Ivabradine use in patients with HFrEF in the heart failure multidisciplinary program (PIC) in a private hospital: first registration and 3-years follow up, Central American (CA) region.

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RESUMEN

Introducción y objetivos: La elevación de la frecuencia cardíaca (FC) en pacientes (p) con insuficiencia cardíaca (IC) con fracción de eyeción reducida (ICFE) se relaciona con un aumento de la mortalidad y la hospitalización por IC; su reducción mejora el llenado del ventrículo izquierdo, aumenta el suministro de oxígeno al miocardio y reduce su consumo, todo lo cual es beneficioso en p con deterioro de la función sistólica del ventrículo izquierdo. El uso de ivabradina (IBRA) en p con ICFE, en ritmo sinusal (SR) y FC> 70 latidos por minuto (lpm), reduce las hospitalizaciones por insuficiencia cardíaca y la mortalidad por insuficiencia cardíaca. El manejo de p con FC avanzada en PIC asegura una reducción de la morbilidad y la mortalidad con los mayores niveles de evidencia. El primer análisis retrospectivo en un PIC en un hospital privado en centroamérica, durante 3 años de todos los casos p con ICFE que recibieron tratamientos (tx) recomendados por Internationat Guidelines y mantuvieron FC> 70 lpm en reposo en SR, con el objetivo de reducirla. El uso de datos clínicos basales, péptidos natriuréticos (NP) y FEVI en reposo, en comparación con las mismas variables en el seguimiento, en una región donde estos PIC están naciendo.

Métodos: 26 p con ICFE durante 3 años de PIC. Se registraron datos generales, tx, estado clínico basal, presión arterial, pulso, NYHA, calidad de vida (QoL), NP, FEVI por ecocardiografía Doppler, y se comparó la respuesta de IBRA tx al inicio y al final. 18 p datos completados; 8 incompleto (datos iniciales o de seguimiento).

Resultados: p ambulatorios, con ICFE (<35%) y SR FC> 70 lpm; 78 años de edad, 17 hombres. Tiempo promedio de Tx con IBRA 11 meses, 53.5% más de 1 año. Medicamentos de referencia, 93% IECA o IRA II; 85% de betabloqueantes y 74% de MRA, dosis máximas toleradas. Ningún paciente usó IBRA antes de la línea base. 20% de CRT. Comportamiento de las variables evaluado: FC (basal 89 lpm frente a 62 lpm después de IBRA 2 meses); BP (sistolica basal de 100 mmHg frente a 123 mmHg de extremo, línea diastólica basal de 55 mmHg frente a 65 mmHg de extremo); FEVI (línea de base 29% frente a 35% de final); BNP línea de base 7.550 pg / ml vs 1.935 pg / ml final. 5 p mejoró NYHA III a NYHA I, 5 p mejoró NYHA III a NYHA II, 3 sufrió deterioro NYHA III; el resto se mantuvo sin cambios. 77% p no se requiere ajuste de dosis (FC por debajo de 70 lpm). 6 p comenzó con 2.5 mg cada 12 horas y aumentó a 5 mg cada 12 horas después de 15 días. Por KCCQ-12 aumenta de 42 a 59 puntos. 1 caso de discontinuación de IBRA debido a bradicardia (FC <50 lpm). 2 p hospitalizados, una neumonía y una descompensación de FC. 3 muertos: 1 infarto de miocardio, progresión de 2 FC.

Conclusiones: 26 p estudiados, registrados y tratados con IBRA en el PIC en un hospital privado en CA, la mayoría de ellas registraron mejorías métricas identificadas como factores pronósticos (FC, BP, FEVI, NP, NYHA y QoL). Esta evaluación, registro y seguimiento de p con ICFE con uso de IBRA en un PIC, es la primera llevada a cabo en CA. Los resultados reflejan la práctica clínica habitual en un CFP, con cardiólogos y enfermeras capacitados para apoyar y dar seguimiento p, y evidencian la importancia del CFP al usar y prescribir fármacos como el IBRA, en una región donde estos PIC son raros.

