JACC Vol. 18, No. 4
October 1991:891–7

COOPERATIVE STUDIES

A Placebo-Controlled Trial of Continuous Intravenous Diltiazem Infusion for 24-Hour Heart Rate Control During Atrial Fibrillation And Atrial Flutter: A Multicenter Study

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The safety and efficacy of a 10- to 15-mg/h continuous infusion of intravenous diltiazem were evaluated in 47 patients with atrial fibrillation or flutter who first responded to 20 mg or 20 mg followed by one or more 25-mg bolus doses of open label intravenous diltiazem. Of the 47 patients, 44 responded to the bolus injection and were randomized under double-blind conditions to receive either a continuous infusion of intravenous diltiazem (10 to 15 mg/h) (23 patients) or placebo (21 patients) for up to 24 h.

Seventeen (74%) of the 23 patients receiving diltiazem infusion and none of the 21 with placebo infusion maintained a therapeutic response for 24 h ($p < 0.001$). Over 24 h, patients receiving diltiazem infusion lost response significantly more slowly than did those receiving placebo infusion ($p < 0.001$). Nonresponders to the double-blind infusion were given an additional bolus injection of open label intravenous diltiazem and administered an open label 24-h intravenous diltiazem infusion. The overall proportion of patients maintaining a response to a 24-h infusion of intravenous diltiazem under double-blind or open label conditions combined was 83% (34 of 41).

Efficacy of the 24-h infusion of intravenous diltiazem was similar in elderly versus young patients, those who did versus those who did not receive digoxin and those weighing <84 versus ≥84 kg. However, intravenous diltiazem appeared to be more effective in atrial fibrillation than in atrial flutter. No significant untoward effects were noted.

A bolus dose or doses followed by a 24-h continuous infusion of intravenous diltiazem can be safely administered to patients with atrial fibrillation or flutter and can rapidly and effectively achieve and maintain heart rate control in most patients. Intravenous diltiazem can serve as a therapeutic bridge in patients with these atrial arrhythmias awaiting initiation or onset of action of long-term antiarrhythmic therapy or cardioversion.

(J Am Coll Cardiol 1991;18:891–7)

Diltiazem is a calcium channel blocking agent that has been used for the treatment of angina pectoris and systemic hypertension (1,2). It has been shown to have chronotropic and dromotropic effects (3) and on the basis of these electrophysiologic properties, intravenous and oral diltiazem have been used for the short- and long-term treatment of a variety of supraventricular arrhythmias (4–11).

Atrial fibrillation and atrial flutter are common sustained arrhythmias occurring in patients with cardiac and pulmonary disease (12). In some patients with these arrhythmias, the ventricular response may be rapid and accompanied by an exacerbation of angina or heart failure. An intravenous diltiazem infusion that is safe and achieves rapid reduction of ventricular response would be useful before initiation of definitive antiarrhythmic therapy or electrical cardioversion to sinus rhythm. The purpose of this multicenter investigation (see Appendix) was to demonstrate the safety and efficacy of a continuous intravenous diltiazem infusion for 24-h heart rate control in patients with atrial fibrillation or flutter.

Methods

The protocol was approved by the Investigational Review Board at each of the five participating medical centers (see Appendix). Each patient gave written informed consent before entry into the study. Patients were enrolled in the study between August 1987 and October 1988.

Study patients. Patients were included in this study if they were >18 years of age and had established atrial fibrillation or atrial flutter with a duration >24 h. The ventricular rate (documented by electrocardiogram [ECG]) had to be ≥120 beats/min over a 15-min baseline period before the study drug was given. Atrial fibrillation was defined by the absence of discrete regular atrial activity; atrial flutter was diagnosed by the presence of discrete flutter waves.

Exclusion criteria included severe congestive heart fail-

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Manuscript received December 12, 1990; revised manuscript received February 6, 1991, accepted April 20, 1991.

