Flecainide in the Treatment of Nonsustained Ventricular Tachycardia

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Thirty-two patients received flecainide acetate for nonsustained ventricular tachycardia after having had unsuccessful treatment with a mean of four antiarrhythmic drugs. The mean left ventricular ejection fraction was 41% in 27. Thirty-one patients had organic heart disease, and 22 patients had arrhythmia-related symptoms. Total suppression of ventricular tachycardia occurred in 22 patients. Thirty patients were discharged from the hospital receiving flecainide at a mean (± SD) dosage of 315 ± 76 mg/d and 26 of these patients attained a mean trough plasma drug level of 567 ± 254 ng/mL. One patient had proarrhythmia and 3 had worsening of heart failure. Twenty-two patients remained in the trial for a mean follow-up of 13 ± 7 months. Five patients died (1 suddenly) during the follow-up period. Our data indicate that flecainide suppresses refractory nonsustained ventricular tachycardia in 69% of patients who have organic heart disease. Serious adverse effects were minimized by initiation of treatment in the hospital and careful surveillance of electrocardiograms and plasma drug levels.

FLECAINIDE ACETATE is a new drug classified generally as a Ic antiarrhythmic agent because of its pronounced negative dromotropic effect on cardiac tissues in the absence of marked alterations in repolarization (1). A few cases of its use in treating recurrent sustained and nonsustained ventricular tachycardia have been reported, but clinical experience with this drug in the United States remains limited (2-7). We describe the combined experience of three arrhythmia centers that have used flecainide to treat patients with nonsustained ventricular tachycardia who had had previous unsuccessful treatment with other antiarrhythmic drugs.

We examined 32 patients who were part of a larger group enrolled in a trial of flecainide for the treatment of ventricular tachyarrhythmias. The results of this trial in patients who had recurrent, sustained ventricular tachycardia or out-of-hospital cardiac arrest have been presented in a separate report (3).

Patients and Methods

Seventeen men and 15 women aged 32 to 76 years (mean ± SD, 56 ± 14) who had recurrent, nonsustained ventricular tachycardia participated in the study between 1 January 1982 and 31 December 1984 at the Jewish Hospital at Washington University in St. Louis, the Medical College of Wisconsin Hospitals in Milwaukee, and Hermann Hospital at the University of Texas Medical School in Houston.

Nonsustained ventricular tachycardia was defined as six or more consecutive ventricular complexes occurring at a rate of more than 100 beats/min, lasting less than 30 seconds, and not requiring artificial termination because of hemodynamic instability. Twenty patients had coronary artery disease that was diagnosed by electrocardiographic findings of infarction in 6 and by angiographic documentation of coronary stenoses in 14. Fifteen patients had sustained myocardial infarctions lasting from 1 to 180 months (mean, 48 ± 55) before entry into trial and 5 patients had stable angina pectoris. Seven patients had mitral valve prolapse, 3 had congestive cardiomyopathy, 1 had rheumatic valvular disease, and 1 had no structural heart disease. Twenty-two of these patients had symptoms believed to be arrhythmia related. The commonest symptom, palpitation, occurred in 18 patients. Other presenting symptoms of syncope, near syncope, and shortness of breath correlated with recorded arrhythmias in 4 patients. Previous unsuccessful antiarrhythmic therapy included the use of one to eight drugs (mean, four). Failure of previous antiarrhythmic therapy was due to intolerance or ineffectiveness as determined by clinical criteria that included the use of telemetry monitoring and ambulatory electrocardiograms. When patients were referred after several unsuccessful drug trials, attempts by the investigators to confirm intolerance or inefficacy of previously administered drugs generally were not made unless they thought inappropriate doses had been given before referral. Left ventricular ejection fraction measured in 27 patients ranged from 18% to 60% (mean, 41% ± 13%).

Patients who had PR intervals of more than 0.28 seconds, second or higher degree atrioventricular blocks, creatinine clearances of less than 20 mL/min, or digitalis-induced arrhythmias, and patients who were pregnant or of childbearing potential were excluded from study participation. Efforts were made to avoid the concomitant use of calcium channel blockers or the enrollment of patients totally dependent on artificial pacing. In all patients, flecainide was the only antiarrhythmic drug used.

