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Research Article

Effects of Ivabradine in Patients with COPD and Non-Paroxysmal Atrial Fibrillation: A Pilot Study

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Abstract

Background: The aim of this study was to evaluate if the addition of ivabradine to the ongoing therapy in COPD patients with non-paroxysmal atrial fibrillation (AF) could improve their heart rate (HR) control. Secondary endpoints were effects on exercise tolerance and self-perceived exertion.

Methods: We enrolled 22 patients with COPD and non-paroxysmal AF; mean age 76.9 ± 8; M/F = 14/8, already treated with HR lowering agents but still with uncontrolled HR. Patients were randomly assigned to one of the two following groups: group 1 (11 patients) started ivabradine in addition of their ongoing therapy; group 2 (11 patients) increased the dose of their HR lowering agent without introducing ivabradine. At baseline and after three weeks all patients performed ECG and six minute walk test (6MWT).

Results: After three weeks heart rate at rest and during 6MWT decreased in both group in a comparable fashion. Distance walked at 6MWT increased in both groups with a greater increase in the group 1 compared to group 2 ($p = 0.002$). Systolic blood pressure decreased significantly in group 2 while was unchanged in group 1 (intergroup $p = 0.0004$). self-perceived exertion improved significantly in the group 1 compared to group 2.

Conclusion: our data suggest that adding ivabradine to an HR lowering agent has comparable effects on HR control than increase the dose of the HR-lowering agents. Ivabradine was more effective in improving exercise tolerance and patient symptoms.

Keywords: *Ivabradine; Atrial Fibrillation; COPD*

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have an increased likelihood of arrhythmias and in particular of atrial fibrillation (AF) [1-3]. The presence of AF in patients with COPD worsen the prognostic profile [4,5] and contribute to the reduced exercise tolerance experienced by these patients. In the case of non-paroxysmal AF, pharmacological interventions aimed to obtain heart rate (HR) control are associated to the treatment of the underlying COPD, and contribute to the hemodynamic stability and clinical improvement of such patients. However the achievement of the of target HR is often hindered by several factors including increased sympathetic tone, use of bronchodilators and presence of comorbidities that restrict therapeutic options. Ivabradine is a pure heart rate lowering agent acting through the inhibition of If current, and it is widely used for patients with stable angina and chronic heart failure in sinus rhythm. Some very preliminary data, published in the last few years, suggest the potential effectiveness of ivabradine, alone or in combination with others HR-lowering agents (HRLA), for obtaining HR control in patients with non-paroxysmal AF [6-9]. Interestingly patients with non-paroxysmal AF treated with ivabradine experienced an improvement of their exercise tolerance and symptoms during both submaximal and maximal exercise, in association to HR reduction considering that ivabradine does not affect respiratory function in patients with COPD

[10] it is an intriguing question whether ivabradine could represent an alternative choice for reducing HR in patients with non-paroxysmal AF, and COPD. To our knowledge there are no studies evaluating this potential use of ivabradine. In this study we tested the hypothesis that the administration of ivabradine to COPD patients with non-paroxysmal AF, in addition to their ongoing therapy, would improve HR control. Secondary endpoints were effects produced by ivabradine on exercise tolerance and rate perceived exertion.

Materials and Methods

We evaluated 22 patients with history of COPD and non-paroxysmal AF admitted to the respiratory rehabilitation division of our Institution after an acute pulmonary event. Subjects were enrolled if they fulfilled the following inclusion criteria: stable clinical conditions and stabilized treatment for the underlying COPD; advanced COPD: expiratory forced volume in the 1st second < 50%; history of non-paroxysmal AF (present for at least 6 months); HR > 100 bpm at a resting ECG; ongoing treatment with an HRLA at submaximal dose. Exclusion criteria were neurological or orthopedic conditions limiting the exercise activity; known concomitant coronary heart disease or chronic heart failure; significant (moderate to severe) valvular disease; hypotension (systolic blood pressure <100 mmHg); advanced kidney disease (Stage III-IV); neoplasms; indication for ablation or electrical cardioversion.

The study protocol was conform to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by San Raffaele Ethics Committee.

