Therapeutic Monitoring of Class I Antiarrhythmic Agents Using High-Resolution Electrocardiography Instead of Blood Samples

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Antiarrhythmic therapy requires monitoring of serum drug concentrations to determine a patient's optimal oral dose of medication. Repeated examination of blood samples, however, is costly and time-consuming, so the present study evaluated whether changes in serum concentrations could be estimated from changes in electrocardiographic (ECG) parameters. Of 36 patients receiving antiarrhythmic drugs for supraventricular or ventricular arrhythmias, 12 were treated with flecainide, 12 with pilsicainide, and 12 with pirmenol. Signal-averaged ECG (SAECG) were recorded before starting drug administration, 1 month later, and twice during ongoing therapy. At the time of the 2nd to the 4th recordings, serum concentrations of the drugs were also measured. As previously reported, all agents, but especially flecainide and pilsicainide, prolonged the filtered QRS (f-QRS) and the duration of low-amplitude signals at the terminal portion of the QRS complex. The SAECG parameters varied between the recordings made during therapy. Differences in the duration of the f-QRS between 2 recordings correlated significantly with differences in serum drug concentrations ($r=0.91$ for flecainide, $r=0.70$ for pilsicainide, and $r=0.61$ for pirmenol). No significant correlation between drug concentration and other SAECG parameters was found. Changes in the serum concentration of flecainide, pilsicainide and pirmenol can be estimated from changes in the duration of the f-QRS on the SAECG and periodic monitoring of such could help reduce the number of repeat measurements of drug concentrations in blood samples. (*Circ J* 2003; 67: 195–198)

Key Words: Flecainide; High-resolution electrocardiography; Pilsicainide; Pirmenol

A patient's optimal dose of oral medication for long-term antiarrhythmic treatment must be determined by therapeutic monitoring, usually frequent measurements of serum drug concentration; however, such measurements are costly and time-consuming. In previous studies, clinical administration of antiarrhythmic agents was found to cause changes in signal-averaged electrocardiographic (SAECG) parameters¹ and each antiarrhythmic agent affected the electrocardiographic (ECG) variables in a different manner^{2,3}. Also, it has been reported that SAECG is more sensitive than a standard ECG in detecting the changes in QRS duration resulting from administration of class I antiarrhythmic drugs^{4,11}. Therefore, the purposes of the present study were to compare the ECG changes caused by administration of 3 class I antiarrhythmic agents (flecainide, pilsicainide and, pirmenol), and to identify the SAECG parameters that might be used to estimate changes in serum concentration of antiarrhythmic agents during monitoring for long-term therapy.

Methods

Patients

We enrolled 36 patients (12 taking flecainide; 12 pilsicainide; 12, pirmenol) who had symptomatic ventricular or supraventricular arrhythmias. The underlying heart diseases included coronary artery disease (CAD), hypertensive heart disease, cardiomyopathy and valvular disease, but in some cases there was no underlying heart disease (Table 1). Of those with CAD, none had unstable angina. Three patients had a history of old myocardial infarction, but their cardiac function were not suppressed. No significant difference was seen in the distribution of diagnoses among the groups treated with each of the 3 drugs. Mean age was 63 ± 17 years. Patients with bundle branch block or other conduction disturbances were excluded.

Informed consent was obtained from the patients.

Measurement of SAECG Parameters

We used a NEC-DP 1100 signal processor for recording and measuring 3 conventional SAECG parameters: (1) the duration of the total filtered QRS (f-QRS); (2) the duration of the low-amplitude ($<40 \mu V$) signal at the terminal portion of the QRS complex (LAS40); and (3) the root mean square voltage of the last 40 ms of the QRS complex (RMS40). The SAECG was recorded in the resting state, and the heart rate during recordings remained within the range of 60–90 beats/min in all patients.

The initial SAECG recording was made before beginning antiarrhythmic therapy, followed by a second recording at 1 month after initiation of drug administration to ensure steady-state conditions. Patients were treated with standard recommended therapeutic doses of each antiarrhythmic drug, but these were sometimes modified according to the age and weight of the patient, as well as by the

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Table 1 Underlying Heart Diseases

	<i>Flecainide</i>	<i>Pilsicainide</i>	<i>Pirmenol</i>	<i>Total</i>
<i>No. of patients</i>	12	12	12	36
<i>Average age (years)</i>	64±13	59±11	67±17	63±17
<i>M/F</i>	7/5	8/4	6/6	21/15
<i>Underlying disease</i>				
<i>Coronary artery disease</i>	3	1	3	7
<i>(old myocardial infarction)</i>	0	1	2	3
<i>Valvular disease</i>	3	4	2	9
<i>Cardiomyopathy</i>	0	1	0	1
<i>None</i>	6	6	7	19