STUDY PROTOCOL

The patients were admitted to a telemetry unit after having had electrocardiographic determination of nonsustained ventricular tachycardia, and were continuously monitored throughout the hospital phase of the trial. After granting informed consent, they had pretreatment evaluations, during which all antiarrhythmic drug treatment was discontinued. This evaluation included a patient history, physical examination, 12-lead electrocardiogram, roentgenogram of the chest, ophthalmologic examination, and measurement of left ventricular function by radionuclide ventriculography or, when indicated, contrast angiography. Twenty-four hour ambulatory electrocardiographic recordings, taken after a clearance from previous antiarrhythmic treatment involving at least five drug half-lives, were repeated during treatment with the highest tolerated dose of flecainide. All tapes were analyzed at a central computerized facility (Cardio Data Systems, Haddonfield, New Jersey).

Flecainide treatment was then begun orally at an initial dosage of 100 mg every 12 hours. If the drug was well tolerated but ventricular ectopy persisted, the dosage was increased in 100-mg/d increments every 2 to 4 days. For the patients enrolled in the study during the first year, the maximum daily dose was limited to 600 mg. The administrators of the drug decreased this limit to 400 mg for all patients enrolled in 1983 and 1984 because of proarrhythmic effects that occurred during treat-

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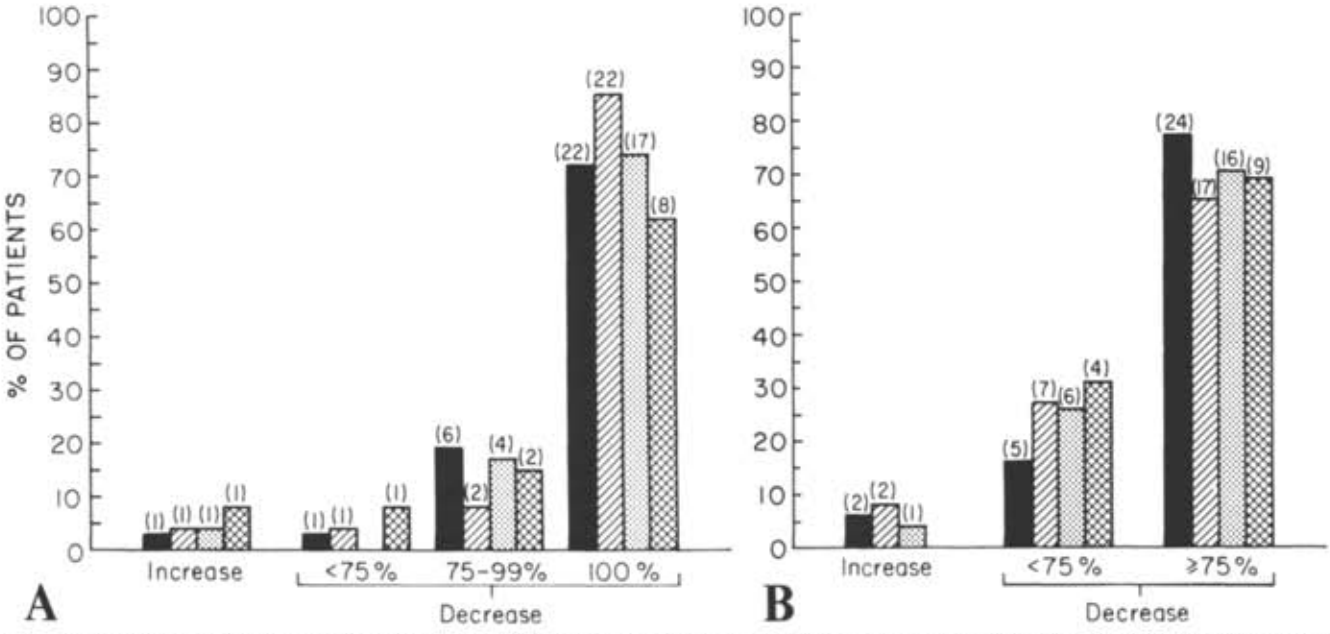