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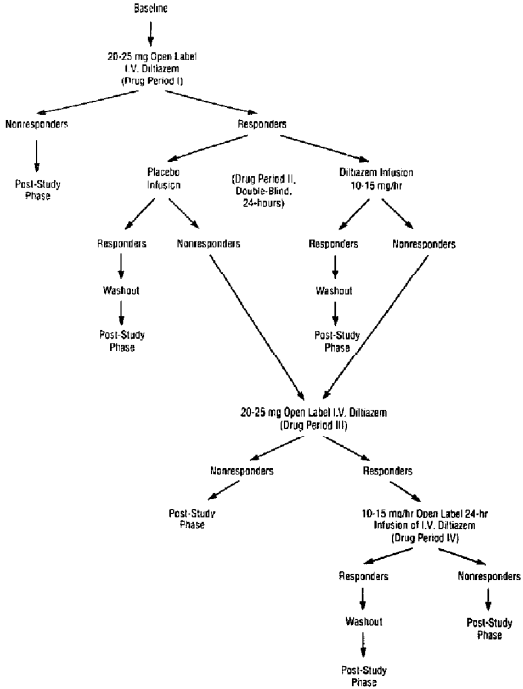


Figure 1. Flow chart of the study design. I.V. = intravenous.

ure (New York Heart Association class III or IV), history of sinus node dysfunction, second- or third-degree atrioventricular (AV) block, Wolff-Parkinson-White syndrome, hypotension with a systolic blood pressure <90 mm Hg, history of allergy or idiosyncratic reaction to diltiazem, clinically significant abnormalities of other organ systems or multifocal atrial tachycardia. No calcium channel blocking agents, type IA or IC antiarrhythmic agents (for example, quinidine, procainamide, flecainide, encainide), amiodarone or a beta-adrenergic blocking agent was given within 5 elimination half-lives before administration of the study drug. Patients who received digoxin preparations before study entry were not excluded provided the dosage was constant over the preceding 1 week and they had no evidence of digitalis intoxication.

Study design (Fig. 1). This was a randomized, double-blind, parallel, placebo-controlled study. Before entry into the study, a medical history was taken and a physical examination performed. If the baseline ECG continued (≥15 min) to confirm the presence of atrial fibrillation or flutter with a mean ventricular rate ≥120 beats/min, the patient was given a 20-mg bolus dose of open label intravenous diltiazem over 2 min (drug period I). Patients who did not have a therapeutic response, defined as a decrease in heart rate to <100 beats/min, ≥20% decrease in heart rate from baseline or conversion to normal sinus rhythm within 15 min, were given a second 25-mg bolus dose of intravenous diltiazem over 2 min and monitored again for a therapeutic response over the next 15 min. Patients who did not have a satisfactory therapeutic response to either dose were entered into the poststudy phase.

Patients who had a therapeutic response during drug period I received under double-blind conditions a 24-h continuous infusion of intravenous diltiazem or placebo at a rate of 10 mg/h (drug period II). An increase in the infusion rate from 10 to 15 mg/h was permitted at any time if the patient lost response while receiving the 10-mg/h infusion. An increase in the infusion rate from 10 to 15 mg/h was permitted before 4 h if response was maintained but a further reduction in heart rate was desired. Patients were observed every 30 min for a therapeutic response while at rest for ≥5 min. Heart rate and rhythm were obtained from 1-min ECG rhythm strips. Heart rate was also obtained from a 48-h Holter monitor.

Patients were considered to have maintained a therapeutic response (infusion responders) if response was not lost during the 24-h double-blind infusion (drug period II). They were considered to have failed to maintain a therapeutic response to drug infusion (infusion nonresponders) if response was lost over two consecutive evaluations spaced 30-min apart while they were receiving the 15-mg/h infusion in drug period II. Infusion nonresponders in drug period II were given an additional 20 mg for 20 mg followed by 25 mg) of intravenous diltiazem (drug period III) and then received an open label continuous infusion of intravenous diltiazem at the rate of 10 mg/h (drug period IV), which could also be increased to 15 mg/h. Response to open label infusion of intravenous diltiazem in drug period IV was defined in a manner similar to that in drug period II. If response was not lost at the end of 24 h in drug period II or IV, the intravenous infusion of diltiazem was stopped and patients entered a 10-h washout period. Subsequent therapy for atrial fibrillation or flutter was at the discretion of each patient's physician.

