Heart rate assessment after the first dose of Fingolimod

Avaliação da frequência cardíaca após a primeira dose de Fingolimode

Andréia Scapini[1], Natália de Moraes Soster[1], Mariana Longhi Zandonai[1], Eduarda Capra Bertolin[1], Andressa Rafaela de Moura Hining[1], Cezar Roberto Van der Sand[2].

ABSTRACT

Objective: To evaluate the cardiovascular function of patients who received the first dose of Fingolimod in a health center in the state of Rio Grande do Sul – Brazil.
Methods: A retrospective database study, gathering clinical data and patients' electrocardiograms who received the first dose of Fingolimod 0.5mg at Centro de Diagnóstico Cardiológico from May 2013 to October 2020.
Results: From 83 patients evaluated 64 (77.1%) were women. The average age of participants was 36.97 (±11.21) years old. Out of the 22 (26.5%) symptomatic patients, drowsiness was the most common symptom. There was a statistically significant difference (p<0.0001) in the heart rate that occurred early from the first hour after taking the medicine and went on to the fifth hour. Regarding systolic blood pressure, there was a difference (p <0.0001) between the measurement before taking the drug and the measurement six hours later. However, there was no difference in systolic pressure every hour between the second hour after drug administration. The same that happened to systolic blood pressure occurred to diastolic blood pressure. There was no statistical correlation between the age group and the analyzed variables.
Conclusions: The clinical, hemodynamic, and electrocardiographic changes verified in the study sample were mild and resolved within 6 hours after the dose, which allows the use of this drug to treat MS safely in the analyzed group.

Keywords: bradycardia; multiple sclerosis; Fingolimod

RESUMO

Objetivo: Avaliar a função cardiovascular de pacientes que receberam a primeira dose de Fingolimode em um centro de saúde do estado do Rio Grande do Sul – Brasil.
Métodos: Estudo retrospectivo de banco de dados, reunindo dados clínicos e eletrocardiogramas de pacientes que receberam a primeira dose de Fingolimode 0,5mg no Centro de Diagnóstico Cardiológico de maio de 2013 a outubro de 2020.
Resultados: Dos 83 pacientes avaliados, 64 (77,1%) eram mulheres. A média de idade dos participantes foi de 36,97 (±11,21) anos. Dos 22 (26,5%) pacientes sintomáticos, a sonolência foi o sintoma mais comum. Houve diferença estatisticamente significativa (p<0,0001) na frequência cardíaca que ocorreu desde a primeira hora após a administração do medicamento até a quinta hora. Em relação à pressão arterial sistólica, houve diferença (p<0,0001) entre a medida antes de tomar o medicamento e a medida seis horas depois. No entanto, não houve diferença na pressão sistólica a cada hora entre a segunda hora após a administração do medicamento. O mesmo que aconteceu com a pressão arterial sistólica ocorreu com a pressão arterial diastólica. Não houve correlação estatística entre a faixa etária e as variáveis Analisadas.
Conclusões: As alterações clínicas, hemodinâmicas e eletrocardiográficas verificadas na amostra estudada foram leves e se resolveram em até 6 horas após a dose, o que permite o uso desse medicamento para o tratamento da SM com segurança no grupo analisado.

Palavras-chave: bradicardia; esclerose múltipla; Fingolimode.

[1]Graduando do curso de Medicina da Universidade do Vale do Taquari
[2]Mestre em Cardiologia, professor do curso de Medicina da Universidade do Vale do Taquari

Corresponding author: Dr. Cezar Roberto Van der Sand, Universidade do Vale do Taquari (Univates), Avenida Independência 383/209 – Porto Alegre/RS, **CEP:** 90035074, +55 (51) 99987 4746, cezarsand@gmail.br.
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INTRODUCTION

Multiple Sclerosis (MS) is the most common non-traumatic cause of neurological deficiency in young adults. It is believed that the disease is caused by an autoimmune condition in which self-reactive T cells attack the myelin sheath, causing demyelination and axonal damage[1]. Relapsing-remitting Multiple Sclerosis (RRMS) is the most common form, and it is defined as MS in which the initial stage is a neurological event followed by periods of stability in between relapses[2].

