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Pharmacology in Emergency Medicine

DILTIAZEM VS. METOPROLOL IN THE MANAGEMENT OF ATRIAL FIBRILLATION OR FLUTTER WITH RAPID VENTRICULAR RATE IN THE EMERGENCY DEPARTMENT

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□ **Abstract—Background: Diltiazem (calcium channel blocker) and metoprolol (beta-blocker) are both commonly used to treat atrial fibrillation/flutter (AFF) in the emergency department (ED). However, there is considerable regional variability in emergency physician practice patterns and debate among physicians as to which agent is more effective. To date, only one small prospective, randomized trial has compared the effectiveness of diltiazem and metoprolol for rate control of AFF in the ED and concluded no difference in effectiveness between the two agents. Objective: Our aim was to compare the effectiveness of diltiazem with metoprolol for rate control of AFF in the ED. Methods: A convenience sample of adult patients presenting with rapid atrial fibrillation or flutter was randomly assigned to receive either diltiazem or metoprolol. The study team monitored each subject's systolic and diastolic blood pressures and heart rates for 30 min. Results: In the first 5 min, 50.0% of the diltiazem group and 10.7% of the metoprolol group reached the target heart rate (HR) of <100 beats per minute (bpm) ($p < 0.005$). By 30 min, 95.8% of the diltiazem group and 46.4% of the metoprolol group reached the target HR < 100 bpm ($p < 0.0001$). Mean decrease in HR for the diltiazem group was more rapid and substantial than that of the metoprolol group. From a safety perspective, there was no difference between the groups with respect to hypotension (systolic blood pressure < 90 mm Hg) and bradycardia (HR < 60 bpm). Conclusions: Diltiazem was more effective in achieving rate control in ED patients with AFF and did so with no increased incidence of adverse effects.** © **2015 Elsevier Inc.**

□ **Keywords—diltiazem; metoprolol; atrial fibrillation; atrial flutter; rate control**

INTRODUCTION

Acute atrial fibrillation is the most common sustained, clinically significant dysrhythmia encountered in the emergency department (ED), and the most common dysrhythmia treated by emergency physicians. Atrial fibrillation accounts for approximately 1% of all ED visits, and nearly 65% of patients presenting to the ED with atrial fibrillation are admitted to the hospital (1,2). In addition, the aging general population has increased the number of visits to the ED of patients with atrial fibrillation by 66% in the last 20 years (3,4).

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Atrial flutter is less common than atrial fibrillation, but its management in the ED is very similar, and the majority of patients with atrial flutter also have atrial fibrillation. Symptomatic relief and ventricular rate control are generally the primary therapeutic objectives in the ED management of acute atrial fibrillation and flutter (AFF). Conversion to sinus rhythm in the ED is considerably less important, and may be undesirable before initiation of anticoagulation. The majority of patients with AFF and rapid ventricular rate do not require immediate electrical cardioversion, which is generally reserved for patients with significant hemodynamic compromise, although recent data advocate its use earlier in therapy (5). However, if a sustained rapid rate is allowed to persist for hours, tachycardia-induced left ventricular dysfunction can result. The need for swift, appropriate action by the emergency physician is highlighted by the fact that up to 18% of patients with AFF develop potentially life-threatening complications, such as congestive heart failure, hypotension, ventricular ectopy, respiratory failure, angina, and myocardial infarction (6,7).

Both beta-blocking agents and calcium channel blockers are commonly used to treat AFF in the ED. Metoprolol is the most commonly used beta-blocker; and diltiazem is the most frequently used calcium channel antagonist (8). Diltiazem was released by the United States Food and Drug Administration for treatment of AFF in 1992. Schreck et al. were the first to demonstrate both the efficacy of diltiazem in the ED management of AFF with rapid rate and its clear superiority over the previously most commonly used pharmacologic agent, digoxin (9).

