Ivabradine, a novel heart rate slower: Is it a sword of double blades in patients with idiopathic dilated cardiomyopathy?

Ivabradin, yeni bir kalp hızı yavaşlatıcısı: İdiyopatik dilate kardiyomiyopatili hastalarda iki tarafı keskin bir kılıç mıdır?

Mona Rayan, Mazen Tawfik, Ali Alabd, Amr Gamal

Department of Cardiology, Ain Shams University, Cairo-*Egypt*

ABSTRACT

Objective: To prospectively assess the safety and efficacy of ivabradine in patients with idiopathic dilated cardiomyopathy.
Methods: We included 35 patients with idiopathic dilated cardiomyopathy with an ejection fraction (EF) <40% and heart rate >70 beats/min despite optimal medical therapy, according to the international guidelines in this prospective, non-randomized, single-arm, open-label safety study. Ivabradine was used as an add-on therapy to the maximally tolerated β-blocker in an increasing titrated dose till a target dose of 15 mg/day or resting heart rate of 60 beats/min for 3 months. During follow-up period the safety, patient tolerance and efficacy of this drug were assessed. All patients underwent 12-lead resting electrocardiography and Holter monitoring at inclusion and after 3 months. Statistical analysis was accomplished using paired t-test and Pearson correlation analysis.
Results: We found a significant reduction in the resting heart rate by a mean of 25.9±9.4%, without a significant change of blood pressure. There was no prolongation of PR, QTc or QRS durations. Ventricular ectopic activity showed significant reduction (p<0.001). There was a significant correlation between the resting heart rate, NYHA and left ventricular ejection fraction (p<0.001 for both). One patient developed photopsia and decompensation was observed in another patient.
Conclusion: Ivabradine is a safe and effective drug in reducing resting heart rate, improving NYHA functional class without undesirable effects on conduction parameters or ectopic activity. *(Anadolu Kardiyol Derg 2011; 11: 402-6)*
Key words: Ivabradine, dilated cardiomyopathy, heart failure, safety, efficacy

ÖZET

Amaç: İdiyopatik kardiyomiyopatili hastalarda İvabradin'nin güvenilirliğini ve etkisini ileriye dönük değerlendirmek.
Yöntemler: Uluslararası kılavuzlara göre, optimal tıbbi tedaviye rağmen ejeksiyon fraksiyonu (EF) %40'dan az ve kalp hızı > 70 atım/dk. olan idiyopatik dilate kardiyomiyopatili 35 hasta alındı. Maksimal tolere edilebilen beta bloker tedavisine ek olarak, artan titre edilen dozlarda hedef 15 mg/gün ya da istiharat kalp atım hızı 60 atım/dk. oluncaya kadar 3 ay süre ile ivabradin kullanıldı. Takip sırasında ilacın güvenilirliliği, hasta toleransı ve etkinliği değerlendirildi. Girişte ve 3 ay sonra tüm hastalara, 12 derivasyonlu istiharat elektrokardiyografisi ve Holter monitörizasyonu yapıldı. İstatistiksel analiz eşleştirilmiş t-testi ve Pearson korelasyon analizi ile yapıldı.
Bulgular: Kan basıncında önemli bir değişiklik olmaksızın, istirahat kalp hızında ortalama-%25.9±9.4'lük önemli bir azalma bulduk. PR, QTc ya da QRS uzaması yoktu. Ventrikül ektopik aktivitesi belirgin azalma gösterdi (p<0.001). İstirahat kalp hızı, NYHA ve sol ventrikül EF arasında önemli bir korelasyon vardı (her ikisi için p<0.001). Bir hastada fotopsi ve diğer hastada dekompansasyon gelişti.
Sonuç: İvabradin ileti parametreleri ve ektopik aktivite üzerine istenmeyen etkiler göstermeksizin, istirahatte kalp hızını azaltan, NYHA fonksiyonel sınıfı iyileştiren güvenli ve etkili bir ilaçtır. *(Anadolu Kardiyol Derg 2011; 11: 402-6)*
Anahtar kelimeler: Ivabridine, dilate kardiyomiyopati, kalp yetersizliği, güvenilirlilik, etkinlik