Despite the multiple drugs for RRMS, none of the treatments changes the course of the primary progressive disease[3]. Fingolimod is the first oral medicament approved to reduce the episodes and decrease the progression and the neurological decline in RRMS[4]. Its mechanism is due to the antagonism of sphingosine-1-phosphate (S1P) receptors, coupled to the G protein, in T lymphocytes, which restricts the outflow of these cells from the lymph nodes to the brain and the spinal cord, preventing the reduction of inflammatory activity and its damage. As a result, there is a redistribution of lymphocytes in the body and a reduction in their influx and the central nervous system. Fingolimod also reduces the secretion of pro-inflammatory cytokines by regulating S1P receptors on astrocytes and decreasing the secretion of IL-17 by T helper lymphocytes 17[5].

Cardiovascular events during the treatment for MS using Fingolimod were described in a clinical program that included three double-blinded, randomized and controlled clinical trials: FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis)[6], FREEDOMS II[7] and TRANSFORMS (Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis)[8]. In the study FREEDOMS (n=1272), the most common severe side effect, reported by seven patients (1.6%), was bradycardia. These episodes occurred during the monitoring period after the first dose. Of the seven patients, six of them were asymptomatic. FREEDOMS II (n=1083) reported bradycardia in 27 patients (7%) after the first dose administration. The third study, TRANSFORMERS (n=1292), reported symptomatic bradycardia in seven patients (1.6%).

This study aims to evaluate the cardiovascular function of patients that received the first dose of Fingolimod at a health center in Rio Grande do Sul – Brazil.

METHODS

A retrospective database study was carried out at Centro de Diagnóstico Cardiológico in Porto Alegre, Rio Grande do Sul. Clinical data and electrocardiogram (ECG) performed in patients that received the first dose Fingolimod 0.5mg at Centro de Diagnóstico Cardiológico from May 2013 to October 2020 were gathered. All the patients that were over 18 years old, diagnosed with MS, with the indication of using the drug and that had realized the first dose at the clinic were included. The variables blood pressure (BP), heart rate (HR) and symptomatology reported by the patients during the first six hours after taking the medicine were collected from the chart of the patients at the medical center.

Regarding the statistical analysis, T test were used to evaluate the independent samples (HR, symptomology, and BP) and analysis of variance (ANOVA) to make a comparison between times, immediately before the first dose and successively until the sixth hour after the medication.

This research has the approval of the Centro de Diagnóstico Cardiológico and the authorization of the participating patients. It was approved by the ethics committee of the responsible institution under protocol CE0012/19.

RESULTS

Eighty-three patients received the first dose of the treatment with Fingolimod at Centro de Diagnóstico Cardiológico between May 2013 and October 2020. All the patients met the inclusion criteria and were part of the sample, from which 19 (22.9%) were men and 64 (77.1%) were women. The average age was 36.97 (±11.21) years old.

Sixty-one (73.5%) patients did not report symptoms during the time of observation. Out of the 22 symptomatic patients, 11 (50%) informed drowsiness, 4 (18.2%) headache, 3 (13.7%) dizziness, 2 (9.1%) palpitations and 1 (4.5%) chest pain. There was no statistical difference between the reported symptoms.

Regarding the previous electrocardiographic findings, 14 (16.87%) participants had changes before treatment, from which 12 (85.71%) had right bundle branch block and 2 (14.29%) isolated ventricular extrasystole. Only one patient (1.2%) had a previous diagnosis of systemic arterial hypertension and needed to use Captopril 25mg during the treatment with Fingolimod for presenting high BP values.

The heart rate averages found were 79.39 (±12.31) beats per minute (bpm) before taking the medicine, 73,01 (±10.15) bpm in the first hour after intaking it, 69.94 (±8.17) bpm in the second hour, 69.17 (±8.64) at the third, 66.78 (±7.71) bpm at the fourth, 66.69 (±8.02) bpm at the fifth and 68.97 (±10.03) bpm at the sixth hour after taking the medicine (Figure 1).

There was a statistically significant difference ($p<0.0001$) in the heart rate over time after the ingestion of Fingolimod. This difference occurred early from the first hour after taking the medicine and went on to the fifth hour. There was no statistical difference between HR0 and HR6, which means before the medicine and six hours after taking it (Table 1).

