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Vernakalant for the treatment of new-onset atrial fibrillation

Abstract

Background: Vernakalant is a novel antiarrhythmic agent with preferential effect on atrial myocardial tissue and limited action on ventricular myocardial tissue. Preliminary experience with vernakalant use suggests that conversion to sinus rhythm in patients with recent-onset atrial fibrillation is usually achieved quickly thus allowing early hospital discharge. The current study aimed to evaluate the efficacy of Vernakalant in a busy emergency department.

Methods: Study population included 146 consecutive patients with recent-onset (less than 7 days) atrial fibrillation. Vernakalant was administered as an initial loading dose under continuous blood pressure monitoring. In the absence of conversion to sinus rhythm after 15 minutes, a second dose of the remaining vernakalant dose was administered. The primary endpoint was conversion to sinus rhythm within less than 1 hour.

Results: We studied 146 patients presenting to the emergency department with recent atrial fibrillation. Overall, 114/146 [78%] patients converted to sinus rhythm. Of these, 94 [82.5%] patients converted to sinus after a single dose. The remaining 20 patients converted to sinus rhythm during the second infusion. The median time to conversion after the first dose was 12.5 minutes. The median combined time to conversion (after the first and the second dose) was 21 minutes. All 114 converted patients were discharged with normal sinus rhythm within 3-4 hours after admission.

Conclusion: Current results validate recent publications regarding the efficacy and safety of Vernakalant for the treatment of new-onset atrial fibrillation and support the endorsement of its use by the guidelines.

Keywords: Paroxysmal Atrial Fibrillation, Rhythm Control, Antiarrhythmic drugs, Vernakalant

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Abbreviation: ACT I, Arrhythmia conversion trial (first); ACT III, Arrhythmia conversion trial (third); AF, Atrial Fibrillation; ECG, Electrocardiogram; ER, Emergency Room; IV, Intra-venous; NSR, Normal Sinus Rhythm; NYHA, New York Heart Association; SD, Standard deviation; ST, ST segment on ECG; QT, QT interval on ECG; QTc, Corrected QT

Introduction

Atrial fibrillation (AF) is the most common clinical-significant arrhythmia affecting at least 1-2% of the population1. Its prevalence increases with age with an incidence of 5% among subjects aged over 65years, and 8-10% among individuals older than 75years.[1,2] AF is associated with an increased risk of embolic stroke, systemic embolization and heart failure. Its prevalence is growing with aging global population and therefore represents a significant public health problem. Early conversion to normal sinus rhythm [NSR] improves symptoms, prevents the detrimental effects of prolonged AF and avoids hospitalization.[3] Conversion of AF can be achieved pharmacologically or by electrical cardioversion. Electrical cardioversion is effective but requires sedation and a fasting state. The European Society of Cardiology guidelines4 recommend the use of flecainide, amiodarone, propafenone, ibutilide or vernakalant for pharmacological cardioversion, with the choice of agent guided by the presence of the underlying heart disease. We report here our preliminary experience with the use of vernakalant in the emergency department setting.

Methods

The study included all consecutive patients with recent-onset atrial fibrillation of less than 7day-duration, who were treated with intravenous vernakalant. All study patients were treated in the emergency department at a large regional hospital serving a population of 400,000 people. The diagnosis of AF was confirmed by a senior physician with 12-lead ECG. The trial was approved by the local institutional review board of Hillel Yaffe Medical Center and all the patients and all patients provided written informed consent.

Exclusion criteria were heart failure with functional class NYHA III or IV, an acute coronary syndrome within the previous 30days, ST-elevation or non ST-elevation myocardial infarction, severe aortic stenosis, systolic blood pressure less than 100mmHg, prolonged QT interval, severe bradycardia, and the use of intravenous class I or III anti-arrhythmic medication within 4hours prior to presentation.

Statistical analysis

Continuous variables were compared using Student's t-test or the Mann–Whitney U test, as appropriate. Continuous variables with a non-normal distribution were presented as median (interquartile range). Categorical variables were expressed as percentages and were compared using Chi-squared or Fisher's exact tests, as appropriate. All tests were two-sided with a significance level of 0.05.

Study protocol

Immediately after consent, an initial loading dose of intravenous of vernakalant (3mg/kg) was infused over 10minutes under continuous monitoring of blood pressure. In case conversion to sinus rhythm after 15minutes was not achieved, a second dose of the remaining vernakalant (2mg/kg) was administered within 10minutes. Blood pressure was monitored throughout the infusion. The patients were observed for possible side effects. ECG was performed when conversion to sinus rhythm occurred or in the presence of suspected arrhythmia.

