Editorial Comment

Atrial Fibrillation
Is There a Safe and Highly Effective Pharmacological Treatment?

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Recent large-scale studies of the efficacy and safety of antiarrhythmic drugs in certain arrhythmias have demonstrated a significantly increased risk of death in the drug-treated patients. One such study is the highly publicized Cardiac Arrhythmia Suppression Trial (CAST) in which the flecainide and encainide limbs were discontinued at 10 months because of a nearly threefold increase in mortality compared with placebo. This increased mortality did not correlate with any other specific risk factor but was presumably due to ventricular proarrhythmia, a complication known to occur with these drugs. The results of this study have caused significant changes in the manner in which premature ventricular contractions and nonsustained ventricular tachycardia are treated in this patient population and suggest the need for a concerted reevaluation of this problem.

Two studies recently published in Circulation, one in this issue by Juul-Moller et al and one in a previous issue by Coplen et al, suggest that a reevaluation of the standard approach to the pharmacological suppression of atrial fibrillation is also warranted, from the standpoints of both drug efficacy and safety.

The study by Coplen et al is a meta-analysis of six independent, double-blind, placebo-controlled studies of quinidine in 800 patients with a history of chronic atrial fibrillation undergoing direct current cardioversion. In this meta-analysis, the efficacy of quinidine in preventing recurrence of atrial fibrillation after cardioversion (50% at 12 months) was significantly greater than that of placebo (25%). However, the authors noted that the unadjusted mortality in the quinidine-treated group was 2.9% compared with 0.8% in the placebo control group, equal to a threefold greater risk of dying in those receiving quinidine (odds ratio, 2.89; p<0.05). Of the seven patients in whom a cause of death was known, three experienced sudden deaths. The authors also noted that two additional patients, who were not included in the statistical analysis, had sudden death after receiving quinidine. None of the three deaths in the placebo group was sudden. These results are strikingly similar to those reported in CAST for the increased risk of dying associated with encaïné and flecainide. The mechanism of sudden death in these studies is unknown, although it is presumably due to proarrhythmia. The type of proarrhythmia produced by quinidine may differ from that of encaïné or flecainide because quinidine may cause torsade de pointes, whereas encaïné or flecainide is more likely to cause sustained or incessant monomorphic ventricular tachycardia.

The data from the meta-analysis study of Coplen et al, like those from another meta-analysis study by Hine et al and from CAST, suggest that a serious increased risk of mortality may occur with the use of many of the class I antiarrhythmic drugs, in patients both with and without underlying heart disease and in those with atrial or ventricular arrhythmias. This risk must therefore be carefully weighed by the physician in relation to the anticipated benefit from and likelihood of arrhythmia suppression before treating a patient with a class I antiarrhythmic drug. The patient should probably also be informed before treatment of the possible increased risk of death from these drugs, in addition to their other frequently reported side effects, so an informed decision can be made as to whether to take the medication. The benefits of suppression of atrial fibrillation primarily derive from the elimination of associated symptoms, which may include palpitations, weakness, syncope, aggravation of heart failure, angina, or, in more extreme cases, myocardial infarction, cerebrovascular accident, or death. Furthermore, suppression of atrial fibrillation may eliminate the need for warfarin-induced anticoagulation and its potential hemorrhagic complications, which would otherwise be prescribed to prevent the embolic complications of recurrent atrial fibrillation. As Coplen et al point out, these benefits may outweigh a 3% annual risk of death from quinidine. Unfortunately, at present the decision to treat remains empiric, without

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conclusive data defining the overall risk-to-benefit ratio. Whether the use of other class Ia antiarrhythmic drugs (e.g., disopyramide) would impart a similar increased risk of death is unknown, although their efficacy in suppression of atrial fibrillation is probably similar to that of quinidine. A recent study of the class Ic drug flecainide suggests that it has a slightly greater efficacy than quinidine in preventing recurrences of atrial fibrillation in similar patients. However, in addition to their potential for causing ventricular proarrhythmia, the class Ic drugs flecainide and encainide have also been shown to produce up to a 10% incidence of atrial proarrhythmic effects, including conversion of atrial fibrillation to atrial flutter and slowing of atrial rate, resulting in dangerous acceleration of ventricular rate due to 1:1 atrioventricular nodal conduction.