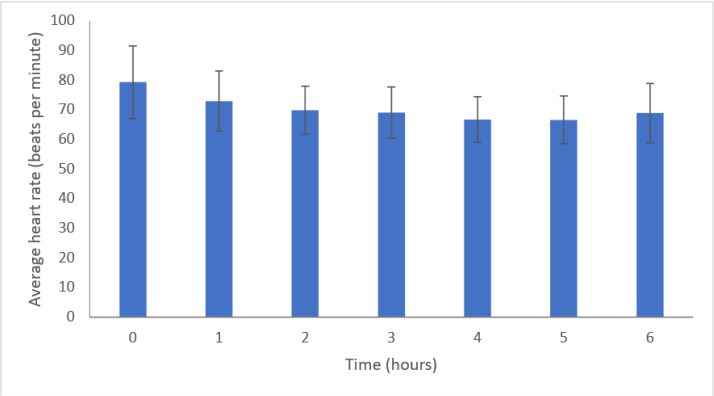

Figura 1. Average heart rate before and 6 hours after Fingolimod administration.

Table 1. Heart rate and blood pressure variation according to time after medication administration. Difference

Tukey:	Difference	Q	(p)
Averages (FC0 e FC1) =	6.39	6.18	< 0.01
Averages (FC0 e FC2) =	9.46	9.15	< 0.01
Averages (FC0 e FC3) =	10.24	9.91	< 0.01
Averages (FC0 e FC4) =	12.61	12.21	< 0.01
Averages (FC0 e FC5) =	12.70	12.29	< 0.01
Averages (FC0 e FC6) =	10.42	10.08	< 0.01
Averages (PAS0 e PAS1) =	6.30	3.86	ns
Averages (PAS0 e PAS2) =	8.72	5.35	< 0.01
Averages (PAS0 e PAS3) =	7.13	4.37	< 0.05
Averages (PAS0 e PAS4) =	9.39	5.75	< 0.01
Averages (PAS0 e PAS5) =	7.41	4.54	< 0.05
Averages (PAS0 e PAS6) =	6.24	3.82	ns
Averages (PAD0 e PAD1) =	2.90	2.44	ns
Averages (PAD0 e PAD2) =	5.49	4.62	< 0.05
Averages (PAD0 e PAD3) =	5.10	4.29	< 0.05
Averages (PAD0 e PAD4) =	7.29	6.13	< 0.01
Averages (PAD0 e PAD5) =	6.34	5.33	< 0.01
Averages (PAD0 e PAD6) =	4.70	3.95	ns

Comparing the quartiles, it is observed that the first and the second ones that correspond to the youngest patients have a bigger initial decrease in HR than the third and the fourth, which include the oldest patients. After the fifth hour, the recovery to normal HR was faster in the youngest patients, while the groups of older patients had a discrete HR recovery. The second and the third quartiles with an average age of 32 and 39 years old respectively had an HR initial decrease with a discrete increase in the third hour and a new decrease in the fourth hour with more expressive attenuation in the sixth hour.

Participants' BP average before and the subsequent six hours after intaking Fingolimod is on Figure 2. Analyzing systolic BP (SBP) there was a significant statistical difference ($p<0.0001$) in SBP of participants when compared to BP immediately before taking the medicine (BP0) and the BP six hours later (BP6). The comparison between SBP0 (before the medicine intake) and at every single hour, shows that there was a SBP statistical difference between the second and fifth hour after the intake. Comparing the first (SBP1) and the sixth (SBP6) hour with the SBP0, it can be verified that a SBP reduction with no statistical relevance. The same that happened to SBP occurred to diastolic BP (DBP).

No statistically correlation was found between the age group and the variables analyzed during the administration of the medication, even when compared by quartiles.