To date, only one prospective, randomized trial has compared the effectiveness of a calcium channel blocker (diltiazem) with a beta-blocker (metoprolol) for rate control of AFF in the ED (10). Despite the relatively small sample size (n = 20 in each group), the authors concluded that both pharmacologic agents were similarly effective. In order to test this finding, we conducted a prospective comparison of metoprolol and diltiazem for the management of patients presenting to the ED with AFF with rapid ventricular rate.

MATERIALS AND METHODS

Study Design

We conducted a prospective, randomized, double-blind study to compare the effectiveness of intravenous metoprolol with that of diltiazem in achieving rate control in adult ED patients with rapid AFF. Approval of the study was obtained from our hospital's Institutional Review Board. All enrolled patients provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization documentation. The study is registered with clinicaltrials.gov, ID#: NCT01914926. The study was done and is reported according to the CONSORT (Consolidated Standards of Reporting Trials) Group (11).

Study Setting and Selection of Participants

This study was set in the adult ED at an urban teaching hospital with an annual ED census of >120,000 patients. A convenience sample of adult patients aged 18 years or older presenting with atrial fibrillation or atrial flutter were evaluated for enrollment. Eligible patients had a 12-lead electrocardiogram (ECG) showing atrial fibrillation or atrial flutter with a ventricular rate of ≥120 beats per minute (bpm) and a systolic blood pressure (SBP) of ≥90 mm Hg.

Patients were excluded if they had any of the following: SBP < 90 mm Hg, ventricular rate ≥ 220 bpm, QRS > 0.100 s, second- or third-degree atrioventricular (AV) block, temperature > 38.0°C, acute ST elevation myocardial infarction, known history of New York Heart Association Class IV heart failure or active wheezing with a history of bronchial asthma or chronic obstructive pulmonary disease (COPD). In addition, patients were excluded if there was prehospital administration of diltiazem or any other AV nodal blockading agent, a history of cocaine or methamphetamine use in the 24 hours before arrival, a history of allergic reaction to diltiazem or metoprolol, a history of sick sinus or pre-excitation syndrome, a history of anemia with hemoglobin < 11.0 g/dL, pregnancy, or breastfeeding.

Interventions

After a patient was identified as fulfilling inclusion and exclusion criteria and informed consent and HIPAA authorization were obtained, data were collected prospectively. These data included demographics, medical history, vital signs, and ECG findings. All patients were immediately evaluated by the treating physician utilizing Advanced Cardiovascular Life Support (ACLS) protocols. At the discretion of the treating physician, intravenous adenosine was administered in order to facilitate identification of the underlying supraventricular tachydysrhythmia. All patients were attached to a monitor that displays cardiac rhythm, heart rate (HR), blood pressure, and oxygen saturation.

Upon enrollment, patients were randomly assigned, in a 1:1 ratio, to receive diltiazem administered parenterally at a dose of 0.25 mg/kg (to a maximum dose of 30 mg) or metoprolol administered at a dose of 0.15 mg/kg (to a maximum dose of 10 mg). Randomization was performed through the use of a computer-generated randomization by one of the investigators (AL) and was given to the

pharmacy investigators. Pharmacy released the study drug in a locked tackle box coded in number sequence to correspond to that of the computer-generated randomization list, upon which the pharmacist also prepared the study drug in blinded fashion. The study medications were packaged in identical-appearing dispensing kits, and each ED physician, nurse, and patient were blinded to study drug. Patients who were randomly assigned to diltiazem received the drug in a syringe that appeared identical to that of metoprolol. Admixture and labeling were performed by the pharmacist in the ED and dispensed to the treating nurse for administration. Total volume within each syringe was adjusted with normal saline to a total of 10 mL to disguise and maintain blinding. The time at which the first dose was administered was denoted as time 0 (baseline). If the primary endpoint was not achieved at time 15 min, then a second escalation dose was administered. If the patient had been enrolled in the diltiazem group, the escalation dose was 0.35 mg/kg (to a maximum dose of 30 mg), and for patients enrolled in the metoprolol group, the escalation dose was 0.25 mg/kg (to a maximum dose of 10 mg). As with the initial dose, the escalation dose was prepared by the pharmacist and given to the treating nurse for patient administration in a blinded fashion.