Table 2 Effect of Flecainide on SAECG Parameters

<i>Patient no.</i>	<i>f-QRS</i>		<i>fQRS (ms)</i>	<i>RMS40</i>		<i>RMS40 (μV)</i>	<i>LAS40</i>		<i>LAS40 (ms)</i>	<i>Conc.</i>		
	<i>no.1 (ms)</i>	<i>no.2 (ms)</i>		<i>no.1 (μV)</i>	<i>no.2 (μV)</i>		<i>no.1 (ms)</i>	<i>no.2 (ms)</i>		<i>no.1 (ng/ml)</i>	<i>no.2 (ng/ml)</i>	<i>conc. (ng/ml)</i>
1	116	125	9	5.4	2.6	-2.8	72	83	11	141	188	47
2	113	122	9	4.1	2.9	-1.2	51	61	10	325	431	106
3	98	106	8	11.3	8.4	-2.9	36	48	12	148	248	100
4	117	125	8	2.7	1.7	-1	72	81	9	194	261	67
5	111	114	3	3.3	5	1.7	53	59	6	105	127	22
6	108	130	22	4	3	-1	0	0	0	281	600	319
7	98	109	11	11.7	5.5	-6.2	46	43	-3	170	233	63
8	106	111	5	5.3	4.4	-0.9	61	71	10	257	328	71
9	120	121	1	3.5	3.4	-0.1	63	62	-1	267	283	16
10	121	126	5	3.2	3.4	0.2	52	58	6	376	401	25
11	104	106	2	5	4.3	-0.7	52	58	6	190	204	14
12	99	110	11	12	6.5	-5.5	46	55	9	192	270	78
Mean	109.3	117.1	7.8	5	4.3	-1.7	50.3	56.6	6.3	220.5	297.8	77.3
			<i>p<0.001</i>			<i>p=0.026</i>			<i>p=0.001</i>			<i>p<0.01</i>

SAECG, signal-averaged ECG.

Table 3 Effect of Pilsicainide on SAECG Parameters

<i>Patient no.</i>	<i>f-QRS</i>		<i>fQRS (ms)</i>	<i>RMS40</i>		<i>RMS40 (μV)</i>	<i>LAS40</i>		<i>LAS40 (ms)</i>	<i>Conc.</i>		
	<i>no.1 (ms)</i>	<i>no.2 (ms)</i>		<i>no.1 (μV)</i>	<i>no.2 (μV)</i>		<i>no.1 (ms)</i>	<i>no.2 (ms)</i>		<i>no.1 (ng/ml)</i>	<i>no.2 (ng/ml)</i>	<i>conc. (ng/ml)</i>
1	118	123	5	8.8	8.2	-0.6	33	52	19	643	786	143
2	90	100	10	7.2	6.8	-0.4	68	79	11	621	951	330
3	105	110	5	9.8	8.5	-1.3	52	36	-16	451	637	186
4	109	111	2	3.1	3.7	0.6	61	81	20	402	484	82
5	124	127	3	9.4	9.1	-0.3	44	53	9	480	564	84
6	113	119	6	5.3	7.3	2	0	0	0	476	640	164
7	106	110	4	2.5	2.1	-0.4	25	46	21	399	486	87
8	117	122	5	6	3.1	-2.9	46	69	23	423	550	127
9	113	121	8	12.9	14	1.1	34	68	34	561	616	55
10	116	127	11	7.2	5.9	-1.3	52	44	-8	469	641	172
11	95	107	12	4.7	3.7	-1	58	66	8	503	774	271
12	115	119	4	13.2	14.1	0.9	42	46	4	549	583	34
Mean	110.1	116.4	6.3	7.5	7.2	-0.3	42.9	53.3	10.4	498	643	145
			<i>p<0.001</i>			<i>p=NS</i>			<i>p=0.027</i>			<i>p<0.001</i>

severity of arrhythmias. At the time of the second recording, serum drug concentrations had been determined.

Two subsequent SAECG recordings were accompanied by blood sampling to determine the changes in the serum concentrations of the drugs. The time interval after the second SAECG recording at which these later paired examinations were carried out ranged from 2 to 4 months.

The patients were followed up at our outpatient clinic and the blood samples were usually taken within 2–4 h of drug administration.

Statistical Analysis

Data are given as mean±SD. Paired two-tailed Student's *t*-Tests were used to compare continuous variables. *P* values less than 0.05 were considered to indicate significance.

Results

Effects of the Drugs on SAECG Parameters

f-QRS Flecainide, pilsicainide and pirmenol all prolonged the *f-QRS* significantly (Tables 2–4).

