Effect of a Single Oral Dose of Pilsicainide on Pacing Thresholds in Pacemaker Patients With and Without Paroxysmal Atrial Fibrillation

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A single oral dose of pilsicainide, a class 1c antiarrhythmic drug, is effective in terminating acute-onset atrial fibrillation (AF), but its effect on pacing thresholds in pacemaker patients is unknown. The present study measured atrial and ventricular pacing thresholds after a single oral dose of pilsicainide in patients with and without AF. Twelve patients with dual-chamber pacemakers were evaluated. Pacing thresholds as well as plasma pilsicainide concentration were measured prior to and then at 30, 60, 90, 120 and 180 min and 24 h following a single oral dose of pilsicainide (150 mg). Six patients had paroxysmal AF and the remaining 6 did not. Pacing thresholds increased significantly (134±83% in the atrium (p<0.05) and in the ventricle (155±11%, p<0.001) following pilsicainide administration in all 12 patients. Plasma concentrations of pilsicainide showed a positive linear correlation with pacing thresholds (R=0.62, p<0.0001 in the atrium; R=0.74, p<0.0001 in the ventricle). Atrial pacing thresholds in the patients with AF showed a significant increase at 90, 120 and 180 min compared with the patients without AF (p<0.05). There was no significant difference in either the ventricular pacing threshold or the plasma pilsicainide concentration in the patients with and without AF. It was concluded that a single oral dose of pilsicainide increases the pacing thresholds in both the atrium and ventricle in a selected group of pacemaker-implanted patients; that is, those who are aged and with AF. Thus, careful attention should be paid to pacemaker-dependent patients, particularly those with paroxysmal AF, when administering pilsicainide. (Jpn Circ J 2000; 64: 750–754)

Key Words: Atrial fibrillation; Atrium; Pacing threshold; Pilsicainide; Ventricle

A single oral dose of the class 1c antiarrhythmic drug, pilsicainide, effectively restores sinus rhythm in patients with paroxysmal atrial fibrillation (AF) and is now used widely in Japan. The intravenous route had been the most commonly used to quickly restore sinus rhythm until the recent reports that a single oral dose of the class 1c antiarrhythmic drugs was effective for the rapid conversion of paroxysmal AF to sinus rhythm. Although it is well known that these drugs increase the pacing threshold in both the atrium and ventricle in patients with permanent pacemakers, there have not been any reports on acute changes in the pacing thresholds with a single oral dose. Therefore, we investigated the effect of a single oral dose of pilsicainide on the pacing thresholds in patients with permanent pacemakers, and compared the effects in patients with and without paroxysmal AF.

Methods

Patients

Twelve patients, who had previously implanted dual-chamber permanent pacemakers for their bradyarrhythmias, were selected (mean age, 72±2 years; 5 males, 7 females; Table 1). The baseline heart disease for permanent pacemaker implantation was 2nd or 3rd atrioventricular block in 4, and sick sinus syndrome in 8 patients. Of the 12 patients, 6 patients had paroxysmal AF. Laboratory data showed normal liver and renal function in all patients.

All cardioactive medications were discontinued at least 7 days before the study. In 6 patients the pacing lead system consisted of model 4193 for the atrium and model 4185 for the ventricle (Guidant, St Paul, MN, USA) and in the remaining 6 patients the pacing lead system consisted of model 432-04 for the atrium and model 430-10 for the ventricle (Intermedics, Angleton, TX, USA).

Study Protocol

Pacing Thresholds After written informed consent was obtained from all patients, pacing thresholds in both the atrium and the ventricle were measured as the control values using programmers (CPI Model 2901, Guidant; RX 5000, Intermedics). Prior to administration of pilsicainide, pacing thresholds were measured noninvasively by decrementing the voltage (6 patients: Vigor DR pacemakers, Guidant) and/or pulse duration (6 patients: Marathon DR pacemakers, Intermedics) and were expressed in terms of amplitude and/or pulse duration. Pacing thresholds were then measured in the same manner at 30, 60, 90, 120 and 180 min and 24 h after a single oral dose of pilsicainide (150 mg).

Plasma Concentration of Pilsicainide After the single oral dose of pilsicainide, a 2-ml blood sample was drawn...
from the cubital vein into a tube containing EDTA in all 12 patients at the same times as the measurement of the pacing threshold. The blood was centrifuged to obtain the plasma and plasma concentrations of pilscainide were measured by high-performance liquid chromatography.

Statistics
All results are shown as mean±SEM and statistical analysis was performed using the paired or unpaired Student's t test. Differences with p values less than 0.05 were considered significant. Changes in pacing thresholds following administration of pilscainide in both the atrium and the ventricle were calculated as % change versus control values.

Results
The 6 patients with paroxysmal AF comprised Group A, the mean age of which was 71±2 years (3 male, 3 female); the mean cardiothoracic ratio (CTR) on chest X-ray was 53.6±1.3% and the mean left ventricular ejection fraction (LVEF) measured by echocardiography was 68±6%. The other 6 patients, who did not have AF, comprised Group B and the mean age of this group was 72±2 years (2 male; 4 female); the mean CTR on chest X-ray was 50.4±1.8% and the mean LVEF was 72±5%. There were no significant differences between the 2 groups in age, sex, baseline heart disease, CTR or LVEF (Table 1).

Correlation Between Plasma Concentration of Pilscainide and Pacing Thresholds
Plasma concentrations of pilscainide showed a positive linear correlation with pacing thresholds (dose dependent effect) in both the atrium and the ventricle (R=0.62, p<0.0001 in the atrium; R=0.74, p<0.0001 in the ventricle; Fig 1).