Study design

At baseline visit, on hospital admission, inclusion and exclusion criteria were evaluated and the informed consent was signed. Eligible patients underwent a full clinical examination, spirometry, electrocardiogram (ECG) evaluation, blood pressure (BP) assessment and performed a 6 minute walk test (6MWT) After baseline screening subjects were randomly allocated on a 1:1 basis to receive ivabradine, in addition to their current treatment (group 1, n = 11) or to titration of their ongoing HRLA (group 2, n = 11). Patients of group 1 started ivabradine 5 mg/bid at baseline. They were re-evaluated after one week with ECG and it was decided either to maintain or to increase the dose of ivabradine to 7.5 mg/bid. At second week according to the result of another ECG it was possible to increase the dose of the CCA/BB, if needed, according to the physician's judgment; conversely the dose of ivabradine was not changed. Group 2: the dose of CCA/BB was increased at baseline and patients were also re-evaluated through ECG each week for eventual further increase of the drug dose. Each therapeutic change was decided according to the physician's judgment. After 3 weeks all patients underwent a final evaluation and performed a second 6MWT.

Exercise tolerance was evaluated by 6 MWT. The test was performed according to the standardized procedure [11]. Each test was supervised by a blinded physical therapist. Patients were asked to walk at their own maximal pace a 100 m long hospital corridor. Every minute a standard phrase of encouragement was told. Patients were allowed to stop if signs or symptoms of significant distress occurred (dyspnea, fatigue) through they were instructed to resume walking as soon as possible.

HR was recorded at baseline, at third minute during the walk test, considered as steady state. Results of 6 MWT were expressed as distance walked (meters). The modified Borg scale was used to rate perceived exertion (RPE) [12].

Statistical analysis

Continuous variables were presented as mean±1 standard deviation (SD) and categorical variables as numbers and percentages if normally distributed. Comparisons between the items were made by t-test, ANOVA and Wilcoxon rank-sum tests for continues variables and chi-square and fisher's exact tests for categorical variables.

Results

At baseline eight patients were taking BBs (bisopolol or carvedilol) and 14 were taking CCA. Mean doses of bisoprolol and carvedilol were 2.5±0.2 mg/day and 12.5 ± 2 mg/day respectively. Mean doses of verapamil and diltiazem were 81.4±23 mg/day and 83.7±33 mg/day respectively. Baseline patient characteristics are presented in table 1. There were no significant differences between the 2 groups

with respect to all variables. The acute event requiring rehabilitation was pneumonia (68% cases). After the first week seven out of eleven (63.6%) of group 1 needed to increase the dose of ivabradine to 7.5 mg/bid. Four out of eleven (36.3%) of group 2 needed titration of CCA/BB. At second week three patients of group 1 needed to increase the dose of their CCA/BB; two patients of group 2 needed further titration of their CCA/BB. At the final evaluation HR at rest and at steady state decreased significantly in both groups compared to baseline, without intergroups differences (0.11). Distance walked at 6MWT increased in both groups with a greater increase in the group 1 compared to group 2 (p 0.002). Borg's score improved significantly in the group 1 compared to group 2. Systolic BP decreased significantly in group 2 while was unchanged in group 1 (intergroup p=0.0004). Diastolic BP decreased in group 2 while was unchanged in group 1. No side effects occurred during the follow up and all subjects completed the study.

	Group 1	**Group 2**
Age, years	77.2 ± 5	76.2 ± 7
Male/female	8/3	6/5
Hypertension, n (%)	9 (82)	9(82)
Diabetes, n (%)	2 (19)	1(9)
Smokers, n (%)	8 (73)	7 (64)
GOLD class III/IV	8/3	7/4
Spirometry		
FEV1 (%)	39.1 ± 7	38.2 ± 8
FVC (%)	67.3 ± 7	66.5 ± 11
IC (%)	53.6 ± 9	54.1 ± 7
RV (%)	177.0 ± 30	178.2 ± 32
TLC (%)	116.4 ± 29	115.1 ± 24
Treatment of COPD		
Steroids, n (%)	11 (100)	10 (91)
B2 adrenergic agonists agents, n (%)	7 (64)	8 (73)
Anticholinergic agents, n (%)	10 (91)	9 (82)
HR lowering agents		
Verapamil, n (%)	5 (45)	7 (63)
Diltiazem, n (%)	2 (19)	1 (9)
Bisoprolol, n (%)	3 (27)	2 (19)
Carvedilol, n (%)	1 (9)	1 (9)

