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Heart rate variability predicts the magnitude of heart rate decrease after fingolimod initiation

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ABSTRACT

Background: Fingolimod is an immunomodulator with a disease modifying effect on relapsing-remitting multiple sclerosis (RRMS). A heart rate (HR) decrease shortly after fingolimod initiation, however, requires a clinical vigilance. The aim of this study was to prospectively investigate whether cardiac autonomic regulation can predict the magnitude of HR decrease after fingolimod initiation.

Methods: Twenty-five patients with RRMS underwent ambulatory 24-h electrocardiogram recording to assess HR variability 20 ± 16 days before fingolimod initiation (baseline) and repeated at the day of fingolimod initiation to assess the magnitude of HR decrease. The percentage of normal RR-intervals with duration more than 50 ms different from the previous normal RR-interval (pNN50) was calculated (among the other HR variability parameters) to assess cardiac autonomic regulation. The maximal HR decrease (ΔHR) after the first dose of fingolimod was assessed in absolute units (beats/min) and in percentage (%).

Results: The maximal ΔHR was −20 ± 11 beats/min (−23 ± 12%) on the average. pNN50 calculated at baseline correlated with ΔHR% ($r=-0.657$, $p < 0.001$). A HR decrease ≥20% was found in 10/14 patients with pNN50≥10%. The positive and negative predictive values of pNN50≥10% to predict ΔHR≥20% were 83% and 69%, respectively leading to accuracy of 76%.

Conclusions: Cardiac autonomic regulation (pNN50 > 10%) at baseline can be used to predict the magnitude of HR decrease after the first dose of fingolimod.

Trial registration: ClinicalTrials.gov (NCT01704183).

1. Introduction

Fingolimod is a disease modifying therapy for relapsing-remitting multiple sclerosis (RRMS) (Cohen et al., 2010; Kappos et al., 2006, 2010; Pelletier and Hafler, 2012). The therapeutic effects of fingolimod on RRMS are mediated via modulation of sphingosine-1-phosphate (S1P) receptors (Matloubian et al., 2004; Mehling et al., 2011). The S1P-receptors are found in lymphocytes and neural cells, as well as in cardiovascular system (Brinkmann, 2007; Chun and Hartung, 2010; Mandala et al., 2002).

The initial cardiac effects of fingolimod mimic that of parasympathetic activation (Brinkmann, 2007; Brinkmann et al., 2010). The first dose of fingolimod results in transient reduction in heart rate (HR) (Cohen et al., 2010; Kappos et al., 2006, 2010; Rossi et al., 2015; Simula et al., 2015). However, the magnitude of the initial HR decrease varies between patients. The abrupt decrease in HR can lead to unintended cardiovascular events in susceptible patients. Thus, identification of patients at risk for greater HR decrease is needed to improve drug safety.

HR variability is a marker of cardiac autonomic regulation and can be assessed noninvasively from the ambulatory 24-h electrocardiogram (ECG) recording (Task Force, 1996). HR variability consists of different components mirroring the parasympathetic and sympathetic components of cardiac autonomic regulation.

We hypothesize that measurement of cardiac autonomic regulation can be used as a screening test to predict the magnitude of HR decrease after fingolimod initiation in RRMS patients. In addition, prognostic information of HR variability regarding to the risk for marked HR decrease after the first dose of fingolimod was evaluated.

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2. Methods

The patients underwent 24-h ambulatory ECG recording 20 ± 16 days before the initiation of fingolimod (baseline) from which heart rate variability in time domain and in frequency domain were computed. In addition, ambulatory ECG was undertaken at the day of fingolimod initiation to assess average HR on hourly basis. Expanded disability status scale (EDSS) was performed to evaluate neurological disability related to RRMS.

The ethics committee of Kuopio University Hospital approved the study protocol. Prior to participation, written informed consent was obtained from the patients after explanation of the aim and risk of all procedures used. The study was registered at ClinicalTrials.gov (NCT01704183).

2.1. Study population

Initially, the study consisted of 27 RRMS patients (Simula et al., 2015). Fingolimod was prescribed on clinical basis, according to the accepted drug label and without randomization. The first dose of fingolimod was given at hospital before 10:00 a.m. Patients were followed before discharge at least six hours or until HR started to recover. None of the patients needed overnight observation. Two patients had insufficient ECG-signal for calculation of HR at the last preceding hour before fingolimod initiation and were excluded from the study. Thus, the final population includes 25 patients, 14 (56%) men and 11 (44%) women.

The patients were 43 ± 11y of age, the diagnosis of RRMS was set 10 ± 7y before the study and EDSS was 3.3 ± 1.8 on the average. Five patients (20%) had one or more of the following co-morbidities: two patients (8%) had type-1 diabetes mellitus with insulin-treatment, three patients (12%) were adequately treated with hormonal substitution for hypothyreosis, one patient (4%) had asthma and one patient (4%) had optimally treated hypertension combined with Raynaud phenomenon. Initiation of fingolimod was the only change in the medication during the study. All patients had fingolimod as a second-line treatment for RRMS due to side effects or lack of efficacy during a first-line treatment. Preceding immunomodulative treatment for RRMS was discontinued at least a day before fingolimod initiation if changed from interferon-1b or glatirameracetate or at least two months before shifting from natalizumab.