Figure 1. Percentage of patients, compared with baseline, who showed reductions in ventricular tachycardia events (*panel A*) and premature ventricular complexes (*panel B*) on 24-hour ambulatory electrocardiographic recordings. Values given for 31 patients at discharge (*solid bars*), 26 patients at 3 months (*hatched bars*), 23 patients at 6 months (*dotted bars*), and 13 patients at 12 months (*cross-hatched bars*).

ment with higher doses. In addition, an interval of 4 days was required between each dose increment. On long-term treatment, only one of the patients reported here received dosages of higher than 400 mg/d. Twelve-lead electrocardiograms were recorded on 25-mm/s paper speed and the PR, QRS, and QTc intervals were measured using calipers before each increase in dosage. Trough plasma flecainide levels were determined in 26 patients before each dosage increment and at the maximum tolerated dose before discharge from the hospital by the laboratory of S. F. Chang (Riker Laboratories, Inc.; St. Paul, Minnesota). Details of this liquid chromatographic method have been published (8-10). If patients had had histories of exercise-induced or exercise-exacerbated arrhythmia, they were given symptom-limited treadmill tests before discharge from the hospital to confirm the effectiveness of treatment during exercise.

Long-term treatment with flecainide was offered after a 75% or greater suppression of episodes of nonsustained ventricular tachycardia, as determined by predischarge ambulatory electrocardiographic recordings (note that for 24-hour ambulatory electrocardiographic monitoring, ventricular tachycardia was defined as more than three consecutive ventricular complexes); a 75% or greater measured reduction in premature ventricular complexes; and good subjective tolerance of the drug in doses found effective according to these criteria.

Patients discharged on flecainide were seen regularly in outpatient clinics for long-term monitoring of drug safety and efficacy and for verification of compliance. Efficacy was verified by patient questioning and repeating 24-hour ambulatory electrocardiographic monitoring 1 month after discharge and thereafter at 3-month intervals (Figure 1). A 12-lead electrocardiogram and blood specimens were obtained at each visit for determination of hematologic and biochemical profiles. Compliance was verified by measurement of plasma drug levels. Follow-up radionuclide angiograms were ordered for patients who were in New York Heart Association class III or IV or for patients who developed signs or symptoms of congestive heart failure.

DATA ANALYSIS

We stored data in a statistical analysis system database using the Washington University mainframe computer system (IBM, Poughkeepsie, New York) and analyzed data using *t*-tests. Pooled values are reported as mean ± SD.

Results

Of the 32 patients in the study, 30 completed the in-hospital phase of the trial and received flecainide after discharge from the hospital. Flecainide treatment was discontinued for early ineffectiveness in 1 patient and because of a proarrhythmic effect in 1 (*see* below). The dosage at discharge ranged from 200 to 500 mg/d (mean, 315 ± 76). Trough plasma flecainide levels, measured in 26 patients, ranged from 203 to 1121 ng/mL (mean, 567 ± 254).

CHANGES ON ELECTROCARDIOGRAMS

Comparison of 12-lead electrocardiographic recordings before and during flecainide treatment showed a statistically significant increase in the mean PR interval from 172 ± 5 ms to 203 ± 6 ms ($p = 0.0001$), and in QRS duration from 98 ± 3 ms to 118 ± 6 ms ($p = 0.0003$). No statistically significant change in heart rate or corrected QT interval occurred during flecainide treatment. These electrocardiographic changes are summarized in Table 1.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

We analyzed baseline and predischarge 24-hour ambulatory electrocardiograms in 31 patients (Table 2). Total suppression of ventricular tachycardia (more than three consecutive ventricular complexes) was achieved in 22 patients, and a greater than 75% suppression was achieved in 6 patients. One patient had a marked reduction in premature ventricular complexes and a less than 75% suppression of episodes of ventricular tachycardia, but remained in the trial because of the marked shortening and slowing of the runs. One patient left the trial

because of a marked increase both in premature ventricular complexes and in the number of episodes of ventricular tachycardia that occurred during treatment. One patient who had had previous electrocardiographic documentation of ventricular tachycardia, but no episodes of ventricular tachycardia recorded on the baseline or predischarge study ambulatory electrocardiograms, had a more than 85% reduction in premature ventricular complexes. Flecainide decreased the number of premature ventricular complexes by 75% or more in 24 patients, and by less than 75% in 5 additional patients. These findings and a comparison of the observations on ambulatory electrocardiograms obtained during long-term treatment are shown in Figure 1.