Table 1: *Baseline findings of patients.*

LVEF: Left Ventricle Ejection Fraction; LVSV: Left Ventricle Systolic Diameter; LVDD: Left Ventricle Systolic Diameter; RVDD: Right Ventricle Diastolic Diameter; FEV1: Forced Expiratory Volume in the 1st Second; FVC: Forced Vital capacity; IC: Inspiratory Capacity; RV : Residual Volume; TLC: Total Lung Capacity

	Group 1		Group 2	
	Baseline	3 weeks	Baseline	3 weeks
Resting HR, bpm	113.4 ± 21	87.9 ± 29*	109.6 ± 45	80.0 ± 31*
Exercise HR, bpm	136.8 ± 42	115.5 ± 41*	138.3 ± 39	110.5 ± 48*
SBP, mmHg	129.3 ± 26	121.2 ± 34	131.8 ± 36	102.5 ± 37*
DBP, mmHg	88.4 ± 16	89.0 ± 22	88.7 ± 21	82 ± 18
Borg scale	7.3 ± 1.6	2.2 ± 0.3*×	7.8 ± 2.1	4.8 ± 1.1*
6mwd, m	178.6 ± 23	325.3 ± 55*×	173.2 ± 28	267.1 ± 46*

Table 2: *Comparison (3 weeks versus baseline) of study endpoints.*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Exercise HR: HR Detected during the 6mwt; mwd: Distance Walked at 6mwt

** Intragroup differences (p < 0.05)*

× intergroup differences (p < *0.05)*

Discussion

In this study we demonstrated that the administration of ivabradine in patients with COPD and non-paroxysmal AF, already taking HRLA but still with uncontrolled HR, was as effective as titrating their ongoing HRLA in reducing HR both at rest and during submaximal exercise. This is the first study evaluating the effects of ivabradine in COPD patents with non-paroxysmal AF. Controlling HR is one of the most important goals for patients with non-paroxysmal AF because it elicits clinical improvement and enhances exercise tolerance of these patients. However, according to current evidences about 20 - 30% of patients with non-paroxysmal AF do not reach HR control with available drugs [13]. For subjects with non-paroxysmal AF and significant COPD pharmacological strategies include CCA, alone or in combination with digoxin, and cardioselective BBs [14]. However, despite current evidences support giving BBs to patients with COPD, data from retrospective studies show that few patients with AF and COPD are treated with BBs compared with those without COPD [5,15]. Therefore there is room for new HR-lowering agents to be used in this condition and for therapeutic strategy implementation. Moreover, lowering HR in subjects with COPD could have positive prognostic implication [16,17]. Jensen., *et al*. [16] evaluated follow up data of a broad population from the Copenhagen City Heart Study demonstrating that resting HR was associated with both cardiovascular and all-cause mortality across all stages of COPD. Our result, despite generated by a small pilot study, seems to indicate that adding ivabradine to a CCA/BB could represent another option for obtaining HR control in these patients. Results of secondary endpoints of this study suggest that a pharmacological strategy combining ivabradine to another HRLA could be associated with more favorable short term outcomes compared to more traditional approaches. Firstly we observed that patients treated with ivabradine presented a greater increase of 6MWT distance than controls at the end of the rehabilitative protocol. Our data comply with similar findings recently published by Mahmoud., *et al*. [18] who administered ivabradine 7.5 twice per day versus placebo to patients with COPD, sinus rhythm, and resting HR over 90 bpm. They observed a significant increase in the 6mwt distance in the treated group compared to placebo. Secondly we documented a significant greater improvement of RPE scale score in patients taking ivabradine compared to controls. A similar result was found by Mahmoud in patients with COPD and sinus rhythm [18] and by our group in subjects with non-paroxysmal AF without significant COPD [8]. We think that, in this study, clinical benefits derived from HR control in patients of group 2 were counterbalanced by the occurrence of hypotension that limited their exercise tolerance and contribute to a worst self-perceived exertion during the walk test.

Conclusion

Our results, though very preliminary, suggest that starting ivabradine instead of increasing the doses of BB/CCA, could represent an alternative choice in COPD subjects with non-paroxysmal AF and uncontrolled HR. Our data show that the addition of ivabradine effectively decreased HR reducing the need of CCA/BB titration and, therefore, avoiding the occurrence of hypotension. This translated into a greater positive impact on exercise tolerance and patients symptoms. This is a small pilot study and further research are mandatory in order to clarify the role of ivabradine in patients who are not in sinus rhythm and in particular in those with advanced COPD.

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