Outcome Measures

The primary efficacy outcome measure was HR < 100 bpm within 30 min of drug administration. The study team, including several ED pharmacists, a research associate, emergency physicians, and experienced research volunteers monitored each subject's SBP and diastolic blood pressure (DBP) and HR at time 0, 5, 10, 15, 20, 25, and 30 min after drug administration to assess if the patient achieved the desired endpoint.

The primary safety outcome measures were HR < 60 bpm and SBP < 90 mm Hg.

Sample Size and Data Analyses

The Power Analysis and Sample Size (PASS) 2008 Program was used to calculate sample size (12). The standard deviations used to calculate the sample size were based on the study by Demircan et al. (10). We estimated a sample size of 200 patients assigned in a 1:1 ratio to receive diltiazem and metoprolol would achieve 80% power to detect noninferiority using a one-sided, two-sample *t*-test. The margin of equivalence is −10.

All data from the data-collection sheet, including sex, demographics, medical history, vital signs, and ECG findings were entered into and analyzed via SPSS software, version 19.0 (2010, IBM SPSS, Armonk, NY). Statistical analyses compared the diltiazem and metoprolol groups using Student's *t*-test, χ^2 test, Kaplan–Meier curve and Cox regression analyses. A p value < 0.05 denoted statistical significant difference between the medication groups.

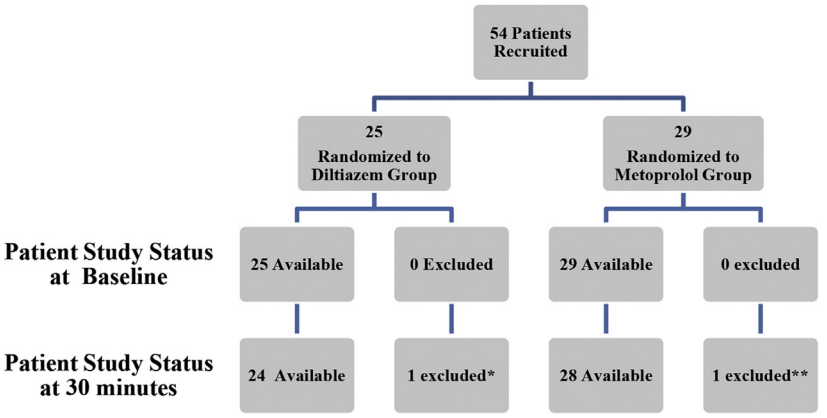
The research associate together with the ED pharmacists monitored study outcomes and safety. The safety-monitoring team observed that significantly more patients in one study group were reaching the desired endpoint. This finding was confirmed by a blinded, independent biostatistician from State University of New York (SUNY) Downstate Medical Center, who recommended stopping study enrollment.

RESULTS

A convenience sample of 54 patients who met inclusion criteria were enrolled in the study from June 2009 to November 2010. Twenty-five patients were randomized to the diltiazem group and 29 were randomized to the metoprolol group. However, 2 patients (1 patient in the diltiazem group and 1 patient in the metoprolol group) were removed from the data analyses: the patient randomized to the diltiazem group became uncooperative, agitated, and removed his intravenous catheter, and the metoprolol group patient's SBP went from 101 to 89 mm Hg 5 min after administering the medication, which led the treating physician to unblind the patient. Patient recruitment and randomization assignment for the trial are illustrated in Figure 1.

The final sample size was 52 patients; 24 were randomized to the diltiazem group (46.9% males, mean age 66.2 years, 21% received adenosine, mean baseline SBP 132.4 mm Hg, mean baseline DBP 88.7 mm Hg, and mean baseline HR 136.8 bpm) and 28 were randomized to the metoprolol group (53.1% males, mean age 69.5 years, 18% received adenosine, mean baseline SBP 129.0 mm Hg, mean baseline DBP 82.5 mm Hg, and mean baseline HR 142.2 bpm). There were no statistically significant differences with regard to sex, age, adenosine administration, baseline SBP, baseline DBP, and baseline HR (p = 0.895, 0.396, 0.786, 0.828, 0.212, and 0.231, respectively) (Table 1).

