although treatment of patients who have incurred an episode of sustained ventricular tachyarrhythmia seems imperative and empirical trials of class I antiarrhythmics have suggested a benefit in this patient group,2 it is important to remember that no placebo-controlled treatment trials have been performed in this patient group. It is possible that controlled trials of class I drugs in this patient group might also show an adverse treatment effect, although placebo-controlled trials are not ethically feasible. Amiodarone and implantable devices are also frequently used for patients with sustained ventricular arrhythmias. The relative efficacy of these three approaches is unproven, and controlled trials comparing these treatment options in this patient group are necessary.

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References


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