Safety, tolerability and efficacy of ivabradine for control of sinus tachycardia in patients undergoing inotropic therapy

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OBJECTIVES: To assess the safety, tolerability and efficacy of ivabradine administered to patients experiencing decompensated heart failure who were undergoing inotropic therapy and developed undesirable sinus tachycardia.

METHODS: The present study prospectively included consecutive patients with ischemic-necrotic cardiomyopathy and an ejection fraction <35% who were admitted for decompensated heart failure while undergoing inotropic therapy and developed undesirable sinus tachycardia. Patients experiencing shock, or requiring respiratory or circulatory mechanical support, or those presenting with a heart rhythm other than sinus were excluded. Hemodynamic measurements using a pulmonary artery catheter were performed before and 3 h after an oral dose of 15 mg of ivabradine. Adverse side effects and tolerance were evaluated.

RESULTS: The present study included 52 patients (32 men, 20 women) with a mean age of 65.6 years and a mean ejection fraction of 31.5%, who were undergoing inotropic treatment (15 µg/kg). Three hours after ivabradine administration, a reduction in mean (± SD) heart rate from 121±6 beats/min to 98±7 beats/min (P=0.00002) was observed, with an incremental increase in systolic volume from 37.9±5 mL to 47.3±8 mL (P=0.00002) and an increase in cardiac output from 4597±550 mL/min to 4825±535 mL/min (P=0.041). No differences were observed in filling pressures, or systemic or pulmonary resistances. There was good clinical tolerance without hypotension, bradycardia or episodes of atrioventricular block.

CONCLUSIONS: Ivabradine proved to be useful and safe for controlling undesirable sinus tachycardia in patients undergoing inotropic treatment.

Key Words: *Heart failure; Inotropes; Ivabradine*

Advanced heart failure is characterized by the exacerbation of compensatory mechanisms including tachycardia and elevation of systemic resistance. The use of intravenous inotropic therapy in decompensated patients to improve deteriorating systolic discharge is associated with several adverse consequences, such as increased myocardial oxygen consumption, proarrhythmic effects and myocardial ischemia, and unavoidably produces undesirable sinus tachycardia.

Therapeutic options for patients presenting with undesirable sinus tachycardia and undergoing treatment with intravenous inotropic agents are extremely limited. Beta blockers cannot be considered due to their negative inotropic effects, and the use of calcium channel blockers has proved to be deleterious. Furthermore, digitalis increases myocardial oxygen consumption, which is already at critical levels in this patient population (1-3).

Published results support the use of the channel inhibitor ivabradine in patients with low ejection fraction, heart failure and sinus rhythm, as well as in individuals developing undesirable sinus tachycardia induced by exogenous catecholamines after major surgery (4-7). Accordingly, the present study aimed to analyze the safety, tolerability and efficacy of ivabradine in patients with ischemic cardiomyopathy and a low ejection fraction who were admitted for decompensated heart failure and developed undesirable sinus tachycardia while undergoing treatment with intravenous inotropic agents.

METHODS

Population

The present study included consecutive patients with ischemic cardiomyopathy and a low ejection fraction (determined to be <35% using echocardiography or ventriculography performed during the previous six months) who were admitted to critical care for decompensated heart failure and experienced sinus tachycardia (heart rate >100 beats/min) while undergoing inotropic therapy (≥10 µg/kg dopamine or dobutamine separately or in combination). Patients were treated with oral ivabradine in an attempt to counteract sinus tachycardia. Inotropes were administered intravenously to patients with a cardiac index (CI) <2.0 L/min/m^2. Inclusion criteria for the present study included: >18 years of age; mean blood pressure between 60 mmHg and 80 mmHg, and systolic blood pressure >90 mmHg without the use of vasopressors; observation of stabilized CI >2.2 L/min/m^2 in the 6 h before the administration of ivabradine; and absence of hypovolemia, defined as a central venous pressure >10 mmHg and pulmonary capillary occlusion pressure >15 mmHg. Exclusion criteria included myocardial diseases of nonischemic etiology; shock (of any cause); need for respiratory mechanical support; need for circulatory mechanical support; inability to take oral medications; concomitant active infections, or oncological or acute digestive pathologies; hemodynamic instability requiring a higher inotropic dose or expansions during the previous 6 h; previous use of or hypersensitivity to ivabradine; inability to place a pulmonary artery catheter; and presence of a heart rhythm other than sinus.