Similarly, there were no statistically significant differences between the groups related to baseline alcohol use and medical history. In the diltiazem group, 21% had history of significant alcohol use, 4% COPD, 29% atrial fibrillation, 8% thyroid disease, and 25% diabetes mellitus. In the metoprolol group, 14.3% had a history of significant alcohol use, 11% COPD, 39% atrial fibrillation, 7% thyroid disease, and 21% diabetes mellitus. The p values were 0.716, 0.617, 0.444, 0.634, and 0.761, respectively (Table 1). Sixty-five percent of study patients presented with new onset atrial fibrillation: 70.8% in the diltiazem group and 60.7% in the metoprolol group (p = 0.444).



*The patient became uncooperative, agitated, and removed his intravenous catheter shortly after enrollment into the study; not included in the data analyses.

** The patient's systolic blood pressure went from 101 to 89 five minutes after administration of the study medication which led the treating physician to unblind the patient; not included in the data analyses.

Figure 1. Patient enrollment and randomization flow chart.

In the first 5 min, 50.0% of the diltiazem group and 10.7% of the metoprolol group reached the target HR of <100 bpm ($p < 0.005$). By 30 min, 95.8% of the diltiazem group and 46.4% of the metoprolol group reached the target HR of <100 bpm ($p < 0.0001$) (Figure 2). The Kaplan–Meier curve demonstrates the same results. Thus, 4.2% of the diltiazem group and 53.6% of the metoprolol group did not reach the target HR of <100 bpm within 30 min (Figure 3). None of the patients in either group required cardioversion, nor did any patients convert to sinus rhythm during the study period.

Figure 4 depicts mean heart rates over time for the two groups. The mean decrease in HR for the diltiazem group was more rapid and substantial than that of the metoprolol group. The mean HR for the metoprolol group did not reach the target of <100 bpm at any time during the 30-min study period. In the diltiazem group, the mean HRs were 136.8 (± 15.3) bpm at baseline, 102.1 (± 21.4) bpm at 5 min, 98.0 (± 22.5) bpm at 10 min, 95.6 (± 21.1) bpm at 15 min, 90.8 (± 13.2) bpm at 20 min, 90.9 (± 14.5) bpm at 25 min, and 90.3 (± 14.4) bpm at 30 min. In the metoprolol group, the mean heart rates were 142.2 (± 16.5) bpm at baseline, 127.3 (± 21.1) bpm at 5 min, 121.7 (± 21.3) bpm at 10 min, 117.6 (± 23.4) bpm at 15 min, 116.9 (± 23.1) bpm at 20 min, 113.5 (± 21.0) bpm at 25 min, and 115.6

Table 1. Demographic Characteristics of Diltiazem and Metoprolol Groups

Characteristics	Diltiazem (n = 24)	Metoprolol (n = 28)	*p* Value
Male, %	46.9	53.1	0.895
Age, y, mean (SD)	66.2 (13.4)	69.5 (14.8)	0.396
Use alcohol, %	20.8	14.3	0.716
Receiving adenosine, %	21.0	18.0	0.786
Baseline SBP, mm Hg, mean (SD)	132.4 (23.8)	129.0 (19.8)	0.828
Baseline DBP, mm Hg, mean (SD)	88.7 (19.4)	82.5 (15.3)	0.212
Baseline HR, beats/min, mean (SD)	136.8 (15.3)	142.2 (16.5)	0.231
History of			
COPD, %	4.0	11.0	0.617
Atrial fibrillation, %	29.2	39.3	0.444
Thyroid disease, %	8.0	7.0	0.634
Diabetes mellitus, %	25.0	21.0	0.761
New onset atrial fibrillation, %	70.8	60.7	0.444

COPD = chronic obstructive pulmonary disorder; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.
At baseline there were no statistically significant differences between the groups.