Data analysis. Analysis of efficacy used the intent to treat principle, which included all randomized patients. The primary response variables used to determine efficacy were the maintenance of therapeutic response (yes or no) and the duration of therapeutic response (hours) in drug period II. Kaplan-Meier survival estimates were plotted to visually compare the two treatment groups with respect to the duration of therapeutic response. The Cox proportional hazards model was then used to test whether patients receiving diltiazem maintained therapeutic response as long as patients on placebo. Maintenance of the response to diltiazem and placebo was compared with the Mantel-Haenszel test. The treatment comparison for both the Cox model and the Mantel-Haenszel procedure was adjusted for investigative site.

Subgroup analyses of the duration of therapeutic response and maintenance of therapeutic response during drug periods II and IV were considered for patients who had atrial fibrillation versus atrial flutter, were <65 versus ≥65 years of age, weighed <84 versus ≥84 kg and received or did not receive digoxin. Clinical variables are presented as mean values ± SD unless stated otherwise. A significant result was declared when $p < 0.05$.

Table 1. Clinical Characteristics of the 44 Patients Receiving Diltiazem and Placebo Infusion in Drug Period II

	Total	Placebo	Diltiazem
Patients studied	44	21	23
Men	41	20	21
Mean age ± SD (yr)	65 ± 7	66 ± 9	65 ± 6
Arrhythmia			
Atrial fibrillation	36	17	19
Atrial flutter	8	4	4
Diagnoses			
Atherosclerotic coronary disease	28	15	13
Chronic obstructive lung disease	15	9	6
Valvular disease	7	3	4
Postcoronary bypass surgery	2	1	1
Concomitant digoxin*	32	16	16

*Digoxin administered within 5 half-lives before administration of a bolus dose or doses of intravenous diltiazem in drug period I.

Results

Clinical characteristics. Forty-seven patients entered the study and received a bolus dose or doses of diltiazem in drug period I. Thirty-seven presented with atrial fibrillation and 10 with atrial flutter. Forty-four of the 47 patients who received an open label bolus dose of diltiazem were classified as bolus responders and were randomized in drug period II of the study. These 44 randomized patients comprised 36 patients with atrial fibrillation and 8 with atrial flutter. The clinical characteristics of the patients receiving diltiazem and placebo infusion in drug period II were similar (Table 1).

Efficacy

Bolus dose or doses. In drug period I, 44 (94%) of 47 patients responded to intravenous diltiazem (36 [97%] of 37 with atrial fibrillation and 8 [80%] of those with atrial flutter). Forty-three patients responded to the 20-mg dose of diltiazem and one patient responded to the 25-mg dose after receiving the 20-mg dose. Three patients did not respond to the 25-mg dose after receiving the 20-mg dose and were entered into the poststudy phase. Of the 43 responders to the 20-mg dose, 3 received the 25-mg dose of intravenous diltiazem for further heart rate reduction after having met response criteria. Response occurred in a mean time of 4 ± 4 min, timed from the beginning of the 2-min bolus dose in the 44 patients who responded to intravenous diltiazem. The mean baseline heart rate for the 43 bolus responders and 4 bolus nonresponders to the 20-mg dose of intravenous diltiazem was 131 and 129 beats/min, respectively ($p = NS$). At 2 min after administration of the 20-mg dose of diltiazem, the mean heart rate was reduced by 17% in all patients, by 19% in bolus responders and by only 4% in bolus nonresponders. Heart rate at 7 to 17 min was still reduced in bolus responders and was little changed in bolus nonresponders. In seven patients who received the 25-mg dose (after the 20-mg dose) of intravenous diltiazem for response or further heart rate