Effect of a Single Oral Dose of Pilscainide on Pacing Thresholds
Prior to administration of pilscainide, pacing thresholds were normal in patients with Vigor DR pacemakers (0.83±0.18 V in the atrium, 0.75±0.09 V in the ventricle: pulse duration =0.40 ms) and with Marathon DR pacemakers (0.16±0.18 ms in the atrium, 0.08±0.01 ms in the ventricle: pulse amplitude =3.0 V).

The time course of the % change of the pacing thresholds in the atrium and ventricle and of the plasma concentration of pilscainide following a single oral dose are shown in Fig 2. The % change of the pacing thresholds increased significantly to 134±8% at 180 min in the atrium (p<0.01) and 155±11% at 120 min in the ventricle (p<0.001) compared with the baseline. The plasma concentration of pilscainide increased gradually and reached a maximum at 180 min. Interestingly, the % change of the pacing thresholds at 90 and 120 min in the ventricle was significantly higher than the % change in the atrium (p<0.05). Fig 3 shows the differences between Groups A and B in the atrial and ventricular pacing thresholds, and in the plasma concentrations of pilscainide. Although there was no significant difference in the plasma concentration of pilscainide between the groups, the % change of the pacing thresholds in the atrium in Group A increased significantly at 90, 120 and 180 min compared with Group B (p<0.05). However, there was no significant difference in the % change of the pacing threshold in the ventricle between Groups A and B. In all patients the % change of the pacing thresholds in both the atrium and the ventricle, and the plasma concentrations of pilscainide recovered to baseline values 24 h after the administration of pilscainide.

Discussion
Atrial fibrillation with or without sinus node dysfunction
is the most common sustained arrhythmia encountered by physicians, with an incidence of 0.4% in the general population and 4% in the hospital population, and it is associated with an increased morbidity and mortality. In its paroxysmal form, AF is costly in terms of hospital care and admissions. Proven rationales for early conversion to sinus rhythm include both clinical and electrophysiologic findings. Alleviation of symptoms and the control of ventricular rate to prevent cardiomyopathy decrease the likelihood of thrombosis and embolization.

Recent studies have shown that a single oral dose of flecainide or procainamide will terminate paroxysmal AF with a success rate of more than 60% within 8 h of administering a loading dose. The rapid increase in the plasma concentration of these drugs, as well as electrophysiologic mechanisms, are important factors in their success. However, it is also well known that daily use of class Ic antiarrhythmic drugs for the prevention of AF increases the pacing threshold in both the atrium and the ventricle. There are not many reports examining the effect of a single oral dose of class Ic antiarrhythmic drugs on the pacing thresholds in pacemaker patients. We previously reported that ventricular pacing failure occurred after a single oral dose of pilsicainide in a pacemaker patient with paroxysmal AF. In that case, the pacing threshold in both the atrium and the ventricle increased up to 5 and 7 times, respectively, after the administration of pilsicainide compared with the baseline.

Pilsicainide is a potent class Ic antiarrhythmic drug with confirmed effectiveness in the management of clinical tachyarrhythmias. It has favorable pharmacokinetics including rapid absorption from the gastrointestinal tract, absence of changes due to the first pass effect and a short half-life (4–5 h). Orally administered pilsicainide is absorbed rapidly and excreted almost exclusively through the kidneys. A single oral dose of pilsicainide is now widely and effectively used in Japan for terminating paroxysmal AF.

In the present study, we investigated the effect of a single oral dose of pilsicainide on the pacing thresholds in 12 patients, with and without AF, who had previously implanted dual chamber pacemakers. The plasma concentration of pilsicainide increased to maximum levels at 180 min after a single oral dose, and the % change of the pacing thresholds in both the atrium and ventricle showed a positive linear correlation with the plasma concentration (maximum (134±8%) at 180 min in the atrium and maximum (155±11%) at 120 min in the ventricle). These data suggest a dose dependent phenomenon, although, interestingly, the % change of the pacing threshold in the atrium at 90 and 120 min was significantly higher than that in the ventricle (p<0.05). Furthermore, these data show significant differences in the % change of the pacing threshold in the atrium at 90, 120 and 180 min following the single oral dose of pilsicainide in patients with paroxysmal AF and in those without it, despite there not being a significant difference in...
Effect of Pilsicainide on Pacing Thresholds

Fig. 3. The time course of the atrial (A) and ventricular (B) % change of the pacing threshold, and of the plasma concentration of pilsicainide (C). Although there was not a significant difference in the plasma concentration of pilsicainide between Groups A and B, the % change of the atrial pacing threshold in Group A at 90, 120, and 180 min following the administration of pilsicainide was significantly higher than in Group B. There was no significant difference in the % change of the ventricular pacing threshold between Groups A and B.

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the plasma pilsicainide concentrations between the 2 groups of patients. Although we did not measure the effective refractory period of the atrium in the present study, as AF may have been induced by the programmed electrical stimulation, it is likely that dysfunction or injury of the atrial muscle, as well as sinus node dysfunction, is involved in paroxysmal AF. In fact, Centurion et al reported that abnormal atrial electrograms were generally localized to the high right atrium in patients with sick sinus syndrome who did not have AF, whereas they were more widely distributed in the right atrium of patients with both sick sinus syndrome and paroxysmal AF. Thus, careful attention must be paid when a single oral dose of pilsicainide is used for termination of recent-onset AF in aged patients with a pacemaker, especially those who are pacemaker dependent.
References


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