We aimed to assess the percentage of patients converted to sinus following the first vernakalant dose and of those requiring the second dose, and the average time to conversion.

Results

Between January 2017 and January 2019, we recruited 146 patients to the study. Patients' baseline characteristics are presented in Table 1. All patients were treated with intravenous vernakalant according to the study protocol. Overall, 114/146 of study patients converted to sinus rhythm with an efficacy of 78%. Ninety-four of the 114 patients (82.5%) converted to sinus rhythm after a single dose of IV vernakalant (3mg/kg). Among the 52 who did not convert after the first dose and required the second vernakalant dose (2mg/kg), sinus rhythm was achieved in 20 patients (38%) (Figure 1). The average time to conversion after the first dose was 12.5minutes. The average combined time after the first and second dose together was 20minutes.

Table 1 Baseline clinical characteristics

110 (75%)	Male n (%)
60.2±12	Age (mean±SD), Years
76 (52%)	Hypertension
30 (20.5)	Ischemic Heart Disease
38 (26%)	Diabetes
13 (8.9%)	Concomitant B-Blocker Therapy

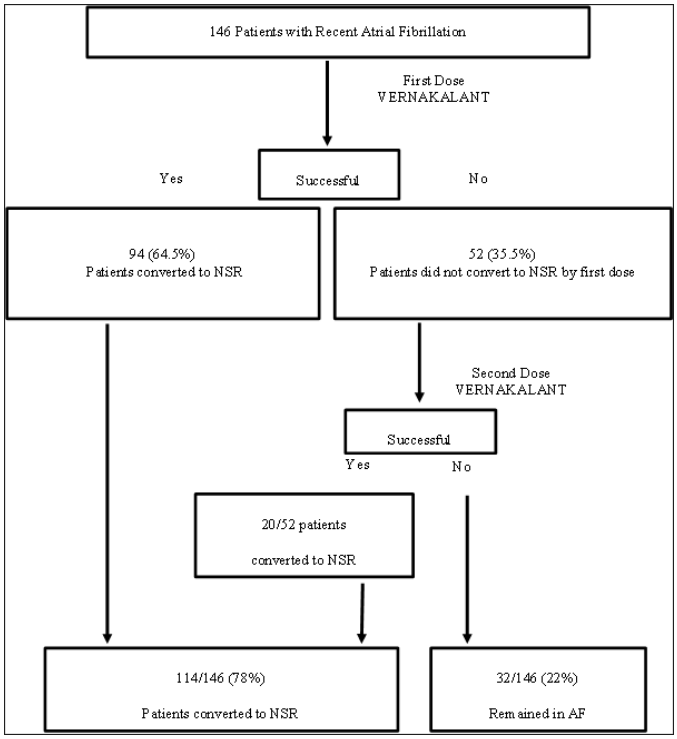

Figure 1 Patient flow chart

All study patients (114\114) who converted to sinus rhythm were discharged home within 3-4hours after admission. Thirty-two patients, who did not convert to sinus rhythm, were admitted to an internal medicine department. Fifteen patients (10%) complained of nausea and altered taste and 10 patients (7%) complained of sneezing and pruritus. There were no other clinically relevant side effects. We observed statistically significant QTc prolongation, but no patient experienced prolongation of the QTc interval to above 500 msec (Figure 2).

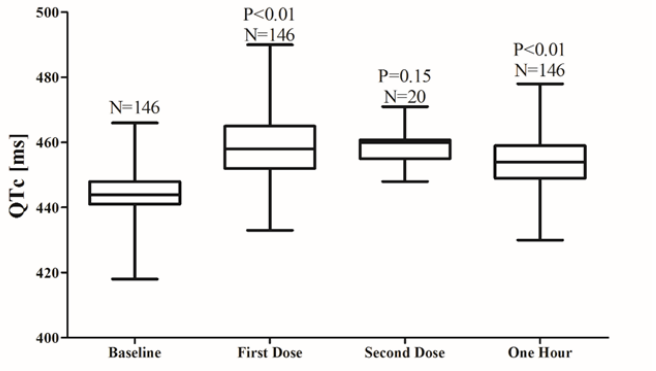

Figure 2 Baseline QT_c and QT_c after the first and the second Vernakalant dose and after one hour later.

Discussion

The principal observation of the study is that among patients admitted to the ER, rhythm control approach with Vernakalant is highly effective and safe and results in rapid conversion to NSR in most patients. This allowed early and safe discharge from the ER.