Address for Correspondence/Yazışma Adresi: Dr. Mona Rayan, Department of Cardiology, Ain Shams University, Cairo-*Egypt*
Phone: 020114533391 E-mail: monarayan17@yahoo.com

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Introduction

There is an increasing interest in the specific role of heart rate (HR) in a number of cardiovascular diseases including myocardial infarction, and heart failure (HF) (1). HR is usually increased in chronic HF and correlates positively with mortality (2). It was speculated that HR lowering is beneficial by possibly increasing left ventricular (LV) filling, preventing LV ischemia. However, HR reduction-related decrease in cardiac output can be harmful and not necessarily offset by the previously mentioned effects (3). The current guidelines from the American College of Cardiology/American Heart Association and European Society of Cardiology all recommend that β-blockers should be an integral component of the pharmacotherapy for all patients with HF who are receiving other standard treatment (4). Unfortunately, b β eta-blockers are contraindicated in certain patients groups such as those with asthma, or with critical limb ischemia. β-blockers also have a significant number of adverse effects including bronchospasm, lethargy, hypotension, worsening of atrioventricular node disease, sleep disturbance and depression and are therefore not suitable for use in a significant number of patients (5).

Experimental studies using I(f) channel blockers, which have pure bradycardic effects, have shown different results, according to the HF model used, and the clinical effects of long-term HR altering on HF are unknown (6). Few studies, including the SHIFT (7), have dealt with the issue of reducing HR per se in the subset of patients with non-ischemic dilated cardiomyopathy.

Aim of the work was to prospectively assess the safety and efficacy of ivabradine in reducing HR in patients with idiopathic dilated cardiomyopathy.

Methods

Study design

The study was designed as prospective, non-randomized, single-arm, open-label safety study.

The study protocol was approved by the Committee of research and medical ethics of the Cardiology department of Ain Shams University in October 2008 and an informed consent was obtained from all patients included in the study.

Patients

One hundred and sixty seven patients suffering from symptomatic HF referred to Ain Shams University, Cardiology department in 2009, were screened and examined for dilated cardiomyopathy. Initial screening for all patients included assessment for ischemic heart disease by history, perfusion study or angiography, routine laboratory test for liver and renal functions, specific investigations for thyrotoxicosis and collagen disease. After screening, 132 patients were excluded due to patients with NYHA class I (25 patients), coronary artery disease (30 patients), significant rheumatic valvular heart disease (12 patients), thyrotoxic heart disease (3 patients), atrial fibrillation (6 patients), severe renal impairment with serum creatinine >3mg/dl (14 patients), severe hepatic impairment with signs of liver cell failure (10 patients), 10 patients took the drug on irregular basis and 28 patients were living far away to be closely followed up.

Exclusion criteria

1. Patients who were less than 18 years old
2. Pregnant females
3. Patients with previous history or currently suffering from ischemic heart disease using rest, stress perfusion scans
4. Patients suffering from atrial flutter or atrial fibrillation
5. Patients suffering from rheumatic heart disease
6. Patients suffering from advanced liver cell failure
7. Patients suffering from advanced renal failure
8. Patients suffering from congenital heart disease
9. Patients suffering from other types of cardiomyopathy
10. Patients with idiopathic dilated cardiomyopathy with HR below 70 bpm prior to inclusion
11. Patients with diseases that cause sinus tachycardia such as moderate to severe anemia.

We included 35 patients suffering from idiopathic dilated cardiomyopathy and systolic HF with NYHA class II-IV and EF <40% by echocardiography.

Protocol of the study

All patients received spironolactone (at least 25 mg/day) and other diuretics, digoxin. Angiotensin converting enzyme (ACE) inhibitor and carvedilol were up-titrated to the maximally tolerated dose. All patients had to be on stable treatment for at least 4 weeks before inclusion with a resting HR >70 bpm. Patients received ivabradine (Procoralan) as an add on therapy in an increasing titrated dose till reaching a resting HR of 60 bpm or reaching 7.5 mg twice daily. The starting dose was 2.5 mg every 12 hours for 2 weeks, then 5 mg every 12 hours for another 2 weeks, then 7.5mg every 12 hours till the end of 3 months. Patients' consent was mandatory for inclusion, and regular follow up visits.