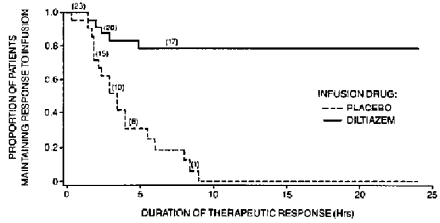


Figure 2. Kaplan-Meier estimates for the proportion of all randomized patients receiving diltiazem or placebo infusion whose response was maintained during drug period II. Numbers in parentheses indicate the number of patients with a response during the time interval.

reduction, the mean baseline heart rate for four bolus responders and three bolus nonresponders was 132 and 131 beats/min, respectively (p = NS). Two minutes after the administration of the 25-mg bolus dose of diltiazem, the mean heart rate was reduced by 17% in all patients, by 30% in four bolus responders and by only 5% in three bolus nonresponders.

Maintenance infusion. Forty-four patients entered the double-blind part of this study (drug period II). Twenty-three patients were randomized to receive the diltiazem infusion and 21 to receive the placebo infusion. During the 24 h of infusion, the mean (± SD) time of administration of the 10-mg/h dose of diltiazem was 11.4 ± 10.4 h. In those patients who were receiving the 10-mg/h dose and later received the 15-mg/h dose, the mean (± SD) time of administration of the 15-mg/h dose was 14.2 ± 9.4 h.

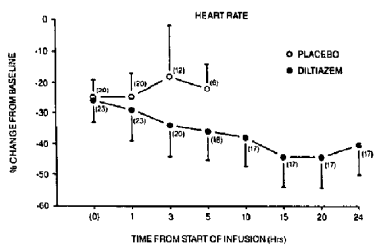
Seventeen (74%) of 23 patients receiving a maintenance infusion of intravenous diltiazem and 0 of 21 patients receiving a maintenance infusion of placebo maintained response during 24 h of drug period II ($p < 0.001$) (Fig. 2). In drug period II, the rate at which patients receiving diltiazem infusion lost response was significantly slower than the rate at which those with placebo infusion lost response ($p < 0.001$). The estimated hazard ratio (diltiazem/placebo) from the Cox model was 0.132 (95% confidence limits 0.047, 0.370). No patients who received diltiazem infusion lost therapeutic response after 5 h, whereas no patients receiving placebo infusion maintained a therapeutic response after 9 h. Figure 3 displays the mean percent change in heart rate from baseline in drug period II (24 h) in patients given diltiazem (including both responders and nonresponders to diltiazem) and patients given placebo.

In the patients receiving diltiazem who maintained response for 24 h during drug period II, there was a marked (31%) decrease in heart rate by 1 h. Thereafter, the heart rate decreased gradually over the remainder of the 24 h (Fig. 4). The mean percent decrease in heart rate from baseline was 34% at 3 h, 37% at 5 h, 38% at 10 h, 44% at 15 h, 44% at 20 h and 40% at 24 h.

Heart rate data obtained in patients given placebo infusion allowed determination of the duration of response to one or more bolus doses of intravenous diltiazem in patients who responded to bolus administration of diltiazem. The estimated 10th, 50th (median) and 90th percentiles for the duration of response in these patients were 1.8, 3.5 and 8.4 h, respectively.

The overall proportion of patients given diltiazem infusion who maintained response in drug period II or IV (double-blind or open label parts of the study) was 83% (34 of 41). Four of the 41 patients had received diltiazem during the double-blind and open label infusion parts of the study. Two of these four patients responded to the open label infusion of diltiazem but are not included as overall responders to the intravenous diltiazem infusion. The proportion of responders was similar in the elderly (≥65 years) versus the young (<65 years), among those who did versus those who did not receive digoxin and among those with a low (<84 kg) versus a high (≥84 kg) body weight. However, the percent of patients with atrial fibrillation who responded to intravenous diltiazem was greater than that of patients with atrial flutter (Table 2).