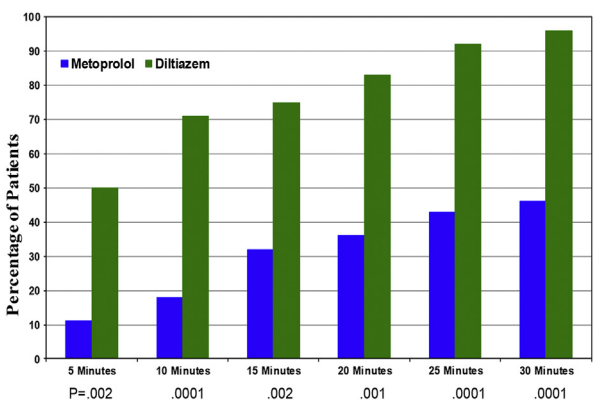


Figure 2. Percentage reached heart rate <100 beats/min. Metoprolol is blue and diltiazem is green.

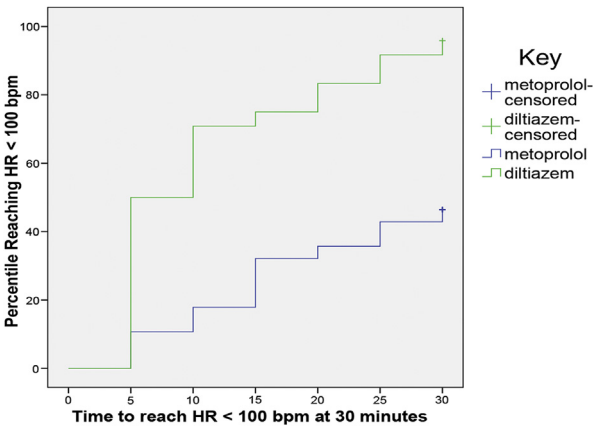


Figure 3. Kaplan–Meier curve. Metoprolol is blue and diltiazem is green. HR = heart rate.

(± 23.0) bpm at 30 min. The *p* values were 0.231, 0.0001, 0.0001, 0.001, 0.0001, 0.0001, and 0.0001, respectively.

In a Cox regression model, the patients receiving diltiazem were 4.66 times (95% confidence interval 2.09 to 10.36; $p = 0.0001$) more likely to reach target HR < 100 bpm within 30 min than were patients receiving metoprolol after controlling for age, sex, baseline HR, baseline SBP, baseline DBP, and administration of adenosine (Table 2).

From a safety perspective, there was no difference between the groups with respect to hypotension (SBP < 90 mm Hg) and bradycardia (HR < 60 bpm). There were 5 metoprolol patients and 1 diltiazem patient with hypotension ($p = 0.199$). Bradycardia occurred in 1 diltiazem patient only and did not occur in the group that received metoprolol ($p = 0.462$).

DISCUSSION

Both diltiazem and metoprolol are commonly used in the acute management of supraventricular tachydysrhythmias, and both agents achieve rate control in AFF by slowing AV nodal conduction and by prolonging AV nodal refractoriness. The American College of Cardiology and the Canadian Cardiovascular Society guidelines on the management AFF offer both of these agents as Class I Recommendations for controlling ventricular rate in AFF and do not favor one over the other (13,14). In the ED, there is a great deal of regional variability in terms of which of these agents is chosen for achieving ventricular rate control in patients presenting with AFF. According to a recent survey of emergency physicians around the world, diltiazem is the predominant agent used for rate control in the United States (95.22%) and Canada (65.36%), while metoprolol is preferred in the United Kingdom (67.64%) and Australasia (65.94%) (15).