Treatment

Ivabradine was administered as a single oral dose of 15 mg. Hemodynamic monitoring was performed using pulmonary artery catheters (Edwards Lifesciences Inc, USA) for all patients. Cardiac output measurements were collected using a thermodilution method, which included a 10 mL injection of saline. Cardiac output profiles included in the database were constructed using seven measurements; the highest and the lowest result were omitted, and the mean was calculated using the remaining five measurements.

Complete hemodynamic measurements were collected 1 h before and 3 h after the administration of ivabradine. Mean arterial pressure,

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TABLE 1
General characteristics of the study population

Characteristic	
Male sex	32 (61.5)
Female sex	20 (38.5)
Age, years, mean (range)	65.6 (42–76)
Diabetes	10 (19.2)
Smoking	18 (34.6)
Hypertension	28 (53.8)
Dyslipidemia	37 (71.15)
Previous myocardial infarction	33 (63.5)
Previous surgery	4 (7.7)
Previous angioplasty	41 (78.8)
Previous treatment	
Angiotensin-converting-enzyme inhibitors	50 (96.2)
Beta-blockers	35 (67.3)
Digoxin	3 (5.8)
Amiodarone	6 (11.5)
Inotropic treatment	
Dopamine	9 (17.3)
Dobutamine	52 (100)

Data presented as n (%) unless otherwise indicated

central venous pressure, pulmonary artery pressures (systolic, diastolic, mean and pulmonary capillary occlusion pressure), cardiac output, CI, systemic and pulmonary vascular resistances, systolic volume, systolic index and left ventricular systolic index were recorded.

Safety and tolerance

The development of sinus bradycardia (heart rate <60 beats/min) was evaluated according to new atrioventricular disturbances, requirement of temporary pacemakers, symptomatic hypotension (systolic blood pressure <90 mmHg) and general intolerance presenting as nausea, vomiting, diarrhea or visual side effects. The Institutional Research Ethics Committee approved the present study. Informed consent was obtained from all patients or their guardians.

Statistical analysis

Statistical analyses were performed using CONICET (*Consejo Nacional de Ciencia y Tecnica* – National Council for Science and Technique, Argentina) using SPSS version 20.0.0 (IBM Corporation, USA). A univariate analysis was performed to compare differences between pre- and post-therapeutic intervention(s). Continuous variables were expressed as mean ± SD, and categorical variables were expressed using counts and percentages. If the data were distributed normally, continuous data were analyzed using the Student's *t* test; if distribution was not normal, the Wilcoxon-Mann-Whitney test was used. Analysis of categorical data was performed using the χ^2 test; P<0.05 was considered to be statistically significant.

RESULTS

Fifty-two patients (32 men, 20 women; mean age 65.6 years) participated in the present study between January 1, 2011 and June 6, 2013. Table 1 summarizes general patient characteristics. Before admission, patients were assigned to a functional class (FC): six (11.5%) in FC 1; 13 (25%) in FC 2 ; and 33 (63.5%) in FC 3. Nineteen (36.5%) patients were admitted in the previous six months for heart failure. The mean left ventricular ejection fraction was 31.5%. Seventeen (32.6%) patients presented with no significant mitral insufficiency. Immediately before the administration of ivabradine, the mean dose of inotropes was 15.2 µg/kg (range 10 µg/kg to 25 µg/kg).