Safety and efficacy

Safety was assessed by careful follow- up using;

1. Clinical data such as symptoms of acute decompensation, low cardiac output symptoms, HR and blood pressure measurement
2. Resting electrocardiogram (ECG) for measuring HR and different intervals
3. Holter monitoring with assessment of HR and arrhythmia.

Achievement of a HR of 60 beats/min without undesirable side effects was considered a measure of efficacy.

Clinical examination

All patients underwent thorough history taking and clinical examination.

Electrocardiography

Resting 12- lead ECG recordings were analyzed for PR interval duration (measured from the start of definite P wave to the start of QRS complex), QRS duration (measured from the start of Q to the end of R wave), and QT interval (measured from the start of QRS complex to the end of T wave, and was divided by the square root of RR interval). All measurements were done both manually and automatically.

Holter monitoring

Three- lead 24-72 hour ambulatory Holter monitoring using Microvit MT101/ software (Schiller Company, EU) was used. Holter recordings were analyzed for average HR, minimum HR, maximum HR, ectopic activity (type, frequency), sinus pauses and its relation to notified patient events. Analysis of the resting HR was that of night recording whereas, average HR was of the whole day and night.

Echocardiography

Transthoracic echocardiographic examination was done by an expert operator, who was blinded to the patient data. A 2.5 MHz probe of Vivid V (Vingmed, GE, USA) empowered with Echopac software was used for the assessment of LV ejection fraction (EF). Utilizing the short-axis parasternal window at the level of papillary muscles, M-mode measurements of the left ventricle were obtained to calculate EF using Teicholtz method. These tests were done twice at the inclusion and 3 months after treatment.

Statistical analysis

Data obtained at day 0 and 90 days were collected, verified, revised and then edited on the PC. The data were then analyzed statistically using SPSS statistical package version 15 (Chicago, IL, USA). Data were reported as mean±SD. Continuous variables were compared using paired Student's t test, categorical variables were compared using Chi-square test. Scale data were correlated and Pearson correlation coefficient was obtained.

Sample size and power of the study

Power calculations were based on the within-patient difference between the baseline scan and the follow-up; 24 patients per group gave 80% power to detect a change in LV EF of 5%.

Results

Demographic, clinical and medications used in the study group are shown in Table 1. The dose of ACE inhibitor was expressed as % of the target dose recommended by the guidelines and the dose of Carvedilol was expressed in total daily dose in mg.

Safety of ivabradine: During the follow up period, one patient ran into decompensation and β-blockers were stopped and resumed after 10 days, another patient developed photopsia when the dose of ivabradine reached 15 mg/day. Titration went slower till the target HR. On other hand, 33 patients completed the follow up period without any complaints or drug modulation.

Effects of the drug on HR: After 3 months, resting HR showed a mean reduction of- 25.9±9.4 beats/min (104.7±15.6 vs. 77.6±9.7 beats/min, p<0.001) without significant blood pressure drop (Table 2). Resting ECG recorded the drop of HR without significant prolongation of intervals (Table 3).

Effect of HR reduction on EF and grade of dyspnea: HR reduction was accompanied by a significant NYHA class improvement, and a significant increase of EF (32.6±6.7 vs. 38.3±9.7%, p<0.001) (Table 4).

A significant positive correlation existed between the degree of HR drop and EF changes (r^2=0.312, p=0.0005) and NYHA class improvement (r^2=0.2704, p=0.0014) (Fig. 1).