Figure 3. Time course of heart rate response to placebo and diltiazem (23 responders and 20 nonresponders) during drug period II (mean values ± SD). The mean baseline heart rate for placebo-treated and diltiazem-treated patients was 130 and 132 beats/min, respectively. (0) on the x axis denotes the last heart rate before the start of infusion. Patient numbers decrease over time as patients lose response and are entered into drug period III.



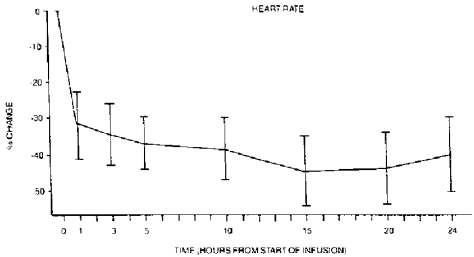


Figure 4. Time course of heart rate response to the diltiazem infusion in 17 responders during drug period II (mean values ± SD). The mean baseline heart rate was 128 beats/min.

The type of response during double-blind or open label infusion parts of the study (drug periods II and IV, respectively) in the majority of diltiazem infusion responders consisted of both a heart rate <100 beats/min and a ≥20% decrease in heart rate from baseline. No patient had conversion to sinus rhythm (Table 3).

Washout of infusion. The 34 patients who maintained response to a 24-h infusion of intravenous diltiazem during either the double-blind (drug period II) or the open label infusion part of the study (drug period IV) entered the washout period. The mean heart rate measurements taken at 1, 3, 5 and 10 h from the end of the 24-h infusion were 81, 87, 94 and 107 beats/min, respectively. The percent of intravenous diltiazem infusion responders who maintained response during the 10-h washout period steadily declined from 94% at 1 h to 53% at 10 h. Nine (26%) diltiazem infusion responders had received additional antiarrhythmic therapy during the washout period.

Table 2. Proportion of Diltiazem Infusion Responders During the Double-Blind and Open Label Infusion Parts of the Study Combined (drug periods II and IV, respectively*)

	No.	Infusion Responders (%)
Arrhythmia subtype		
Atrial fibrillation	34	88
Atrial flutter	7	57
Age group (yr)		
<65	21	81
≥65	20	85
Concomitant digoxin		
With†	29	86
Without	12	75
Body weight‡ (kg)		
<84	22	86
≥84	18	83

*Forty-one patients received an infusion of diltiazem for the first time during either drug period II (23 patients) or drug period IV (18 patients). †Digoxin administered within 5 half-lives before administration of a bolus dose or doses of intravenous diltiazem in drug period I. ‡Body weight was not measured in one patient.

Symptom evaluation. Symptoms were evaluated before (at baseline) and on completion of the study. Of the 34 patients who responded to the double-blind or open label infusion of intravenous diltiazem, 15 noted a lessening of symptoms of palpitation, dizziness or weakness from the baseline period. Nine patients did not note a change in symptoms and in 10 patients, symptoms were not present or not assessed. Of the seven patients who did not respond to intravenous diltiazem during the double-blind or open label infusion, four noted a decrease in symptoms and three noted no change.

Subsequent therapy. Forty-one of the 47 patients who entered the study were given other antiarrhythmic therapy for control or prophylaxis of the arrhythmia during the poststudy phase. The majority of patients received oral diltiazem (25 patients) and intravenous or oral digoxin (15 patients).

Safety

Blood pressure. Before administration of bolus doses of intravenous diltiazem, the mean baseline systolic and diastolic blood pressure was 128 ± 20 and 83 ± 12 mm Hg, respectively. At 2 min after the 20-mg bolus dose of diltiazem, there was a significant ($p < 0.001$) decrease from baseline in mean systolic and diastolic blood pressure in both bolus responders and nonresponders (by 13 ± 17 and 10 ± 12 mm Hg, respectively).

