Pilot Study: Noninvasive Monitoring of Oral Flecainide's Effects on Atrial Electrophysiology during Persistent Human Atrial Fibrillation Using the Surface Electrocardiogram

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Background: The relation between flecainide's plasma level and its influence on human atrial electrophysiology during acute and maintenance therapy of atrial fibrillation (AF) is unknown. Therefore, this study determined flecainide plasma levels and atrial fibrillatory rate obtained from the surface ECG during initiation and early maintenance of oral flecainide in patients with persistent lone AF and assessed their relationship.

Methods and Results: In 10 patients (5 males, mean age 63 ± 14 years, left atrial diameter 46 ± 3 mm) with persistent lone AF, flecainide was administered as a single oral bolus (day 1) followed by 200–400 mg/day (days 2–5). The initial 300 mg flecainide bolus resulted in therapeutic plasma levels in all patients (range 288–629 ng/ml) with no side effects. Flecainide plasma levels increased on day 3 and remained stable thereafter. Day 5 plasma levels were lower (508 ± 135 vs 974 ± 276 ng/ml, $P = 0.009$) in patients with daily mean flecainide doses of 200 mg compared to patients with higher maintenance doses. Fibrillatory rate obtained from the surface electrocardiogram measuring 378 ± 17 fpm at baseline was reduced to 270 ± 18 fpm ($P < 0.001$) after the flecainide bolus but remained stable thereafter. Fibrillatory rate reduction was independent of flecainide plasma levels or clinical variables.

Conclusion: A 300 mg oral flecainide bolus is associated with electrophysiologic effects that are not increased during early maintenance therapy in persistent human lone AF. In contrast to drug plasma levels, serial analysis of fibrillatory rate allows monitoring of individual drug effects on atrial electrophysiology.

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Flecainide's influence on electrocardiographic parameters during sinus rhythm has been studied previously.¹ QRS and PR intervals lengthened significantly either after acute oral administration or after chronic treatment, and the QRS interval changes were significantly correlated to serum flecainide concentrations. Since a large pharmacodynamic variability has been recognized, it was, however, concluded that determination of flecainide-free plasma concentration may not be

sufficient to forecast electrophysiologic effects in individual patients.²

Flecainide is frequently used in the setting of atrial fibrillation (AF). Its acute effects on atrial electrophysiologic parameters have been studied in experimental^{3,4} and human AF⁵ showing consistently a cycle length prolongation. In contrast to the already evaluated relation between flecainide's plasma levels and ventricular effects, its relation with effects on atrial electrophysiology

Table 1. Characteristics of the Study Population (n = 10)

Male/Female	5/5
Age (years)	63 ± 14
Underlying heart disease	
None	3
Systemic hypertension	7
Duration of atrial fibrillation (months)	5.3 ± 4.1
Concomitant medication ^a	
Digitalis	6
Beta-blocker	2
Calcium antagonist	6
Left atrial diameter (mm)	46 ± 3
Left ventricular ejection fraction (%)	59 ± 4

^aMore than one possibility.

during acute and early maintenance therapy is unknown.

Fibrillatory rate obtained from the surface ECG reflects the average cycle length of electrical atrial activation during AF.^{6,7} Atrial effects of class I and III antiarrhythmic medication may be monitored⁶⁻⁸ and predicted^{6,9} directly with this test. While in a previous study atrial rate has been shown to be associated with flecainide-induced conversion to sinus rhythm,^{6,9} the purpose of this study was (1) to determine flecainide plasma levels and atrial fibrillatory rate during days 1-5 of flecainide initiation in patients with persistent lone AF and (2) to assess a possible relationship between flecainide plasma levels and fibrillatory rate changes. Subsequently, the possible role of serial fibrillatory rate or drug plasma level analyses for monitoring individual drug effects on atrial electrophysiology was explored.

PATIENTS AND METHODS

Patients

The subjects of this observational study were 10 consecutive patients with AF referred to our institution for cardioversion of this arrhythmia. Patients aged >18 years were eligible when they (1) had AF >24 hours, (2) were hemodynamically stable (ventricular rate between 50 and 120 bpm and systolic pressure >100 mm Hg), (3) had no known or suspected coronary artery disease or dilated cardiomyopathy, (4) had AF not associated with hyperthyroidism, electrolyte disturbances, or infection, (5) were not taking class I or III antiarrhythmic drugs

at the time of study entry, and (6) had normal renal function.