Palabras clave: falla cardíaca, Ivabradina, cardiomiopatía, Procoralan®.
ABSTRACT

Introduction and objectives: Heart rate (HR) elevation in patients (p) with heart failure with reduced ejection fraction (HFrEF) is related to increased mortality and hospitalization for HF; its reduction improves the filling of the left ventricle, increases the myocardial oxygen supply and reduces its consumption, all of which is beneficial in p with impaired left ventricular systolic function. Use of ivabradine (IBRA) in p with HFrEF, in sinus rhythm (SR) and HR > 70 beats per minute (bpm), reduces hospitalizations for HF and mortality for HF. The management of p with advanced HF in PIC ensures a morbidity and mortality reduction with the highest levels of evidence. The first retrospective analysis in a PIC at a private hospital in CA, during 3 years of all case p with HFrEF who received treatments (tx) recommended by International Guidelines and maintained HR > 70 bpm at rest in SR, with the purpose of reducing it. The use of baseline clinical data, natriuretic peptides (NP) and LVEF at rest, compared with same variables in follow up, in a region where these PICs are born.

Methods: 26 p with HFrEF for 3 years of PIC. General data, tx, baseline clinical condition, BP, pulse, NYHA, quality of life (QoL), NP, LVEF by Doppler Echocardiography were registered, and IBRA tx response was compared baseline and end. 18 p completed data; 8 incomplete (baseline or follow-up data).

Results: Ambulatory p, with HFrEF (<35%) and SR HR > 70 bpm; age 78 years, 17 men. Tx average time with IBRA 11 months, 53.5% more than 1 year. Baseline medications, 93% ACEIs or ARAs II; 35% beta-blockers and 74% MRA, maximum tolerated doses. No patient used IBRA prior baseline. 20% CRT. Variables behavior assessed: HR (baseline 89 bpm vs 62 bpm after IBRA 2 months); BP (baseline systolic 100 mmHg vs 123 mmHg end; baseline diastolic 55 mmHg vs 65 mmHg end); LVEF (baseline 29% vs 35% end); BNP baseline 7,550 pg/ml vs 1,935 pg/ml end. 5 p improved NYHA III to NYHA II, 3 had deterioration NYHA III; rest remained unchanged. 77% p no dose adjustment required (HR below 70 bpm). 6 p began with 2.5 mg every 12 hours and increased to 5 mg every 12 hours after 15 days. By KCCQ-12 increase 42 to 59 points. 1 discontinuation case of IBRA due to bradycardia (HR < 50 bpm). 2 p hospitalized, one pneumonia and one HF decompensation. 3 dead: 1 myocardial infarction, 2 HF progression.

Conclusions: 26 p studied, registered and treated with IBRA in the PIC at private hospital in CA, most of them registered metric improvements identified as prognosis factors (HR, BP, LVEF, NP, NYHA and QoL). This assessment, registration and follow up of p with HFrEF with use of IBRA in a PIC, is the first one carried out in CA. Results reflect the usual clinical practice in a PIC, with cardiologists and nurses trained to support and follow-up p, and evidence the importance of PIC when using and prescribing drugs like IBRA, in a region where these PICs are rare.

Key words: Heart failure, Ivabradine, Cardiomyopathy, Procoralan®

INTRODUCTION

The heart rate (HR) elevation is related to increased mortality and hospitalization for HF, its reduction improves the filling of the left ventricle, increases the myocardial oxygen supply and reduces its consumption, all of which is beneficial in patients with impaired left ventricular systolic function.1

Ivabradine is a selective inhibitor of the If currents in the pacemaker cells of the sinoatrial node, which, in humans, induces to a heart rate reduction without modifying the interventricular or atrioventricular conduction or contractility.2 It has been demonstrated that the use of Ivabradine in patients with heart failure in functional class II-IV, despite treatment, with a maximum dose or below it, with a beta-blocker or in those who do not tolerate it or when the use of beta-blockers is contraindicated, added to ACE inhibitors (ACEIs) or ARAs II or mineralocorticoid receptor antagonists (MRAs)1-3, with decreased systolic function (left ventricle (LV) ejection fraction (EF) less than 35%), in sinus rhythm and with a HR greater than 70 bpm reduced hospitalizations for HF and mortality for HF and, if this is greater than 75 bpm, it reduced cardiovascular mortality.4

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For the analysis, anonymized records were used, identified by the values provided by the IT Department and the anonymized medical records review.