LAS40 All 3 drugs significantly prolonged *LAS40*, but

Table 4 Effect of Pirmenol on SAEKG Parameters

Patient no.	f-QRS		fQRS (ms)	RMS40		RMS40 (μV)	LAS40		LAS40 (ms)	Conc.		
	no.1 (ms)	no.2 (ms)		no.1 (μV)	no.2 (μV)		no.1 (ms)	no.2 (ms)		no.1 (ng/ml)	no.2 (ng/ml)	conc. (ng/ml)
1	120	124	4	10.7	6.7	-4	22	50	28	721	1079	358
2	141	148	7	5.7	4.8	-0.9	131	137	6	744	1672	928
3	100	103	3	7.6	6	-1.6	50	82	32	440	942	502
4	110	111	1	2.9	3.5	0.6	60	59	-1	769	785	16
5	114	116	2	5.4	4.8	-0.6	43	62	19	372	501	129
6	112	117	5	2.6	1.2	-1.4	0	0	0	980	1221	241
7	93	96	3	14.8	11.9	-2.9	28	33	5	580	684	104
8	102	106	4	6	3.3	-2.7	0	0	0	1097	1355	258
9	89	96	7	9.2	5	-4.2	45	42	-3	689	1198	509
10	106	115	9	4.8	3.5	-1.3	0	0	0	549	602	53
11	116	128	14	4.7	1.7	-3	57	65	8	519	1308	789
12	111	112	1	2.5	2.9	0.4	43	59	16	370	434	64
Mean	109.4	114.3	4.9	6.4	4.6	-1.8	39.9	49.1	9.2	653	982	329
			$p<0.001$			$p=0.002$			$p=0.022$			$p<0.003$

Fig 1. Correlations between f-QRS and flecainide serum concentration. **Fig 2.** Correlations between f-QRS and pilsicainide serum concentration.

particularly pilsicainide (Tables 2–4).

RMS40 RMS40 was decreased equally by flecainide and pirmenol, and pilsicainide had a minimal effect only (Tables 2–4).

Mean serum concentrations at 1 month after beginning therapy were 218 ng/ml for flecainide, 480 ng/ml for pilsicainide, and 514 ng/ml for pirmenol; these concentrations were within the therapeutic range in all patients.

Changes in Serum Drug Concentration and the SAEKG Parameters

Serum concentrations of flecainide correlated strongly with change in f-QRS ($r=0.91$; Fig 1) as did those of pilsicainide ($r=0.70$; Fig 2) and pirmenol ($r=0.61$; Fig 3). The other 2 SAEKG parameters (RMS40 and LAS40) did not show a significant correlation with the serum concentration of any of the 3 antiarrhythmic agents.

Discussion

Monitoring of the serum concentration of antiarrhythmic agents by repeated blood samples is costly, and unpleasant for patients. In the present study, with flecainide in particular, we observed a significant correlation between serum drug concentration and changes in the f-QRS on SAEKG.

In clinical practice, prolongation or shortening of the f-QRS can be taken to suggest excessively high or low concentrations of flecainide, and to indicate the need for a

Fig 3. Correlations between f-QRS and pirmenol serum concentration.

blood sample to determine the serum drug concentration. On the other hand, if the f-QRS is stable, frequent serum determinations probably are unnecessary.

The mechanism of prolongation of the f-QRS by class I antiarrhythmic drugs is thought to be a potent blockade of the sodium channels that slows phase 0 depolarization and intraventricular conduction.⁵ The rate at which these drugs bind to or dissociate from the sodium channels is sufficiently slow for a strong blocking action to be exerted, even during sinus rhythm. However, the kinetics of each of these

drugs (and especially the affinity for the Na⁺ channel) differ. Flecainide⁶ and pilsicainide exhibit very slow kinetics, whereas pirmenol has different features, including a shorter time constant¹ which indicates that presumption of the serum concentration of pirmenol during sinus rhythm will be more difficult than with the other 2 drugs. Furthermore, our study results imply that of the 3 class I antiarrhythmic agents we studied, flecainide has the most stable concentration, which is surprising considering that it has been found to have nonlinear kinetics even in patients with normal kidney and liver function.⁷ Therefore, even in patients with normal renal function, and without heart failure, chronic administration of the drug may lead to its unexpected accumulation, probably because of genetically poor metabolism, so monitoring the plasma concentration is necessary.⁷

Most of the class Ia and class Ic antiarrhythmic drugs are excreted mainly by the kidney and therefore their use in patients with impaired renal function must be carefully monitored by clinicians.⁸

The main limitation of the present study is that SAECG parameters can be affected by many factors not associated with antiarrhythmic therapy, such as transient ischemia, changes in autonomic tone, and conduction disturbances.^{9,10} However, we conclude that changes in the serum concentration of flecainide, pilsicainide and pirmenol can be estimated from changes in the duration of f-QRS, which is prolonged in a dose-dependent manner, during SAECG recording. Such a screening test could improve the therapeutic monitoring of these antiarrhythmic agents by reducing the frequency of serum drug assays.

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