Immediately before initiation of maintenance infusion and after administration of one or more bolus doses of diltiazem, mean systolic blood pressure was reduced from baseline by 12 ± 14 and 11 ± 18 mm Hg ($p = 0.733$) and mean diastolic blood pressure by 11 ± 13 and 8 ± 12 mm Hg ($p = 0.446$) in the diltiazem and placebo infusion groups, respectively. During maintenance infusion, the reduction from baseline in mean systolic and diastolic blood pressure ranged from 9 ± 20 to 15 ± 19 mm Hg and 8 ± 10 to 10 ± 15 mm Hg in the diltiazem-treated patients, respectively, and from 0 to 4 ± 16 mm Hg and 2 ± 5 to 3 ± 11 mm Hg in the

Table 3. Type of Response (no. of patients) in 34 Diltiazem Infusion Responders During Drug Periods II and IV

Type of Response*	Time (h)						
	1	3	5	10	15	20	24
20% decrease in heart rate from baseline	31	32	34	34	34	34	32
Heart rate <100 beats/min	25	28	30	32	31	32	32
No response	2	2	0	0	0	0	1

*None had conversion to sinus rhythm during the 24-h infusion.

placebo-treated patients, respectively. There was no difference in systolic and diastolic blood pressure in the responders and nonresponders to diltiazem infusion.

Digoxin. Thirty-two patients (16 each in the placebo and diltiazem infusion groups) had received digoxin within 5 half-lives before receiving intravenous diltiazem in drug period I. No patient who had received digoxin had an elevated plasma digoxin concentration or exhibited signs or symptoms of digoxin toxicity. Prestudy plasma digoxin concentrations were similar in the two infusion groups (placebo 0.71 ± 0.36 ng/ml; diltiazem 0.73 ± 0.25 ng/ml; therapeutic range 0.9 to 2.1; p = NS) and did not appreciably change from prestudy to poststudy (placebo 0.65 ± 0.24 ng/ml; diltiazem 0.78 ± 0.33 ng/ml).

Adverse events. There was no death, prolonged hospitalization, permanent disability or dosage reduction as a result of an adverse event. Significant side effects included hypotension in two patients; one patient was quadriplegic (baseline blood pressure 110/60 mm Hg). Thirty-seven minutes after initiation of the placebo infusion, the patient experienced light-headedness and slight tightness in his chest. His systolic blood pressure at the time was 80 mm Hg (diastolic blood pressure was not obtained). The placebo infusion was discontinued and the patient was treated with normal saline solution. He recovered in 2.5 h with a blood pressure of 96/60 mm Hg and had no sequelae. One patient (baseline blood pressure 110/70 mm Hg) received 50 mg of captopril 1.5 h after initiation of the 10-mg/h infusion of diltiazem. At 3 h of infusion, the patient developed hypotension (80/60 mm Hg). The diltiazem infusion was discontinued and the patient was treated with normal saline solution. The patient recovered in 13 min with a blood pressure of 99/64 mm Hg and had no sequelae.

Discussion

Efficacy of intravenous diltiazem in atrial fibrillation and flutter. In this study, a 24-h continuous infusion of intravenous diltiazem (10 to 15 mg/h) given after a bolus dose (20 mg alone or 20 mg followed 15 min later by 25 mg) was safe and effective treatment for control of heart rate during atrial fibrillation or atrial flutter in 83% of patients. Efficacy with the 24-h infusion of intravenous diltiazem was similar in elderly versus young patients, those who did versus those who did not receive digoxin and those weighing <84 versus ≥84 kg. However, intravenous diltiazem appeared to be more effective in patients with atrial fibrillation than in those with atrial flutter. With this regimen of diltiazem bolus and maintenance infusion, heart rate was controlled within approximately 4 min and control was maintained for 24 h. After the infusion was stopped, heart rate remained well controlled in about 50% of the patients for up to 10 h.