Three hours after ivabradine administration, a reduction in mean (± SD) heart rate from 121±6 beats/min to 98±7 beats/min (P=0.00002) was observed. In addition, a significant increase in cardiac output, systolic volume and systolic volume index was recorded.

TABLE 2
Pre- and postivabradine hemodynamic parameters

Parameter	Preivabradine	Postivabradine	P
Heart rate, beats/min	121±6	98±7	0.00002
Arterial pressure, mmHg	73.7±9	73.8±11	0.9
Right ventricular pressure, mmHg	12.3±2.8	12.1±2.2	0.66
Pulmonary pressure, mmHg	22.4±2	21.7±2	0.11
Pulmonary capillary pressure, mmHg	17.6±2.8	16.7±2.6	0.059
Cardiac output, mL/min	4597±550	4827±535	0.041
Cardiac index, L/min/m^2	2.21±0.3	2.33±0.3	0.052
Systolic volume, mL	37.9±5	49.3±8	0.00002
Left ventricular systolic performance index, g/m^2	41.1±3	43.9±2	0.049
Systemic resistance, dyn•s•cm^{-5}	1082±197	1030±181	0.018
Pulmonary resistance, dyn•s•cm^{-5}	83.6±18	92.6±25	0.07

Data presented as mean ± SD unless otherwise indicated

There were no noted differences in systemic or pulmonary resistance (Table 2). None of the patients experienced bradycardia, atrioventricular conduction disturbances or required temporary pacing. After administration was complete, ivabradine intolerance was not observed in any of the patients during a length of time equal to five plasma half lives of the drug (60 h of observation).

DISCUSSION

The main finding of the present study was that ivabradine controlled undesirable tachycardia in patients with ischemic cardiomyopathy admitted with decompensated heart failure and undergoing intravenous inotropic therapy. A mean reduction in heart rate of 19% was observed, without affecting positive inotropic effects. The drug was well tolerated, and no new bradyarrhythmias or atrioventricular conduction disturbances were observed, nor did other intolerances emerge. This result is important because there is limited literature regarding the use of ivabradine in patients with decompensated heart failure requiring inotropic treatment.

Link et al (6) previously described a case involving a 50-year-old patient with ischemic cardiomyopathy presenting with low cardiac output syndrome who was receiving 18 µg/kg of dobutamine and was experiencing sinus tachycardia up to 120 beats/min. With the addition of 7.5 mg ivabradine twice per day, a 34% reduction in heart rate (from 115 beats/min to 75 beats/min) was observed without further decrease. In addition, an increase in CI from 1.5 L/min/m^2 to 2.0 L/min/m^2 was reported.

Cavusoglu et al (7) reported two series of patients with decompensated heart failure undergoing dobutamine treatment who received ivabradine to counteract undesirable sinus tachycardia induced by an inotropic agent. In the first series, a total of 73 patients with an ejection fraction <35% undergoing dobutamine treatment at three different doses (5 µg/kg, 10 µg/kg and 15 µg/kg) were examined. They received two doses of ivabradine (7.5 mg every 12 h) and were compared with a control group (receiving no other negative chronotropic treatment) and a third group receiving beta blockers. Ivabradine counteracted induced sinus tachycardia in patients receiving 10 µg/kg and 15 µg/kg of dobutamine, although no difference was observed in patients receiving 5 µg/kg of dobutamine. In the second series, sinus rhythm measured using Holter monitors in 69 patients undergoing treatment with dobutamine was compared with a control group receiving no negative chronotropics (29 patients), a group that received 7.5 mg ivabradine administered every 12 h (26 patients) and a third group that received beta blockers (15 patients). The group that underwent treatment with ivabradine did not exhibit an increase in heart rate (unlike the control and beta blocker group); however, the patients

did exhibit an increase in the number of ventricular extrasystoles and the number of ventricular arrhythmias, which were reduced in the beta blocker treatment group (8).

Roubille et al (9) considered the negative chronotropic use of the drug in patients with cardiogenic shock treated with dobutamine; however, hemodynamic data were not reported.