ADVERSE EFFECTS

Twenty-three patients had cardiac or noncardiac adverse effects during the in-hospital phase of the trial (Table 3). The commonest cardiac adverse effect was worsening of preexisting congestive heart failure, which occurred in three patients. This effect was controlled in each patient by an adjustment in dose of diuretics. These patients had left ventricular ejection fractions before treatment of 23%, 23%, and 36%, respectively. New rate-related left bundle branch block was seen in three patients during flecainide treatment. One patient had a proarrhythmic response consisting of an eightfold increase in the number of ventricular tachycardia episodes, a sixfold increase in the number of premature ventricular complexes over 24 hours, and the development of nonsustained ventricular tachycardia during an exercise test, which had not been seen before treatment with flecainide.

The commonest noncardiac side effect, blurring of vision, occurred in 14 patients and was associated with dizziness or headache in 5 patients. Other less frequent side

Table 1. Changes in Electrocardiographic Recordings in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia*

	Baseline*	After Treatment*	*p* Value
Heart rate, *beats/min*	72 ± 3	69 ± 2	NS
PR interval, *ms*	172 ± 5	203 ± 6	0.0001
QRS duration, *ms*	98 ± 3	118 ± 6	0.0003
QTc interval, *ms*	456 ± 9	449 ± 7	NS

* Values expressed as mean ± SD. NS = not significant.

Table 2. Results of 24-Hour Ambulatory Electrocardiographic Monitoring in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia

Patient Number	Diagnosis	Before Treatment			After Treatment			Dose	Plasma Level
		Premature Ventricular Complexes	Couplets	Runs*	Premature Ventricular Complexes	Couplets	Runs		
		← *n* →			← *n* →			*mg*	*ng/mL*
1	Coronary artery disease	4364	8	0	558	2	0	200	598
2	Mitral valve prolapse	3041	146	50	1468	0	0	500	986
3	Mitral valve prolapse	7309	283	4	1256	1	0	200	927
4	Coronary artery disease	2555	60	8	10	0	0	300	379
5	Mitral valve prolapse	31 552	5630	71	2486	62	0	300	527
6	Coronary artery disease	9804	5	1	13 225	6	0	200	465
7	Cardiomyopathy	11 602	429	34	2399	56	5	300	279
8	Mitral valve prolapse	28 258	629	29	20 427	5	0	300	883
9	Primary electrical disorder	11 521	108	2	1520	0	0	400	ND†
10	Coronary artery disease	12 966	74	9	2837	8	1	200	203
11	Coronary artery disease	11 121	676	95	964	205	4	300	463
12	Mitral valve prolapse	1909	15	2	119	0	0	300	515
13	Coronary artery disease	20 759	1941	356	885	4	1	300	1121
14	Coronary artery disease	15 647	0	5	6	0	0	400	ND
15	Coronary artery disease	1811	68	2	43	0	0	400	ND
16	Coronary artery disease	33 303	2452	291	15	0	0	400	ND
17	Coronary artery disease	4444	612	366	550	0	0	300	478
18	Coronary artery disease	2701	208	3	303	10	0	200	851
19	Coronary artery disease	49 269	3136	3280	8689	94	1	300	333
20	Coronary artery disease	35 403	5034	109	1642	30	0	300	369
21	Coronary artery disease	51 137	3040	434	126	0	0	200	ND
22	Coronary artery disease	13 746	2028	190	43	0	0	300	400
23	Coronary artery disease	31 476	1938	197	23 428	144	16	400	494
24	Cardiomyopathy	3600	100	16	97	14	11	300	747
25	Cardiomyopathy	6865	194	12	37 274	690	94	300	273
26	Coronary artery disease	2566	252	22	139	0	0	400	426
27	Coronary artery disease	8496	224	2	12	2	0	400	ND
28	Coronary artery disease	11 112	366	7	51	0	0	300	490
29	Rheumatic valvular disease	13 420	1160	64	1070	112	0	400	1052
30	Mitral valve prolapse	2666	1028	40	...	...	...	400	416
31	Mitral valve prolapse	4827	208	3	14	0	0	300	458
32	Coronary artery disease	28 864	2518	22	14 165	16	0	300	622

* Three consecutive ventricular complexes.
† ND = not determined.