2.2. Analysis of heart rate and heart rate variability

Twenty-four-hour ambulatory ECG recordings were performed with portable Schiller Medilog AR12plus recorders (Schiller Medilog, Schiller AG, Switzerland). Three bipolar ECG leads (modified chest leads V1 and V5 and modified aVF) were used to record signal with a sampling frequency of 250 Hz. Digital recordings were analyzed with Darwin Holter analysis system (Schiller Medilog, Schiller AG, Switzerland) and exported in MIT-format for subsequent HR variability analysis. During the ECG recordings, the patients were allowed to perform their normal daily activities.

The average HR of the last pre-dose hour before fingolimod dosing was calculated from the ambulatory ECG. After the first dose of fingolimod, the average HR for each consecutive post-dose hour was calculated from the ambulatory ECG, and the nadir of hourly average HR was determined. The difference between pre-dose HR and nadir HR (ΔHR) was calculated and expressed in absolute values (beats/min, bpm) as well as in percentage (%).

Percentage decrease in HR may reflect the hemodynamic changes better than absolute decrease or nadir HR. In this setting, percentage decrease in HR by one fifth was chosen to classify patients to have ΔHR < 20% or ΔHR≥20%. The values for different HR variability measures were computed using the WinCPRS software (Absolute Aliens Oy, Turku Finland) according to the recommendations (Task Force, 1996). The standard deviation of all the RR-intervals (SDNN), the percentage of normal RR-interval with duration more than 50 ms different from the previous normal RR-interval (pNN50) and the root mean square of successive differences in RR-interval (rMSSD) were calculated as the time domain measures of HR variability. The power spectra were quantified with non-parametric fast Fourier transformation by measuring the area in three frequency bands: 0.005–0.04 Hz (very low frequency, VLF), 0.04–0.15 Hz (low frequency, LF) and 0.15–0.40 Hz (high frequency, HF). The ratio of the LF power band and HF power band (LF/HF-ratio) was also computed.

2.3. Physiological correlates of heart rate variability

High HR variability is considered to reflect enhanced cardiac parasympathetic regulation. In time domain analysis, pNN50 and rMMSD are indicators of cardiac parasympathetic regulation (Task Force, 1996). In frequency domain analysis, the HF band reflects mainly parasympathetic cardiac modulation (Pomeranz et al., 1985), whereas the LF band is thought to reflect both parasympathetic and sympathetic cardiac modulation (Pagani et al., 1997; Eckberg, 1997). LF/HF ratio reflects sympatho-vagal balance of cardiac autonomic regulation (Task Force, 1996).

2.4. Statistical analyses

Kolmogorov-Smirnov test was applied to verify the normal distribution of variables. Logarithmic (ln) transformation was made to normalize distributions as needed. Results are expressed as mean ± standard deviation (SD). To test the significances of differences between the groups, independent samples *t*-test was used for continuous variables and Chi-square analysis for categorical variables. A least square regression analysis was used to study univariate linear correlations. The predictive values and accuracy were calculated with standard methods (Fletcher and Fletcher, 2005). All analyses were conducted at the two-tailed level and p-value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics (version 22, IBM Corporation and others, Chicago, USA).

3. Results

3.1. Heart rate response

The average HR at baseline was 81 ± 11 bpm (range 69–109 bpm). All the patients demonstrated HR decrease after fingolimod initiation. The lowest HR (61±8.5 bpm) was reached at the 5th post-dose hour, on the average. The average ΔHR was −20 ± 11 bpm (range: −2–48 bpm) and the mean of ΔHR% was −23 ± 12% (range −2–44%). None of the patients developed symptomatic bradycardia.

Eleven patients (44%) were classified to have HR decrease < 20% and 14 (56%) patients to have HR decrease ≥20%. Patients with < 20% and ≥20% decrease in HR were similar with respect to age, gender, EDSS, RRMS duration and HR at baseline (Table 1).

3.2. Heart rate variability

In the time domain analysis before fingolimod therapy, SDNN was 146 ± 43 ms, pNN50 was 11 ± 8.8% and rMSSD was 35 ± 24 ms, on the average. In the power spectra, the mean powers of TP, VLF, LF and HF spectral components were 13,112 ± 7827 ms^2, 3235 ± 1990 ms^2, 1077 ± 712 ms^2 and 430 ± 542 ms^2, respectively and LF/HF-ratio was 4.37 ± 2.97, on the average.

Enhanced parasympathetic cardiac regulation at baseline (pNN50≥10%) was demonstrated in twelve patients (48%). These patients did not differ from the rest of the patients with respect to age (42 ± 9.7y vs 45 ± 13y), gender (female 8/12; 67% vs 6/13; 46%), EDSS (3.0 ± 1.6 vs 3.6 ± 1.9), RMSS duration (9.6 ± 7.5y vs 11 ± 7.0y)