Effects of Cilostazol on Heart Rate and Its Variability in Patients with Sick Sinus Syndrome

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Abstract

Objective: Heart rate (HR) variability is an important factor for the prognosis of heart disease. We examined the effects of cilostazol, a quinolone derivative, on HR and HR variability in patients with sick sinus syndrome.

Design: Non-blind sequential single-group study.

Patients: 12 patients, aged 53 to 84 years, with type I or II sick sinus syndrome classified according to the Rubenstein system.

Methods: Patients received cilostazol (100 or 200 mg/day) orally for at least 2 months, and 24-hour ambulatory electrocardiogram monitoring was performed before and after the start of cilostazol administration. Plasma atrial natriuretic polypeptide (ANP) levels and cardiothoracic ratio were also measured as markers of heart failure. Twelve age- and gender-matched volunteers were used for control measurements of HR variability.

Results: The mean HR and minimum HR were significantly increased, by an average of 15 and 10 beats/min, respectively, at 8.6 ± 2.5 weeks (mean ± SD) after the start of cilostazol treatment. The number of pauses (defined as an RR interval >2.5 sec) was significantly decreased. The circadian variation of HR, determined by cosine fitting, was increased by cilostazol treatment and was not different from that of the controls. The time-domain and frequency-domain variability of HR were changed to within or closer to within the control ranges. Plasma ANP level and cardiothoracic ratio were significantly decreased after the initiation of cilostazol treatment.

Conclusion: Cilostazol improved the slow HR in patients with sick sinus syndrome and ameliorated the HR variability, indicating that cilostazol has therapeutic utility for the treatment of the slow HR associated with sick sinus syndrome.
Sick sinus syndrome is a pathological condition characterised by sinus nodal depression, including marked sinus bradycardia, prolonged sinus pauses, sinus arrest or sino-atrial blocks.\textsuperscript{[1]} Pacemaker implantation is frequently required in patients with sick sinus syndrome with symptoms associated with bradycardia, such as syncope, faintness, dizziness and heart failure.\textsuperscript{[2,3]} Controlling the heart rate (HR), i.e. maintaining the HR within the physiological range, is important for the treatment of sick sinus syndrome.

Cilostazol, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1H)-quinolinone, was initially developed as an antiplatelet agent acting by selective inhibition of type III phosphodiesterase (PDE) [cyclic GMP-inhibited cyclic AMP PDE].\textsuperscript{[4]} Cilostazol exerts a suppressive effect on platelet function and a positive haemodynamic effect on peripheral circulatory insufficiency.\textsuperscript{[5,6]} Activity of PDE III has been observed not only in platelets but also in the myocardium.\textsuperscript{[7,8]} Although cilostazol shows effects on platelets, it is possible that cilostazol may also affect the sinus node of the heart, especially the automaticity and responsibility for nervous drive.

We hypothesised that cilostazol treatment could increase the HR of patients with sick sinus syndrome and improve their haemodynamic condition through PDE inhibition in the myocardium. There is only one report of a study that examined the effects of cilostazol on the HR in patients with atrial fibrillation and sick sinus syndrome.\textsuperscript{[9]} That report only examined HR; however, HR variability is now well known to be an independent factor for the prognosis of heart disease.\textsuperscript{[10,11]} It is also important to examine markers of heart failure in addition to the HR response. The plasma level of atrial natriuretic polypeptide (ANP) has been established as a marker of heart failure.\textsuperscript{[12,13]} Additionally, the cardiothoracic ratio by chest x-ray has been used widely as an index of heart failure. Accordingly, using 24-hour ambulatory monitoring of the electrocardiogram (ECG), we examined the effects of cilostazol on the HR and its variability in patients with sick sinus syndrome. We also measured plasma ANP levels and cardiothoracic ratio as markers of heart failure.

Patients and Methods

Patients

We studied 12 patients (seven males, five females) with type I or II sick sinus syndrome classified according to the system of Rubenstein.\textsuperscript{[14]} Their ages ranged from 53 to 84 years (mean ± SD, 73 ± 9 years). The criteria for cilostazol administration were as follows: total beats per 24 hours <70 000, maximal RR interval >2.5 sec, and/or minimal HR <40 beats/min. Sick sinus syndrome was associated with essential hypertension in five patients and with ischaemic heart disease in three. The remaining four patients did not show other complicating heart disorders. The patients’ medication was unchanged throughout the course of this study.

Informed consent to participate in the study was obtained from each patient, and the study conformed with the Guidelines for Clinical Studies as set out in the Declaration of Helsinki (revised version 1997).\textsuperscript{[15]}

Twelve age- and gender-matched volunteers served for control measurements of HR variability.

Cilostazol Administration

The patients took oral cilostazol 100 or 200 mg/day (50 or 100mg twice a day), depending on the HR response. Compliance with cilostazol administration was checked at least once every 2 weeks by interview. 24-hour ambulatory ECG monitoring (SM-28; Fukuda Denshi Co., Tokyo, Japan) was performed before and around 8 weeks (mean ± SD, 8.6 ± 1.7 weeks) after the start of cilostazol administration. The 24-hour ambulatory ECG was recorded twice in three patients before starting cilostazol administration to confirm the reproducibility of the pretreatment 24-hour ambulatory ECG indices. In one patient, 24-hour ambulatory ECG data were recorded before and 90, 210, 330, 450 and 660 days after the start of