Table 1. Demographic and clinical data of the study group

Variables	n=35
Age, years	44.2±7.5
Sex, male, n (%)	21 (60)
Smoking, current, n (%)	6 (17.1)
Hypertension, n (%)	7 (20)
Diabetes, n (%)	9 (25.7)
NYHA class II, n (%)	2 (5.7)
NYHA class III, n (%)	30 (85.7)
NYHA class IV, n (%)	3 (8.5)
SBP, mmHg	100±17.1
DBP, mmHg	68.2±12.4
Resting HR, beats /min	101.5±14.8
ACEI (% of target dose)	43.5
Carvedilol, mg daily	17.8±13.6

Data are presented as mean±SD and number (percentage)
ACEI - angiotensin converting enzyme inhibitor, DBP - diastolic blood pressure, HR - heart rate, NYHA - New York Heart Association, SBP - systolic blood pressure

Table 2. Blood pressure changes throughout the study

Variables	Baseline	3 months	Percent change, %	*p
SBP, mm Hg	100±17.1	104.1±14.6	4.9±9.5	>0.05
DBP, mm Hg	68.2±12.4	67.6±8.3	0.5±12.1	>0.05

Data are presented as mean±SD
*paired Student's t-test
DBP - diastolic blood pressure, SBP - systolic blood pressure

Table 3. Functional class and EF changes during the study

Variables	Baseline	3 months	Percent change, %	*p
NYHA II, n (%)	2 (5.7)	17 (48.6)	15 (42.9)	<0.001
NYHA III, n (%)	30 (85.7)	17 (48.6)	-13 (37.1)	<0.001
NYHA IV, n (%)	3 (8.5)	1 (2.9)	-2 (5.6)	<0.001
EF, %	32.6±6.7	38.3±9.7	17.5±3	<0.001

Data are presented as mean±SD and number (percentage)
*Chi-square and paired Student's t tests
EF - ejection fraction, NYHA - New York Heart Association class

Holter monitoring showed a significant drop of both day (166.6±8.8 vs.148.8±10.8 beats/min p<0.001) and night (70.4±4.5 vs. 55.7±4.4 p>0.001) maximal HRs with no recorded sinus pauses. The incidence of ventricular ectopic beats showed a significant drop (17.8±8.2 vs. 10.5±6.5, p<0.001) (Table 5).

Discussion

Among the new perspectives in HF management, pure HR reduction with ivabradine offers a promising approach. The rationale for adding a pure HR-lowering agent to a β-blocker is to further reduce the burden of a persistent high resting HR, despite therapy with a β-blocker, on the myocardial cell (6).

In the current study, we prospectively assessed the long-term safety of ivabradine in efficiently reducing HR to 60 bpm in patients with idiopathic dilated cardiomyopathy using several parameters. We found that effective HR reduction (a mean of 25.9 beats/min) was hemodynamically safe and tolerated as it was not associated with symptoms or significant change in both systolic and diastolic blood pressure. These findings are supported by the results of Mulder et al. (7) who found that blood pressure was little affected by the drug, with no hypotension at peak or through drug effect with any dose of ivabradine.

Table 4. Resting ECG parameters during the study

Variables	Baseline	3 months	Percent change, %	*p
Heart rate, beats/min	104.7±15.6	77.6±9.7	-25.9±9.4	<0.001
PR interval, msec	144.2±15.2	143.1±14.5	-0.8±4.6	>0.05
QTc, msec	427.1±11.0	426.5±11.3	-0.14±2.7	>0.05
QRS duration, msec	110±9	111.1±9.3	1.0±3.3	>0.05

Data are presented as mean±SD
*paired Student's t-test
ECG - electrocardiogram, QTc - corrected QT interval

Table 5. Holter monitoring parameters of the study group before and after treatment

Variables	Baseline	3 months	Percent change, %	*p
Maximum HR, beats/min	166.6±8.8	140.8±8.2	10.7±22.7	<0.001
Minimum HR, beats/min	70.4±4.5	55.7±4.4	14.4±2.2	<0.001
Bigeminy	1.0±0.8	1.0±0.5	18.2±12.5	>0.05
PVCs	17.8±8.2	10.5±6.5	41.1±32.1	<0.001

Data are presented as mean±SD
*paired Student's t-test
HR - heart rate, PVC - premature ventricular complexes