In common practice, however, cardiology consultants often consider metoprolol to be the ventricular rate control agent of choice. In part, this may be due to calcium channel blockers being relatively contraindicated for rate control in heart failure patients with left ventricular dysfunction because of the negative inotropic effects. This may also be due to calcium channel blockers having developed a poor reputation as a result of epidemiological data, suggesting an increase in 5-year all-cause and cardiac-related mortality in elderly hypertensive patients treated with nifedipine vs. beta-blockers (16). Although this concern is well noted, nifedipine is a dihydropyridine calcium channel blocker, and there is no published literature to substantiate that diltiazem, a nondihydropyridine calcium channel antagonist, administered for short-term use in AFF is associated with increased risk of mortality.

Even in long-term studies, no mortality risk has been identified in elderly patients discharged from the hospital on calcium channel blockers. In one study that examined calcium channel blockers and their safety in patients with coronary artery disease, Jollis et al. reported a retrospective cohort study using data from the medical charts and

Table 2. Multivariable Analyses (Cox Regression) of the Association of Reaching a Heart Rate of <100 beats/min Within 30 min

	Within 30 min		
Variables	Hazard Ratio	95% CI	*p* Value
Diltiazem	4.657	2.093–10.363	0.0001
Adenosine	0.424	0.131–1.377	0.153
Sex	0.516	0.219–1.212	0.129
Baseline SBP	0.997	0.983–1.012	0.709
Baseline DBP	1.001	0.981–1.021	0.931
Baseline HR	0.982	0.955–1.010	0.203
Age	1.013	0.984–1.043	0.390

CI = confidence interval; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.
Diltiazem is compared to metoprolol. In this study a positive hazard ratio is beneficial.

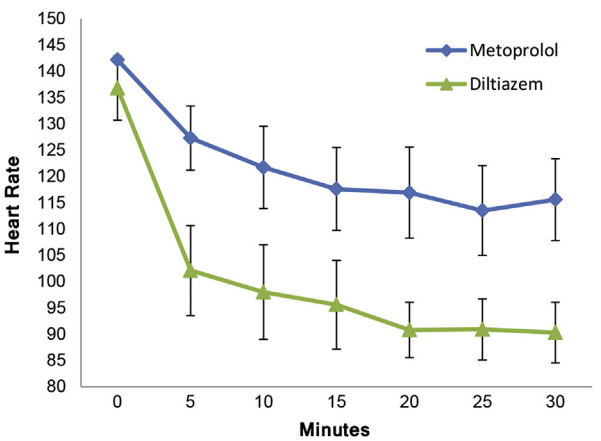


Figure 4. Mean heart rate over time with 95% confidence interval error bars. Metoprolol is blue and diltiazem is green.

administrative files of 141,041 Medicare patients with a principal diagnosis of acute myocardial infarction consecutively discharged from the hospital alive during an 8-month period between 1994 and 1995 (17). During this time period, elderly patients discharged from the hospital after a myocardial infarction (n = 51,921) commonly received prescriptions for calcium channel blockers. Diltiazem was the most commonly prescribed (n = 21,175), followed by nifedipine (n = 12,670), amlodipine (n = 11,683), and verapamil (n = 3639). After adjusting for illness severity and medications taken, calcium channel blockers were not associated with increased mortality at 30 days and 1 year. The only exception was the few patients (n = 116) treated with bepridil, which differs from other calcium channel blockers due to its propensity to prolong repolarization and its prodysrhythmic effects in the elderly.

Anecdotal observation in the ED management of AFF is that metoprolol is disappointing in achievement of rate control and often, as was the case in the Demircan study, requires the need to institute rescue dosing of diltiazem or other rate control agents (10). This practice can be hazardous, as concurrent calcium channel blocker and beta-blocker administration can precipitate heart failure, atrioventricular block and bradycardia due to their synergistic negative dromotropic, inotropic, and chronotropic effects (18).