Table 3. Adverse Effects of Flecainide in 32 Patients with Nonsustained Ventricular Tachycardia

	Patients*
	n
Proarrhythmia	1
Congestive heart failure	3
Rate-related left bundle branch block	3
Blurring of vision	14
Headache	4
Dizziness	5
Weakness	1
Fatigue	1
Nausea	2
Insomnia	1
Vertigo	1
Tinnitus	1

* Of the 32 patients, 23 had adverse effects and treatment was discontinued because of adverse effects in 1. Note that the same patient may have had more than one side effect.

effects were nausea, insomnia, weakness, fatigue, vertigo, and tinnitus. None of these noncardiac side effects were severe enough to warrant discontinuation of treatment and they responded to either a decrease in dose of flecainide or a change in drug dispensation from twice to three times a day.

LONG-TERM TREATMENT

Thirty patients completed the in-hospital phase of the trial and received long-term treatment. Of the 30 patients who entered the outpatient phase of the study, 22 remained in the trial at follow-ups ranging from 4 to 28 months (mean, 13 $\pm$ 7). The courses of patients during the in-hospital and long-term phases of the treatment are shown in Figure 2. Dosages of flecainide were decreased during follow-up in 5 patients because of recurrent noncardiac side effects. Two of these five patients had undesirably high plasma levels of flecainide (1121 and 1752 ng/mL). Three patients required dosage increases to maintain total suppression of complex forms of ventricular ectopy during ambulatory monitoring. Mean plasma flecainide levels increased from 604 ng/mL to 714 ng/mL in 8 patients who had measurements at discharge from the hospital and 6 months afterwards with no intercurrent change in drug dosage; the change is not statistically significant.

Flecainide treatment was discontinued in one patient at his request after 11 months of successful therapy. Treatment also was discontinued in one patient after 4 months because of persistent chest wall paresthesia, constipation, and impotence. The relationship of these symptoms to the use of flecainide is unclear because some symptoms have persisted after withdrawal of the drug. In one patient, treatment had to be discontinued for late ineffectiveness at 12 months.

Five patients died during the follow-up period. One patient died suddenly after 7 months of treatment, 4 weeks after a 24-hour ambulatory electrocardiogram had shown total suppression of ventricular tachycardia and complex ectopy. Two patients died of acute myocardial infarctions and one patient died on the way to the hospital after an episode of prolonged chest pain. Among the three patients who died after ischemic events, two had histories of recurrent angina pectoris, and one died of hemodynamic consequences of the infarction. The fifth patient who died during flecainide treatment had become critically ill from intractable respiratory insufficiency. The flecainide plasma level had increased from 875 ng/mL 2 weeks earlier to 2306 ng/mL at the time of death, during which time the patient had been receiving a stable dosage of flecainide. The patient died of a combination of intractable respiratory insufficiency and hypotensive ventricular rhythm of 110 beats/min that probably had been caused by toxic amounts of flecainide. None of the patients had any biochemical or hematologic adverse effects during follow-up.

LEFT VENTRICULAR FUNCTION

Of the 32 patients enrolled in the trial, 27 had measurements of left ventricular ejection fraction done before initiation of therapy. Fifteen had left ventricular ejection fractions of 40% or greater, and 12 had fractions of less than 40%. All 12 patients who had ejection fractions of less than 40% were discharged on flecainide, and 4 died during follow-up. One died suddenly, 1 died after a prolonged ischemic episode, 1 died during an acute myocardial infarction, and 1 died of respiratory failure. At a mean follow-up of 12 months, 8 of the patients who had marked left ventricular dysfunction were still receiving flecainide and had significant suppression of ventricular