The clinical characteristics of the study population are summarized in Table 1. All patients provided written informed consent for participation.

Study Protocol

In all patients, a transthoracic echocardiogram was performed in order to determine left atrial diameter and left ventricular ejection fraction.

Flecainide (Tambacor, 3M, Borken, Germany) was initiated on an inpatient basis under continuous ECG monitoring. A single oral dose of 300 mg (day 1) was followed (days 2-5) by a maintenance therapy of 200 (100 bid) to 400 mg/day (200 bid). These dosages represent the clinically relevant range and were assumed to result in a large variability of flecainide plasma concentrations.

Patients received concomitantly either oral anticoagulation therapy to maintain an international normalized ratio between 2.5 and 3.5, or weight-adapted low molecular weight heparin following exclusion of left atrial thrombus formation by transesophageal echocardiography.

At study entry (baseline) and 4 hours following the flecainide morning dose, a 2-minute ECG recording was performed on days 1-5. In each patient, a high-gain, high-resolution electrocardiogram (Predictor, Dr. Kaiser Medizintechnik GmbH) was recorded with the subject relaxed in a supine position after a 5-minute equilibration period. Electrodes were applied in an orthogonal X (X+: left mid-axillary line at the fourth intercostal space, X-: right mid-axillary line at the fourth intercostal space), Y (Y+: left manubrium sternum margin, Y-: left xiphisternum margin), and Z (Z+: fourth intercostal space at the right sternal margin, Z-: directly opposite on the posterior chest wall) lead system.

Signals were analog-to-digital converted at 2000 Hz, a 12-bit resolution and a frequency response at 0.05-300 Hz. Electrograms were stored on optical disk and transferred to a personal computer for further signal processing.

AF was differentiated from atrial flutter using standard ECG criteria.¹⁰ Analysis of fibrillatory frequency was obtained from ECG lead Z (corresponding with standard ECG lead V1). After high-pass filtering, the QRS complexes were subtracted using a template matching algorithm. The resulting fibrillatory baseline signal was subjected to Fourier

Figure 1. Signal processing technique used for the measurement of frequency content of the ECG. Top panel: ECG segment with AF. Middle panel: Typical appearance of the signal after filtering and subtraction of the QRST using a template matching algorithm. Bottom panel: Frequency power spectrum produced by Fourier transformation of the signal in the middle panel. Atrial fibrillatory rate was calculated as dominant frequency $\times$ 60.

transformation, displayed as a frequency power spectrum and the dominant frequency was determined in the 3–12 Hz range (Fig. 1) as described previously.^{6,7} Frequencies were converted to fibrillatory rates (rate = frequency $\times$ 60) and expressed in fibrillations per minute (fpm) as advocated previously.¹¹

In all patients, a standard 12-lead ECG (Pawewriter XLi, Hewlett Packard) was obtained at baseline and on day 5. Paper speed was 50 mm/s and amplitude was 10 mm/mV with standard filter settings (0.5–40 Hz). Averaged QRS duration as well as RR and QTc intervals was determined.

Flecainide plasma levels were measured immediately following ECG recordings on days 1–5 using high performance liquid chromatography.

Statistical Analysis

All continuous variables are presented as mean $\pm$ one standard deviation. ECG parameters before and after drug administration were compared using Student's *t*-test for paired data (two measurements) or univariate ANOVA with repeated measurements (multiple measurements). Student's *t*-test was used to compare both day 5 flecainide plasma levels and fibrillatory rate reduction between patients receiving daily mean flecainide doses of 200 mg (100 mg bid) versus those with higher doses. Possible relationships between fibrillatory rate reduction and flecainide plasma levels, mean flecainide doses, and clinical variables were explored using linear regression analysis. A *P*-value < 0.05 was considered statistically significant.

RESULTS

In 3 patients (30%), sinus rhythm occurred after 2, 4, and 24 hours, respectively, following flecainide bolus, while one of those had early AF recurrence. Initial flecainide maintenance dose was 200 and 400 mg/day in 5 patients each. Minor adverse reactions were observed in 2 patients. In both the patients, the maintenance dose was reduced from 400 to 200 mg/day because of asymptomatic pauses in one (on day 4) and new left bundle branch block and diarrhea in another patient (on day 3).

