Effect of Verapamil on Prevention of Atrial Fibrillation in Patients Implanted with an Implantable Atrial Defibrillator

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Summary

Background: The role of verapamil in the prevention of atrial fibrillation (AF) in patients with recurrent AF is unknown.

Hypothesis: The aim of this study was to evaluate the effect of verapamil on the prevention of AF in patients implanted with an implantable atrial defibrillator (IAD).

Methods: The effects of verapamil (240 mg/day) on the total duration of AF, number of AF recurrences, and number of cardioversions were prospectively evaluated in a randomized, crossover fashion over an 8-week period in 11 patients (9 men, 2 women; mean age: 60 ± 6 years) implanted with an IAD.

Results: Implantable atrial defibrillators successfully converted 13 of 14 (93%) spontaneous episodes of AF. There was no significant difference in the efficacy of cardioversion (86 vs. 100%, $p = 0.8$), the total duration of AF (173 ± 198 vs. 270 ± 241 h, $p = 0.5$), the number of AF episodes (8.5 ± 9.0 vs. 9.3 ± 10.2 , $p = 0.3$), and the number of cardioversions (1.7 ± 2.4 vs. 1.8 ± 2.1 , $p = 0.7$) with or without treatment with verapamil.

Conclusions: The results of the present study suggest that treatment with verapamil has no significant effect on the prevention of AF in patients treated with an IAD.

Key words: verapamil, atrial fibrillation

Introduction

Recent studies in animals and humans suggest that atrial fibrillation (AF) induced changes in electrical and mechanical

properties of the atrium, which in turn facilitate the maintenance and recurrence of AF.^{1–4} These changes in atrial properties appear to be mediated by cellular calcium overload and can be blunted by verapamil.^{3–6} The implantable atrial defibrillator (IAD) is an effective device for the detection and documentation of AF episodes.^{7–10} The purpose of this study was to evaluate prospectively the effect of verapamil on the efficacy of cardioversion and the total AF burden in patients implanted with an IAD for recurrent AF.

Methods

Study Population

The study population consisted of 9 men and 2 women (mean age 60 ± 6 years) who were treated with an IAD for symptomatic, recurrent AF. All patients had symptomatic AF (mean AF duration: 32 ± 39 months) before implantation of IAD and were subsequently maintained in sinus rhythm by repeated cardioversion with IAD. Five patients had no cardiovascular disease and six patients had hypertension. Before IAD implant, each patient had recurrences of AF despite treatment with a class I or III antiarrhythmic drug. Mean left ventricular ejection fraction was 0.54 ± 0.1 , and mean left atrial diameter by echocardiography was 4.5 ± 0.7 cm.

Implantable Atrial Defibrillator System

A previously described IAD (Guidant, St. Paul, Minn., models 3000, 3020) was used.^{7–10} In brief, the IAD performed atrial sensing and defibrillation between the right atrial and coronary sinus coil electrodes from either a single-pass lead or from two separate leads. A standard bipolar endocardial ventricular pacing lead was used for R-wave synchronization and ventricular pacing. The intracardiac atrial and ventricular electrograms were used in specific algorithms for AF detection and R-wave synchronization.⁹ The device stored data on the date and time of the onset of episodes of AF, the duration of the 170 most recently detected AF episodes, and the atrial and ventricular intracardiac electrograms from the 6 most recently identified episodes of AF. The IAD delivered R-wave synchronized, 3/3 ms or 6/6 ms, biphasic shock with a maximum output of 300 V (Guidant, models 3000 and 3020).

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Study Protocol

The study protocol was approved by the local ethics committee, and written informed consent was obtained from each patient. Patients were randomized to receive verapamil 240 mg/day in a crossover fashion for 8 weeks, while their antiarrhythmic agents (amiodarone: 5, sotalol: 2) were kept constant. There was a 2-week washout period between the crossover from each treatment arm. Throughout the study, the IAD was programmed to monitor mode when patients were outside the hospital, as described previously.⁷⁻¹⁰ In the monitor mode, the device stored episode data, but did not deliver shocks. The device was programmed to "wake up" every 120 min for AF detection and the episode data were stored in the device. Patients were instructed to come to the hospital or clinic for each episode of symptomatic AF. All symptomatic AF episodes were confirmed with the device data log. The device's shock therapy was delivered by the physician for those AF episodes that persisted during the time of assessment in the hospital or clinic. Sedation was administered by intravenous midazolam at the request of the patient.

The device's episode log was used to document the duration and number of AF episodes with an accuracy of ± 2 h. An AF episode detected during only one sensing interval was defined as persisting for 2 h, but actually may have persisted from 1 min to 3 h and 59 min. The longest single episode of AF that could be recorded with this device was 340 h. If 170 AF episodes were detected, then the episode was defined as lasting 340 h. However, this observation could have been due to paroxysmal episodes of AF that were present during each sensing interval. In addition, in this instance, the episode may have persisted beyond 340 h.