These recent reports of the potential for serious proarrhythmia and increased risk of sudden death from the class I antiarrhythmic drugs will likely lead to an increased interest in the potential efficacy and safety of the newer class III antiarrhythmic drugs. It has been previously shown that the class III drug amiodarone, although electrophysiologically complex, is highly effective in preventing recurrence of atrial fibrillation. Unfortunately, its potential toxicity even at low dose (i.e., <600 mg/day) often limits its use for long-term therapy. In contrast, other class III drugs such as sotalol or N-acetylclopropiamide produce less serious toxicity and have been shown to be effective in the treatment of atrial fibrillation in humans. The study of Juul-Møller et al. assesses the efficacy and safety of the class III antiarrhythmic drug sotalol compared with quinidine in the suppression of atrial fibrillation after direct current cardioversion. The study population comprised 183 patients with chronic atrial fibrillation with or without underlying heart disease. The dosages for sotalol and quinidine (slow-release tablet) were 80 or 160 mg b.i.d. and 600 mg b.i.d., respectively. The drugs were administered in an open-label, randomized fashion. The primary efficacy of sotalol was comparable to that of quinidine, with 52% of patients receiving sotalol and 48% of patients receiving quinidine remaining in sinus rhythm at 6 months of follow-up. Of particular interest is that patients who relapsed into atrial fibrillation while on sotalol (34%) had significantly slower ventricular responses (78 versus 109 beats/min, respectively) than those who relapsed while on quinidine. Furthermore, sotalol appeared to have a significantly better side effect profile than did quinidine. Only 11% of patients were withdrawn from sotalol due to adverse effects, whereas 27% were withdrawn from quinidine (p < 0.05). Only 28% of patients receiving sotalol had side effects compared with 50% of those receiving quinidine (p < 0.01). These characteristics of sotalol represent significant advantages over quinidine. Although no deaths were directly related to sotalol or quinidine in this study, ventricular proarrhythmia did occur with torsade de pointes in one patient receiving sotalol and ventricular fibrillation in one patient receiving quinidine. Whether sotalol will produce as great a risk of sudden death as reported by Coplen et al for quinidine is unknown and will require further large-scale study in patients with atrial fibrillation.

Although the data of Juul-Møller et al suggest that sotalol is no more effective than quinidine in preventing recurrences of atrial fibrillation, the authors acknowledged that nearly half of the patients were receiving only 80 mg b.i.d. sotalol rather than 160 mg b.i.d. The decision regarding dosage was based solely on the clinical judgment of the patient’s physician that the patient was adequately β-blocked at the lower dose. Despite the fact that equal numbers of patients relapsed at each dose level, it is entirely possible that some patients who relapsed on the lower dose might not have done so at the higher dose. If this were the case, sotalol might have had a better efficacy in suppression of atrial fibrillation than quinidine. Thus, further study of the efficacy and safety of sotalol in the suppression of atrial fibrillation, particularly at the higher dose of 160 mg b.i.d., appears warranted, and such a study is in progress in the United States.

Thus, these two studies on the effects of quinidine and sotalol suggest that the use of currently available class I antiarrhythmic drugs in the pharmacological suppression of atrial fibrillation must be carefully reevaluated. It is possible that newer class III antiarrhythmic drugs such as sotalol may be safer and more effective, but a large-scale, double-blind, placebo-controlled study will be required.

References


(Circulation 1990;82:2248–2250)
Atrial fibrillation. Is there a safe and highly effective pharmacological treatment?

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*Circulation.* 1990;82:2248-2250
doi: 10.1161/01.CIR.82.6.2248

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/6/2248.citation

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