**METHODOLOGY**

A study with a population of 54 patients older than 40 years of age with HF who attended private outpatient care with cardiologists in the Greater Metropolitan Area of Costa Rica. For the data collection, a registration instrument was used in order to consider the relationship of all the relevant clinical data related to the prescribed dose, at the program entry after April 2013 and their follow up in outpatient care until August 30, 2016. The anonymized data were reviewed, and all patients who did not use ivabradine, after having sought the reason of non-use of the drug, were excluded.

The different dosage schedules used by physicians, who are cardiologists registered in the College of Physicians and Surgeons of Costa Rica, were identified. Modifications and periods for making the modification were assessed. Dosage changes over time were identified, as well as the impact on the rest of the pharmacotherapy. Because it is not a prospective study, six variables that were to be identified in all cases were validated in a baseline condition, even if it was before beginning the PIC. The variables were: heart rate, (systolic and diastolic) blood pressure, variations in the NYHA functional class, changes in the left ventricular ejection fraction (LVEF) measured by echocardiography with the Simpson method and natriuretic peptides BNP or Pro-BNP.

The data were analyzed and it was specified that there could be variables not found at the beginning or at the end of the evaluation period, but there should be at least 4 variables in order to consider if there was improvement in general, potentially attributable to the use of the ivabradine.

Every three to five months, the Kansas City Cardiomyopathy Questionnaire was administered to all PIC patients since April 2013; therefore, they were included in the general results of the baseline and end condition, with the purpose of considering if there was any impact on the quality of life.

**RESULTS**

Of a total of 54 patients that were included in this analysis, 26 were treated with ivabradine according to the International Guidelines for the treatment of HF.

The drugs considered as baseline are described as follows:

- 93% received angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARAs II) if they did not tolerate the first ones.
- 85% beta-blockers.
- 74% mineralocorticoid receptor antagonists.

The age range was from 46 to 95 years with an average of 78 years; 17 men and 9 women.

The dosage schedules shown in table 1 were identified. In Costa Rica, ivabradine is only available with the name Procoralan® 5 mg and Procoralan 7.5 mg. Four (4) different dosage schedules were identified. The ones that are mostly used are those that correspond to 5 mg BID (twice a day) at the beginning (50% of the treated patients). Treatment was started in 69% of them following the international guidelines: in association with beta-blockers in those who were not properly controlled with an optimum dose of these drugs.

Six patients were identified with a dose of 7.5 mg BID with good tolerance. The dose was reduced in only 2 patients due to bradycardia.

**Variable behavior**

Table 2 includes the averages of heart rate in baseline condition and at the end of the control, blood pressure, left ventricular ejection fraction, and natriuretic peptides BNP or Pro-BNP.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dosage schedules.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Total number of patients (n = 26) %</td>
</tr>
<tr>
<td>2.5 mg BID</td>
<td>6 (23)</td>
</tr>
<tr>
<td>5 mg AM / 2.5 PM</td>
<td>1 (4)</td>
</tr>
<tr>
<td>5 mg BID</td>
<td>13 (50)</td>
</tr>
<tr>
<td>7.5 mg BID</td>
<td>6 (23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Modification of three variables from the baseline condition and at the end of the control.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Baseline</td>
</tr>
<tr>
<td>Heart rate in beats per minute (bpm)</td>
<td>89</td>
</tr>
<tr>
<td>Systolic blood pressure mmHg</td>
<td>100</td>
</tr>
<tr>
<td>Diastolic blood pressure mmHg</td>
<td>55</td>
</tr>
<tr>
<td>Ejection fraction (EF) measured by echocardiography</td>
<td>29</td>
</tr>
</tbody>
</table>

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ventricular ejection fraction. All the patients were in sinus rhythm since their baseline condition. The results recorded at the end, occurred after receiving ivabradine during at least 2 months.