To date, only the Demircan trial has prospectively compared the relative effectiveness of a calcium channel blocker and a beta-blocker in achieving rate control in ED patients with AFF (10). In that study, 20 patients were randomized to each of the two treatments and both medications were found to be effective. At 20 min after administration, 18 of 20 (90%) patients in the diltiazem group had reached rate control and the remaining 2 patients achieved rate control after an escalating dose (0.35 mg/kg) of diltiazem was administered. Similarly, 16 of 20 (80%) patients in the metoprolol group achieved rate control at 20 min and, as noted here, the remaining 4 patients reached that goal only after subsequently receiving diltiazem. No adverse effects were reported. It is unclear whether the study was adequately powered to conclude no significant difference in either agent's effectiveness, although the authors do note that diltiazem's rate control effect began earlier and that its percentage decrease in ventricular rate at different time intervals was higher than that of metoprolol.

More recently, Scheuermeyer and colleagues published a retrospective comparison of beta-blocker and calcium channel blocking agents used for atrial fibrillation in 259 patients without underlying medical illness in Canada between 2006 and 2010 (19). They examined admission rate as a surrogate marker for successful rate control and secondarily compared ED length of stay and adverse events. Patients were treated at the attending physician's discretion utilizing metoprolol, atenolol, diltiazem, and verapamil without a predetermined treatment algorithm. They found no difference between the calcium channel blocker and beta-blocker groups.

In our study, 24 patients were randomized to the diltiazem group and 28 were randomized to the metoprolol group. Target rate control was achieved by 30 min in 95.8% of the diltiazem patients vs. only 46.4% for metoprolol. Fifty percent of the diltiazem group achieved target HR within the first 5 min, vs. only 10.7% in the metoprolol group. There were no significant differences with respect to hypotension or bradycardia.

Limitations

Treatment regimens were based on standard manufacturing dosing regimens. We chose a maximum dose of metoprolol (10 mg) based on the Demircan study and current ACLS guidelines (10). Pharmacologic safety studies indicate that metoprolol could be used at a higher dose, however, given that the typical bolus dose is 5 mg intravenously, doses >10 mg were considered to be excessively high by our hospital's Institutional Review Board and a consensus of our participating emergency physicians. It is possible that a larger dose of metoprolol may have produced different results in both efficacy and safety.

The diltiazem dosing was consistent with manufacturer's recommendations; however this study included a maximum dose of 30 mg if needed, in contrast to the Demircan study, in which the investigators set the dose limit for diltiazem at 20 mg (10). In this study, there were no instances of crossing over to administration of the alternative drug if the endpoint was not achieved, in contrast to the Demircan study, in which diltiazem was used subsequent to beta-blocker administration to achieve rate control in 4 patients (10).

Furthermore, inclusion bias may have been introduced through use of convenience sampling, as an investigator and pharmacist were required to be present in the ED at the time of patient enrollment. Patient enrollment was limited to the hours of 8 AM to 11 PM, Monday to Friday. In addition, local emergency medical services protocols for the administration of diltiazem in the prehospital setting also diminished the number of potential study patients.

CONCLUSIONS

Diltiazem was more effective than metoprolol in achieving rate control in ED patients with AFF at all time points within 30 min and did so with no increased incidence of adverse effects.

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ARTICLE SUMMARY

1. Why is this topic important?

This topic is important because diltiazem (calcium channel blocker) and metoprolol (beta-blocker) are both commonly used to treat atrial fibrillation and flutter (AFF) in the emergency department (ED). However, there is considerable regional variability in emergency physician practice patterns and debate among physicians as to which agent is more effective. To date, only one small prospective, randomized trial has compared diltiazem and metoprolol for rate control of AFF in the ED and concluded no difference in effectiveness between the two agents.

2. What does this study attempt to show?

This study attempts to show the relative effectiveness of diltiazem and metoprolol for rate control of AFF in the ED.

3. What are the key findings?

The key finding is that diltiazem was more effective than metoprolol in achieving rate control in ED patients with AFF at all time points within 30 min and did so with no increased incidence of adverse effects.

4. How is patient care impacted?

Physicians should consider choosing diltiazem rather than metoprolol for rapid, safe, and effective rate control of AFF in the ED.