Any approach regarding the use of ivabradine as a selective negative chronotropic agent in patients with sinus rhythm and inotropic-induced tachycardia is based on the fact that the drug acts exclusively on sinoatrial node cells, which interfere with the entry of sodium and potassium ions through channels activated by hyperpolarization and regulated by cyclic nucleotides. This causes diastolic depolarization (phase 4), consequently reducing heart rate without negatively affecting inotropism or lusitropism due to the absence of If channels in other regions of the heart. This accounts for the absence of deleterious cardiac effects observed in our population (10,11).

The importance of heart rate for survival in patients with heart failure and other conditions is significant, a fact that has been extensively documented given that tachycardia has a major effect on myocardial oxygen consumption. Due to its effects on heart rate, ivabradine reduces myocardial oxygen consumption, maximizing oxygen supply and myocardial perfusion by prolonging diastole and favouring coronary vasodilation during exercise or other forms of stress. Unlike ivabradine, beta blockers tend to extend systole due to their negative inotropic effect on contractility, which consequently reduces diastolic time at rest or during stress. A prolonged diastole in patients with left ventricular dysfunction improves ventricular filling and systolic volume, which results in an improvement of the efficacy and work of the pump, as was observed in our patients (12-15).

Colin et al (16) reported that ivabradine reduces heart rate by increasing the diastolic time and calcium-troponin C unbinding, consequently favouring diastolic relaxation. Fang et al (17) demonstrated that a reduction in heart rate caused by ivabradine produces several myocardial effects, such as a reduction in oxygen consumption, thereby decreasing oxygen debt, improving endocardial nitric oxide bioavailability, increasing activation of nitric oxide synthase and a dependent increase in nitric oxide-induced coronary vasodilation. The final effect of these related factors is the optimization of the fixation process and breakdown of myosin and actin crossbridges, a process that is strictly ATP-dependent (16-18).

Safety and tolerance

Hemodynamic parameters obtained using pulmonary artery catheters revealed an absence of hemodynamic deterioration in decompensated patients requiring intravenous inotropic agents, as well as excellent clinical tolerance to 15 mg of orally administered ivabradine.

The safety of ivabradine has been previously tested in >5000 patients, with visual side effects being the most commonly reported, including the appearance of phosphenes, stroboscopic effects and blurry vision. Visual manifestations are reported in 2% to 15% of patients treated, and are rarely sufficiently severe to abandon treatment. The presence of Ih receptors in the eyes can cause these visual side effects. Other side effects may include confusion, dizziness, dyspnea or food intolerance, which were not observed in our study population (19). Unlike beta blockers, ivabradine does not produce hypotension, sexual dysfunction, bronchospasm or a rebound effect after sudden discontinuation of treatment (20,21).

Early in 2012, the use of ivabradine in patients with chronic heart failure was approved by the European Medicine Agency, based on the results of the SHIFT study (4). Guideline recommendations from the European Society of Cardiology established the role of ivabradine in patients experiencing heart failure, sinus rhythm, ejection fraction <35% and heart rate >70 beats/min, who are symptomatic under optimal medical treatment.

Our findings are a modest contribution toward the putative use of ivabradine in decompensated patients undergoing intravenous inotropic therapy; however, further studies are required.

Limitations

The present study reports a noncontrolled series with a limited number of patients, all of whom had an ischemic etiology of cardiomyopathy treated exclusively with beta-adrenergic inotropes, with the addition of ivabradine for a short interval of time. Effects of prolonged use of ivabradine, as well as its effects in other etiologies of heart failure remain to be determined.

CONCLUSIONS

Ivabradine was useful and safe for achieving selective negative chronotropic effects in counteracting undesirable sinus tachycardia, which developed in patients with decompensated heart failure treated with intravenous inotropic agents who could not receive or were intolerant to beta blocker agents. Randomized studies with an appropriate number of patients are needed to collect more information regarding its suggested benefit.

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