Regarding heart rate control, an average reduction of 17 bpm was achieved, which was considered an adequate response.\(^5\)

The systolic blood pressure (BP) was more elevated than the diastolic BP. The LVEF measured by echocardiography showed an improvement of 6% on average at the end of the analysis. In recent years, determining the natriuretic peptides (BNP) and their N-terminal fraction (NT-proBNP) values has shown to be of great support for the diagnosis of patients with suspected HF.\(^6-8\) In multiple studies, they have been qualified in different fields (primary care consultations, hospital emergency services) and have been shown to have a high negative predictive value. In this study, 16 patients had an average baseline BNP of 7 550 pg/ml, and 1 935 pg/ml on average at the end. Two patients had the NT-proBNP measured once (reported values: 973 pg/ml at baseline condition. In another one, it was 3 266 pg/ml at baseline in one of the patients and 253 pg/ml at the end).

**Variation behavior in the NYHA HF functional class**

It was identified that 5 patients had improved from NYHA III at the baseline to NYHA I at the end, other 5 patients presented improvement from NYHA III to NYHA class II, 5 patients did not improve the baseline NYHA functional status III and the NYHA III was maintained at the end of the study, and finally, in 3 patients there was deterioration and went from NYHA functional class II to NYHA III at the end.

The therapy duration and the survival condition within the analysis period were assessed.

There was an 88.5% survival, 3 patients died as shown in detail in Table 3. All deaths occurred in the first year of follow up.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number in #</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Due to HF Deterioration</td>
<td>2</td>
<td>7.7</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>11.5</td>
</tr>
</tbody>
</table>

In the first three years of the program, patients that had not used ivabradine prior to the baseline condition were included. Ivabradine was used by 53.5% of patients for more than one year. One patient received treatment with ivabradine for 33 months.

There was a patient in bradycardia with less than 50 bpm to whom ivabradine was interrupted. Serious adverse events were not related to ivabradine according to the treating physicians.

From the beginning of the PIC, 54 patients to date, 48% received ivabradine and most of them were on beta-blockers (85%). Overall, it was well tolerated. The most common side effects with ivabradine according to the physicians.

In table 5, the analysis of case material of patients who did not receive ivabradine (n = 28) is reported; of those, 16 patients had no indication.\(^10-12\)

<table>
<thead>
<tr>
<th>Duration interval in months</th>
<th># of patients</th>
<th>Deceased # of patients %</th>
<th>Living # of patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 11</td>
<td>12</td>
<td>3</td>
<td>11.5</td>
</tr>
<tr>
<td>12 to 23</td>
<td>8</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>≥ to 24</td>
<td>6</td>
<td>6</td>
<td>22.5</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>23</td>
<td>88.5</td>
</tr>
</tbody>
</table>

**Table 3**

*Cause of death.*

**Table 4**

*Treatment duration.*

**Table 5**

*Causes of NON-use of ivabradine (n= 28 of 54 patients)*
Of the other 12 patients who did not use ivabradine, two causes were recent admission to the PIC, in titration stage of other drugs \((n=6)\), and the use of ivabradine is not mentioned in the medical records of the rest \((n=6)\). With the Kansas City Cardiomyopathy Questionnaire \((KCCQ-12)\), it was possible to determine an increase from 42 to 59 points, which was considered positive, and which may be related to the use of ivabradine, but not to mention other pharmacological and non-pharmacological interventions during the study which may also have contributed to this improvement. There was only one drug withdrawal registered due to significant bradycardia \((\text{less than } 50 \text{ bpm})\).

In the PIC, of the 26 patients, all the variables were obtained from 18 of them. Of the remaining group of patients \((n=8)\), four to five variables were found in baseline status, the same as at the end, which allowed the assessment of the improvement tendency.

**CONCLUSIONS**

Of the 26 patients that were studied, registered and treated with ivabradine in the PIC at HCB, most of them registered metric improvements identified as prognosis factors \((\text{heart rate, blood pressure, left ventricular ejection fraction, natriuretic peptides, functional class modification according to NYHA and quality of life})\). All the patients were assessed during an average period of 11 months. In patients with incomplete data, at least four to five variables were found in baseline literature are bradycardia, arterial hypotension, atrial fibrillation and status, the same as at the end. phosphene; only the first one was observed. The initial dose of ivabradine did not exceed 5 mg twice daily in patients younger than 75 years.

This registration, follow up and management of patients with HF through a PIC shows the importance that this type of programs has when using and prescribing drugs like ivabradine.

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