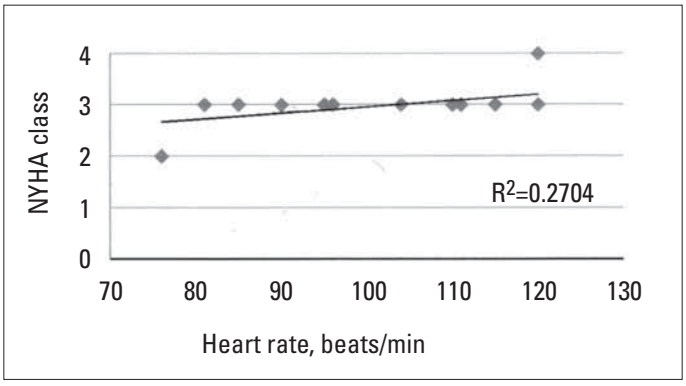

Figure 1. Correlation between heart rate and NYHA class

Enhanced HR, generally observed in patients with congestive HF is a double-edged weapon as it tends to preserve the cardiac output at the cost of impaired left ventricular (LV) filling, increased myocardial O2 consumption, and reduced coronary perfusion time. Thus, HR slowing should, in theory, be beneficial in HF (8).

In the present study, HR drop was associated with significant improvement of NYHA class. This is supported by the study of Logeart et al. (9) who found a significantly lower NYHA class (2.2+0.6 vs. 2.6+0.5, p=0.03) in patients with HF paced at 75 bpm as compared with pacing at 55 bpm.

We found that, the drop in HR was not associated with prolonged conduction (PR interval, QRS duration, and corrected QT interval). This finding is considered an important issue in the setting of HF. Two studies support this observation; they found that ivabradine reduces HR without any observed effects on the cardiac conduction system. In one study, 14 patients received a single intravenous administration of ivabradine (0.2 mg/kg). Resting HR was lower by approximately 14 bpm. As expected, the QT interval was prolonged by 37.5 s. However, when QT was corrected for HR (QTc), there was no QTc prolongation. Ivabradine did not modify the PR and QRS intervals or the conduction properties and refractoriness of the atrium, atrioventricular node, His-Purkinje system and ventricles (10).

The LVEF is a well validated marker of left ventricular remodeling process that contributes to systolic left ventricular dysfunction after cardiac inflammation or injury. Changes in the LVEF are an important surrogate for the progression of myocardial disease and subsequent clinical outcomes (11).

In the present study, the use of ivabradine and HR drop was associated with significant improvement in EF. This is supported by a recent meta analysis of 26 β-blocker trials that reported a strong correlation between magnitude of HR reduction and improvements in LVEF (r^2=0.53; p=0.005) (12). The only subgroup in the BEAUTIFUL trial to demonstrate benefits from ivabradine was patients with baseline HRs greater than 70 beats/min (13).

Based on our results of Holter monitoring, the administration of ivabradine was associated with effective and a well tolerated HR reduction throughout the recording period without any significant bradycardia and sinus pauses. In the reported clinical trials there were few problems with drug- induced bradycardia and minimal patient withdrawal (7).

We reported visual disturbances in one patient when ivabradine dose reached 15 mg /day. In clinical studies (10), there is a less than 1% withdrawal rate because of side effects. Visual symptoms were reported in less than 2% of patients receiving 5 mg twice daily. It appears to be a dose-dependent effect. Ivabradine is selective for I_f channels but due to its pharmacological

effect, it can also interact with the structurally similar retinal I_h channel, involved in the response to light stimuli. Extensive testing showed that Ivabradine was not associated with any alteration of ocular structures or permanent visual disorders. Most visual symptoms are mild, occurring only as occasional brief episodes often associated with abrupt changes in light intensity, and have minimal impact on patients' daily activities with no deleterious effects on their quality of life (10).

Study limitations

As we were concerned with the safety of ivabradine in reducing the HR in a special subset of HF that was not evaluated before, a relatively small number of patients was included and ivabradine was used as an add-on therapy. Therefore, further larger randomized studies should be undertaken to investigate the morbidity and mortality benefits of ivabradine in patients with idiopathic dilated cardiomyopathy.

Conclusion

Based on the results of the current study, we concluded that the use of ivabradine in patients with idiopathic dilated cardiomyopathy and sinus rhythm is effective and safe. HR drop was accompanied by a significant improvement in the systolic function, NYHA class and a drop in ventricular ectopic activity. Its use was o't associated with conduction abnormalities.

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Conflict of interest: None declared.

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