Study limitations. Our study has potential limitations. We could not determine if diltiazem prolonged the duration of atrial fibrillation or atrial flutter because the duration of the study was approximately 48 h. We did not include patients with class III or IV heart failure or hypotension (<90 mm Hg).

Comparison with previous investigations. There have been no studies of intravenous diltiazem administered as a 24-h infusion for heart rate control in patients with atrial fibrillation or atrial flutter. Previous investigations (6–10) have shown that a bolus dose of intravenous diltiazem generally administered over 2 min promptly reduces the rapid ventricular rate in patients with atrial fibrillation or flutter; the duration of response has been reported (8) to range between 1 and 3 h. In our study, the response to a bolus dose or doses of intravenous diltiazem was rapid (within minutes of the bolus injection) and the median duration of response to the bolus dose was 3.5 h. It would be desirable to maintain control of the ventricular rate over an extended period of time. Prompt and sustained rate control with intravenous diltiazem may have improved cardiac hemodynamics and symptoms of angina or heart failure, which may also have contributed to the heart rate slowing we observed over 24 h with this infusion.

Comparison of intravenous diltiazem and other intravenous agents that lower heart rate. In this study, we did not compare intravenous diltiazem with other intravenous antiarrhythmic agents that slow ventricular rate in atrial fibrillation or flutter, such as beta-adrenergic blocking agents, digoxin or verapamil. Esmolol, a new beta-blocker, was shown to be effective for slowing heart rate in atrial fibrillation (13–15); however, dose titration with esmolol frequently resulted in a high incidence of symptomatic hypotension (13). Digoxin can decrease the ventricular response in atrial fibrillation or atrial flutter without causing hypotension, but its rate of onset is typically slow, and it has not been shown to result in conversion of atrial fibrillation to sinus rhythm (16). Intravenous verapamil may be more likely than diltiazem to cause or exacerbate heart failure because verapamil has a greater negative inotropic effect than does

diltiazem (17). In addition, verapamil has not been tested under controlled conditions as a sustained infusion in patients with atrial fibrillation or flutter.

Conversion to sinus rhythm. Conversion of atrial fibrillation or flutter to sinus rhythm is a more useful outcome than a reduction in ventricular rate. However, normal sinus rhythm is often difficult to achieve or maintain in many patients with atrial fibrillation or flutter, who have impaired left ventricular function, enlarged atria or a long duration of the arrhythmia. Class IA and class IC antiarrhythmic agents are useful for converting atrial fibrillation or flutter to sinus rhythm, but their onset is slow and their efficacy for conversion is not high. In addition, class IA agents may cause significant hypotension when administered intravenously and their parasympatholytic effects may lead to an acceleration of the ventricular rate during treatment of atrial fibrillation or flutter. In a recent analysis (18) of multiple trials of quinidine given to maintain sinus rhythm after direct current cardioversion of atrial fibrillation, 50% of patients maintained sinus rhythm at 12 months. However, this result was attained at the price of a threefold increased incidence of cardiac death. Class IC agents such as flecainide and encainide are restricted to patients *without* structural heart disease because of their high incidence of serious proarrhythmia and are contraindicated when the ejection fraction is low or heart failure, or both, is present (19–21). The benefits of maintaining sinus rhythm in a given patient must be weighed against the risk of proarrhythmia, drug side effects and patient intolerance of the medical regimen.

Conclusion

Bolus doses (20 mg, 25 mg) followed by a 24-h continuous infusion of intravenous diltiazem (10 to 15 mg/h) can be safely administered to patients with atrial fibrillation or flutter and can rapidly and effectively achieve and maintain heart rate control in most patients. Intravenous diltiazem has applicability as a "therapeutic bridge" in patients with these atrial arrhythmias awaiting initiation or onset of action of long-term antiarrhythmic therapy or cardioversion.

We thank Jan Christy-Bittel, RN for assistance in monitoring the study.

Appendix

The Intravenous Diltiazem Atrial Fibrillation/Atrial Flutter Study Group

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