Statistical Analysis

Continuous variables are expressed as mean ± 1 standard deviation. Statistical comparisons were performed with a paired Student's *t*-test. The time interval to recurrence of symptomatic AF episodes was estimated by the Kaplan-Meier method and was compared by using the log-rank test. *P* values < 0.05 were considered to be statistically significant.

Results

Treatment of Spontaneous Episodes of Atrial Fibrillation

Nine patients (71%) received IAD therapy for spontaneous symptomatic AF episodes during the study period. The IAD successfully converted 13 of 14 (93%) spontaneous episodes of AF with a mean of 1.7 ± 2.1 shock per episode. There was no significant difference in efficacy of cardioversion during treatment with or without verapamil (6/7 episodes, 86% vs. 7/7 episodes, 100%, $p = 0.8$). The mean number of atrial defibrillation shocks given for cardioversion was similar during treatment with or without verapamil (1.7 ± 2.4 vs. 1.8 ± 2.1 , $p = 0.6$).

Atrial Fibrillation Recurrence

In all, 120 AF episodes were detected during the entire study period. The mean number of AF episodes (8.0 ± 8.0 vs. 9.1 ± 10.8 , $p = 0.8$), the mean duration of AF episodes (44 ± 84 vs. 45 ± 87 h, $p = 0.9$), and the total duration of AF (418 ± 511 vs. 586 ± 409 h, $p = 0.5$) documented by the IAD within an 8-week period were not significantly different in these seven patients between treatment with or without verapamil.

For the symptomatic AF episodes, there were also no significant differences in the arrhythmia-free time interval for the first (median AF free interval: 262 vs. 114 h, $p = 0.1$) and second episodes (median AF free interval: 130 vs. 104 h, $p = 0.2$) of AF recurrence with or without treatment with verapamil (Fig. 1).

Discussion

Despite the use of antiarrhythmic therapy, the recurrence rate of AF after successful cardioversion in patients with persistent AF remains high.¹¹⁻¹³ Prior animal and human studies have shown that AF induces changes in the electrophysiologic and mechanical properties of the atria, which may account for an increased vulnerability for recurrence of AF after car-

FIG. 1 Kaplan-Meier analysis comparing the recurrence of the first (A) and the second (B) episodes of atrial fibrillation between during no treatment (■) and during treatment with verapamil (△).

dioversion.¹⁻⁴ Although the underlying mechanisms of these AF-induced electrophysiologic and mechanical changes are unknown, intracellular calcium overload appears to play an important role. Recent studies have demonstrated that pretreatment with verapamil can significantly blunt the electrophysiologic and mechanical changes caused by rapid atrial pacing or short episodes of artificially induced AF.⁴⁻⁶ Prior studies also suggested that use of calcium-channel blocking agents during AF appeared to reduce recurrence.¹⁴⁻¹⁶

To our knowledge, this is the first study prospectively evaluating the effect of verapamil on AF recurrence in patients with persistent AF treated with an IAD. It is likely that after a long period of AF, in addition to electrophysiologic and mechanical changes related to calcium overloading, genetic, morphologic, and further electrophysiologic changes occur.¹⁷⁻¹⁹ Therefore, oral verapamil had no significant effect on the total burden of AF in patients with a history of long-standing AF, who may have already developed structural disease in the atrium. Furthermore, the continuation of other antiarrhythmic medication, specifically amiodarone, which has a marked calcium-channel blocking effect, may reduce the impact of verapamil on the prevention of AF.

Limitations

The major limitation of this study is the fact that the IAD was programmed to detect AF every 2 h. Depending on when the AF episode occurred relative to the timing of AF detection, some episodes of AF and early reinitiation of AF after cardioversion may not have been sensed, while multiple episodes may have been defined as a single episode. Because of this device limitation, the duration and number of episodes may have been over- or undercounted. The small number of patients enrolled and the crossover design of the study are limitations. The present study may not have sufficient power to demonstrate a small significant benefit of verapamil on prevention of AF, and the actual effect of verapamil on the efficacy of cardioversion cannot be clearly assessed. Therefore, further study on the effect of verapamil on the incidence of AF in a greater patient group, using more adequate diagnostic devices with continuous detection and documentation of the AF burden, will be desirable.

Conclusions

The results of the present study suggest that in patients treated with an IAD, treatment with verapamil does not affect the efficacy of the device's therapy, and has no significant effect on the total AF burden as assessed by the mean number of AF episodes, the mean duration of AF episodes, and the total duration of AF as documented by the IAD.

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