The initial 300 mg flecainide bolus resulted in therapeutic plasma levels in all patients (range 288–629 ng/ml) with no side effects. Flecainide plasma levels increased on day 3 (Fig. 2) and remained stable thereafter. Day 5 plasma levels were lower (508 ± 135 vs 974 ± 276 ng/ml, *P* = 0.009) in patients with daily mean flecainide doses of 200 mg compared to patients with higher maintenance doses.

Fibrillatory rate measured 378 ± 17 fpm at baseline. It was reduced to 270 ± 18 fpm (*P* < 0.001) after the flecainide bolus but not any further during maintenance therapy (Fig. 2). On day 5, fibrillatory rate reduction was 123 ± 25 fpm (range

Figure 2. Mean $\pm$ one standard deviation of flecainide plasma levels (left panel) and fibrillatory rate (right panel) during the first 5 days of oral flecainide administration.

80–164 fpm) in 8 patients (2 patients converted to and remained in sinus rhythm and were subsequently not included in this subanalysis). Rate reduction was similar (120 ± 35 vs 126 ± 14 fpm, $P = 0.748$) between patients with mean flecainide doses

of 200 mg compared to patients with higher doses. It was also independent of flecainide plasma levels (Fig. 3), baseline fibrillatory rate, or other clinical variables.

There was a significant QRS duration prolongation (91 ± 10 vs 103 ± 11 ms, $P = 0.039$) when comparing baseline with day 5 measurements. In contrast, RR (681 ± 99 vs 743 ± 190 ms, $P = 0.448$) and QTc intervals (427 ± 19 vs 430 ± 36 ms, $P = 0.872$) were not significantly changed. There was no correlation between both mean flecainide dosage or flecainide plasma levels and QRS duration, RR or QTc intervals.

DISCUSSION

This study, for the first time, concomitantly monitored flecainide's effects on plasma levels and atrial fibrillatory rate obtained from the surface ECG during the initiation phase of this drug. Conversion rate, time to conversion, and side effects of this study, which lacks, however, a placebo group, were within the range of previous investigations.^{12,13}

Plasma concentrations are often considered in the evaluation of antiarrhythmic drugs' therapeutic efficacy. That approach is based on the assumption that the drug's myocardial concentration is in equilibrium with its plasma concentration. Subsequently, its pharmacologic effects should be proportional to the myocardial drug

Figure 3. Relationship between day 5 flecainide plasma levels and fibrillatory rate reduction stratified by mean flecainide dose (● = 300 mg bolus + >200 mg/day; ○ = 300 mg bolus + 200 mg/day). Please note higher plasma levels in patients with higher maintenance doses. Fibrillatory rate reduction shows a large interindividual variability (80–164 fpm), which is, however, independent of flecainide plasma levels or mean flecainide dose.

concentration. Previous studies on procainamide¹⁴ or amiodarone¹⁵ have shown, however, that plasma concentrations only poorly reflect myocardial concentrations. When considering this, it is not surprising that we have found no correlation between flecainide's plasma concentration and its effects on fibrillatory rate. A 300 mg bolus resulted in a rate reduction, which was not enhanced, even though flecainide's plasma concentration increased, especially pronounced in patients on higher flecainide doses.

Furthermore, specific antiarrhythmic characteristics need to be considered. As with this study, flecainide has been found to decrease the fibrillatory rate (increase atrial cycle length) in both animal^{3,4} and induced human AF.⁵ Conduction slowing of fibrillatory wavefronts preferentially at pivot point (points of high curvature) together with refractoriness prolongation might be responsible for this observation.⁴ In experimental AF in dogs, it has been demonstrated that flecainide increases atrial refractoriness and reduces conduction velocity in a tachycardia-dependent manner.³ This could explain the initial rate decrease when fibrillatory rate was higher compared to no significant rate changes when fibrillatory rate was already lower. It needs to be emphasized, however, that a differentiation between the individual contribution of refractoriness prolongation or conduction slowing is currently not possible when determining atrial fibrillatory rate or cycle length.

QRS duration was significantly prolonged in our patients after flecainide treatment which has been shown previously.^{1,2} In contrast to these studies that were performed in sinus rhythm, no relation between QRS prolongation and flecainide plasma concentrations was found in our study. This is further support for plasma concentrations not being adequate to monitor electrophysiologic drug effects.²

In conclusion, a 300 mg oral flecainide bolus is associated with electrophysiologic effects that are not increased during early maintenance therapy in persistent human lone AF. In contrast to drug plasma levels, serial analysis of fibrillatory rate allows monitoring of individual drug effects on atrial electrophysiology.

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