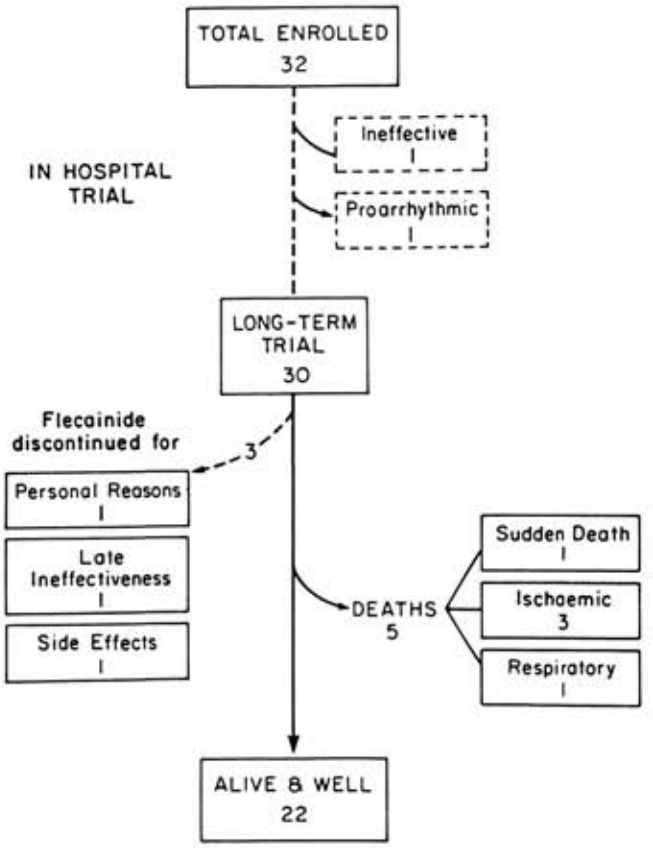

Figure 2. Flow diagram showing the results of in-hospital and long-term trials using flecainide to treat nonsustained ventricular tachycardia (mean follow-up, 13 months; range, 4 to 28).

Table 4. Analysis of Flecainide Treatment in 32 Patients by Diagnosis and Ventricular Function

	Patients		Results of Treatment		
	Total	Discharged on Flecainide	Treatment Discontinued	Eventual Death	Sudden Death
	n				
Diagnosis					
Coronary artery disease	20	20	2	3	1
Other	12	10	1	1	0
Left ventricular ejection fraction					
< 40%	12	12	0	3	1
≥ 40%	15	13	1	0	0
Not measured	5	5	2	1	0

tachycardia. Of the 15 patients who did not have marked left ventricular dysfunction (ejection fraction of 40% or greater), 13 were discharged from the hospital receiving flecainide. One patient from this group had flecainide treatment discontinued during long-term follow-up because of late ineffectiveness, and 12 have remained on treatment with adequate suppression of ventricular tachycardia. None of the patients from this group died. The outcome in relation to left ventricular function is shown in Table 4.

CORONARY ARTERY DISEASE

Of the 32 patients, 20 had coronary artery disease and all were discharged from the hospital receiving flecainide. Four of these patients died (1 suddenly) and the others remained on flecainide, achieving adequate suppression of ventricular tachycardia throughout follow-up. Of the 12 patients who had other diagnoses, 10 were discharged from the hospital receiving flecainide. Treatment was later discontinued in 1 of these patients due to subjective intolerance. One patient who had no coronary artery disease died of intractable respiratory insufficiency and 9 remained on flecainide with adequate suppression of ventricular tachycardia. Results are summarized in Table 4.

Discussion

The limited clinical experience accumulated thus far in the United States with the use of flecainide has shown the drug to be safe and highly effective in suppressing chronic, stable ventricular ectopy in patients who have no advanced organic heart disease (11, 12). The true efficacy and safety of an antiarrhythmic drug, however, can only be measured when it is given to patients at risk who, in general, have overt structural or ischemic heart disease associated with high-grade ventricular ectopy or sustained tachyarrhythmias. The proarrhythmic and myocardial depressant potentials of an antiarrhythmic drug will be reflected best in these patients. Reports from earlier trials of flecainide in high-risk patients raised concerns of an unacceptably high incidence of major proarrhythmic complications (7). Our observations in this group of patients indicate that flecainide can achieve long-term suppression of nonsustained ventricular tachycardia in a high percentage of patients with ischemic or structural heart disease even after several previous unsuccessful antiarrhythmic trials, and even in the presence of significant left ventricular dysfunction. Furthermore, proarrhythmic or other limiting adverse effects occurred infrequently. We believe that the low rate of serious complications in our trial, similar to that seen by others (13), is attributable to our strict adherence to the following rules: treatment was initiated in the hospital; dosage began with no more than 200 mg/d and loading doses were not used; increases in dosage were not made more often than every 4 days; dosages higher than 400 mg/d were not given; and plasma levels higher than 1 μg/mL were avoided. We therefore recommend following these rules when flecainide therapy is initiated in patients who have ventricular arrhythmias associated with advanced organic heart disease.