Vernakalant is a novel antiarrhythmic agent that blocks multiple ion channels with a preferential effect on potassium channels that are more abundant in atrial myocardial tissue; therefore, the effect on ventricular tissue is minimal. As a result, Vernakalant selectively prolongs the atrial refractory period without significantly affecting ventricular refractoriness.[5] Several studies have demonstrated that Vernakalant was significantly more effective than placebo for the conversion of recent-onset AF lasting more than 3hours but less than 7days to NSR and was well tolerated.[6] Table 2 summaries the current evidence on Vernakalant and its use in ER. In the present study, this medication was found to be very effective. Overall 114 out of 146 [78%] converted to NSR. The majority of patients 94/114 [82.5%] converted to NSR within minutes after the first infusion. The action was fast- 12minutes by the first dose and 20minutes by the second dose.

Vernakalant was generally well tolerated, 10 patients complained of nausea and altered taste (dysgeusia), one patient developed transient hypotension that returned to normal limits after completion the drug infusion. In the Arrhythmia conversion trial (ACT I) and (ACT III), intravenous Vernakalant was found to be more effective than placebo in achieving cardioversion of recent AF onset.[7] The results of the current study demonstrate the safety and efficacy of intravenous Vernakalant in patients with recent onset atrial fibrillation presenting to a busy emergency department and highlight the fact that Vernakalant rapidly and effectively converts recent onset atrial fibrillation to sinus rhythm.

Vernakalant reduces the need for electrical cardioversion and associated conscious sedation or anesthesia. The rapid time to conversion in vernakalant-treated patients is consistent with previous phase 3 studies of IV vernakalant in patient with AF. The benefits of early cardioversion include a lower need for mid-term anticoagulation, less electrical cardioversion and no need for lengthy and costly hospital admissions.

Two phase III studies evaluated the efficacy of vernakalant in this setting. In ACT I, patients with AF episodes admitted within 48hours were given vernakalant or placebo.[6] Vernakalant was superior to placebo in terminating AF. In ACT III, patients with episodes lasting

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up to 45days could be randomized to vernakalant, but the efficacy after 7days of AF was lower.[7] In both studies, the rate of conversion to sinus rhythm with vernakalant in patients with short-duration AF was approximately 51%, which is significantly lower than in our study.[8] In addition, Vernakalant was found to be more effective in restoring sinus rhythm than Amiodarone8, Flecainide[9] and Ibutilide.[10]

Recent study from Netherland showed that an approach of "wait and see" results in similar cardioversion rates at 4weeks.[11] In this study, patients randomized to the delayed cardioversion approach were scheduled for an office visit within 48hours for continuation of care, and electrical cardioversion was scheduled for those who remained in AF. This approach proved effective since two-thirds of the patients converted spontaneously to NSR within one month. However, this required multiple clinic visits, and is not applicable in many areas outside the settings of a clinical trial. Thus, despite the results of this study, we believe that our study is more relevant for most hospitals. It should be noted, that despite the fact that vernakalant has no known effect on ventricular activity, there was a prolongation of QT compared to baseline ECG, which is unexplained.

Table 2 Summary of current data on Vernakalant

	Study Population (AF Duration)	Design	Median time to conversion [min]	Conversion to NSR [%]	Number of Patients	
					Vernakalt	Placebo/Control
B. Aires, Argentina[12]	<48 hours			84.5%	121	--
Malmö, Sweden	<48 hours	cohort registry	11 min	70%	351	--
Vienna, Austria [10]	<48 hours	randomized controlled trial	10 min vs 26 min	69% vs 43%	49	51 Ibutilide
Kuopio, Finland [9]	<48 hours	single center non-randomized retrospective study		67% vs 46%	100	100 flecainide
Dublin, Ireland [13]	<48 hours		8 min	83%	42	--
Valencia, Spain [14]	<48 hours	Multicenter, analytical, prospective cohort study	8 min after first dose	78%	165	--
Vienna, Austria [15]	<48 hours	Single center experience		79% vs 68%/71%	68	107 Ibutilide / 59 flecainide
Hadera, Israel	<48 hours		12.5 min after first dose	78%	146	--

Study limitations

This main limitation of our study is the relatively small number of patients followed-up for a short period, and there is no control group. However, study population included a consecutive series of unselected patients which seems to support the generalizability of the current findings verifying the efficacy and safety of use of vernakalant in patients presenting to the emergency department with new-onset atrial fibrillation. Furthermore, our study did not include a clinical follow-up, therefore we cannot estimate the impact of vernakalant therapy on longer-term clinical outcome and the rate of recurrent atrial fibrillation after IV vernakalant infusion.

Conclusion

In conclusion, Intravenous vernakalant is a highly effective and safe therapy to terminate recent onset AF. Our results support the use of Vernakalant for the treatment of new-onset AF.

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Conflicts of interest

There are no conflicts of interest and no relationships with industry.

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