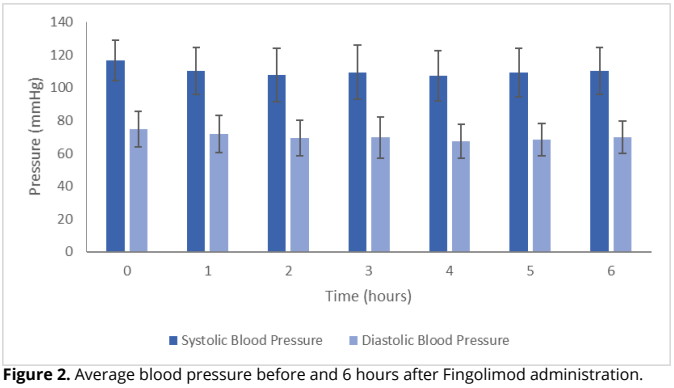

Figure 2. Average blood pressure before and 6 hours after Fingolimod administration.

DISCUSSION

Of the 83 patients evaluated 77.1% were women which is consistent with the data found in the literature since MS prevails in females. Koch-Henrilsen et al. (2010) showed that one of the biggest changes in demographic epidemiology of MS in the last decades was the increase in the incidence of the disease in women, even indicating a relationship with environmental factors[9].

The most prevalent adverse effects reported were drowsiness (13.25%), headache (4.8%), dizziness (3.6%), palpitations (2.4%), hypertension (1.2%) and chest pain (1.2%). This prevalence is similar to the one reported by other authors. Calabresi et al. (2014) presented that the side effects that the patients reported the most were headache (23%), dizziness (10%) and nausea (18%)[7]. Cohen et al. (2010) showed that the most prevalent adverse effects related to Fingolimod were headache (23.1%), fatigue (10.3%) and infections such as nasopharyngitis (20.5%) and lower respiratory tract infection. Most of these adverse events occurred in the first dose of the treatment with improvement over 24 hours, which is consistent with the literature[8].

From the symptomatic bradycardia reported by Kappos et al. (2010), the most prevalent symptoms were dizziness (7.3%) and chest pain (0.9%), changes that resolved within twenty-four hours after taking the medicine[6].

This study revealed that a decrease in HR occurred after the first dose of Fingolimod. The biggest reduction in

HR occurred in the fourth and the fifth hour after taking the drug, with a variation of -16% concerning the measure before Fingolimod, rising again in the sixth hour. The data presented in the literature are consistent with the findings in this article. Calabresi et al. (2014) showed a decrease in HR in the first hours after taking the medicine, with the lowest values reported between the fourth and the sixth hour[7]. In addition, Cohen et al. (2010) presented a bigger decrease in HR between the fourth and the fifth hour, which attenuated after the sixth hour[8]. In the study by Kappos et al. (2010), there was a decrease in HR after the first dose of Fingolimod. Following the same pattern as in other studies, the lowest HR was reached in the fifth hour, rising again in the sixth hour[6]. A 2014 Brazilian study showed a significant change in HR only in the third and fourth hours. In the same study, the subsequent increase in HR was earlier than observed in the literature and occurred in the fifth hour after the dose of Fingolimod[10].

Of 83 patients who participated in this study, the most frequent cardiac disorder was bradycardia. Kappos et al. (2010) and Calabresi et al. (2014) verified first and second-degree atrioventricular blocks in ECGs performed in the first hours after ingesting the drug [6,7] . Cohen et al. (2010) also reported first and second-degree atrioventricular blocks, in addition to bradycardia, as electrocardiographic findings in patients who used Fingolimod[8].

In the current study, a more pronounced BP reduction was observed in the fourth hour after taking the medicine, with an increasing value in the following hours. The only report of hypertension occurred in a previously hypertensive patient. Fragoso et al. (2014) did not find significant differences between SBP and DBP values measured during the subsequent six hours after the patients had taken the first dose of Fingolimod[10]. Calabresi et al (2014) reported an average increase in SBP of 3.89 mmHg and DBP of 1.51 mmHg after three months of treatment[7].

CONCLUSION

The clinical, hemodynamic and electrocardiographic changes verified in the study sample, evaluated during the first six hours after the first dose of Fingolimod, were mild and resolved within 6 hours after the dose. The findings of this study, which were realized in a sample of the Brazilian population, are similar to the ones of produced in other parts of the world and allowed the use of this drug to treat MS safely in the analyzed group.

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