A negative inotropic effect with worsening of signs and symptoms of congestive heart failure can be an adverse effect from antiarrhythmic therapy and was seen in 3 of our patients. This side effect, which was anticipated on the basis of studies done by Legrand and colleagues (14) and Josephson and colleagues (15), occurred only in the presence of preexisting left ventricular dysfunction and was alleviated after adjustment of standard therapy for congestive heart failure. Flecainide must be used with caution in the treatment of patients who have severely depressed left ventricular function and an unstable cardiac output that causes variations in renal elimination of the drug. This mechanism may have resulted in flecainide accumulating to toxic levels in our patient who died of respiratory insufficiency.

Unlike serious adverse effects, nonlimiting side effects (visual ones, in particular) occurred frequently and required rearrangement of therapy for several patients. Overall, however, the drug was well tolerated on a long-term basis and few patients abandoned the trial because of side effects. Recently, Meinertz and associates (16) reported a long-term increase in plasma concentration of flecainide with no change in total daily dosage. In our study, a small rise in plasma flecainide level was measured in eight patients between discharge from the hospital and 6 months of follow-up, which suggests that even after 4 days of treatment, stable levels may not have been reached in some patients.

LIMITATION OF THE STUDY

Our trial was not controlled because strict comparisons with the effects of other antiarrhythmic agents were not its intent. Thus, our results should not be interpreted as demonstrative of the superior antiarrhythmic activity of

flecainide over other agents. Earlier randomized comparative trials in a low-risk population did, however, show a greater efficacy of flecainide in suppressing ventricular ectopy compared with that derived from both quinidine and disopyramide (12, 17).

A few patients included in this report had three or fewer episodes of ventricular tachycardia during baseline electrocardiographic monitoring. The short- and long-term elimination of nonsustained ventricular tachycardia in such patients thus may have been a reflection of mere spontaneous variability of the arrhythmia. In general, however, these patients had been selected for entry into the study because of frequently recurrent ventricular tachycardia as well as refractoriness to antiarrhythmic treatment. The absence of complex and high-grade ventricular ectopy on ambulatory electrocardiographic recordings during long-term treatment therefore was most likely a reflection of drug effect.

Although we tried to enroll patients who had symptoms, we recognize that suppression of symptoms as an endpoint of treatment in patients who have nonsustained tachyarrhythmias is unreliable and highly subjective, particularly when the trial does not involve controls. Therefore, we preferred to base our assessment of drug effect on 24-hour electrocardiographic measurements. In many of our patients, however, the effective control of arrhythmia was associated with the disappearance of symptoms, particularly palpitations, and these results contributed to the high compliance to, and acceptance of, long-term treatment.

Although one patient who received long-term treatment with flecainide died suddenly, this trial does not contribute information on the value of antiarrhythmic therapy in patients who have organic heart disease and a history of nonsustained ventricular tachyarrhythmias; only a large-scale placebo-controlled study could resolve this issue. In the meantime, if treatment is indicated for a patient who has nonsustained ventricular tachycardia, flecainide represents one of six choices available to the clinician. Because of its potentially serious side effects, we urge caution in its use, particularly in the early phase of treatment in patients who have underlying myocardial disease.

CONCLUSIONS

Results of this study indicate that flecainide can provide effective long-term suppression of nonsustained ventricular tachycardia in almost 70% of patients with organic heart disease. Adverse effects occurred in several patients initially, but tended to be nonlimiting. Aggravation of heart failure occurred in 9% of patients. Although proarrhythmic complications occurred infrequently, we recommend the initiation of treatment with flecainide in the hospital where the rhythm can be monitored. In addition, plasma drug levels should be surveyed closely both during the initial phase of treatment and during long-term follow-up.

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