

Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: A probable proarrhythmic effect

Flecainide acetate, a new antiarrhythmic agent, possesses favorable pharmacokinetic and hemodynamic properties and demonstrates highly favorable antiarrhythmic activity in patients with ventricular arrhythmias. However, the proarrhythmic potential of flecainide deserves further evaluation. In 7 (13%) of 55 consecutive patients treated with oral flecainide, 200 to 600 mg/day, for complex ventricular arrhythmias (including sustained ventricular tachycardia in 14), we observed the appearance of new or more sustained exercise-induced (five patients) or spontaneous (two patients) wide complex tachycardia. The mechanism of wide complex tachycardia appeared to be ventricular tachycardia in all seven. In our series, episodes were self-remitting or successfully treated. In four patients, wide complex tachycardia did not recur during exercise testing during alternative antiarrhythmic therapy (three patients) or no antiarrhythmic therapy (one patient). These observations raise the possibility of flecainide-related proarrhythmia, manifested as an increased propensity to exercise (activity)-induced wide complex tachycardia, which was not reliably predicted by results of Holter recordings or programmed electrical stimulation. Patients with complex ventricular arrhythmias beginning long-term treatment with oral flecainide should be considered for treadmill exercise testing together with ambulatory monitoring as part of the initial assessment of drug efficacy. (*AM HEART J* 1987;113:1071.)

Maria I. Anastasiou-Nana, M.D., Jeffrey L. Anderson, M.D., James R. Stewart, M.D., Barry J. Crevey, M.D., Frank G. Yanowitz, M.D., Joan R. Lutz, R.N., and Theresa A. Johnson, R.N. *Salt Lake City, Utah and Ann Arbor, Mich.*

Management of complex ventricular arrhythmias remains a therapeutic problem in many instances because the efficacy of antiarrhythmic agents may be inadequate or adverse effects intolerable.¹⁻⁴ An adverse effect that is being increasingly recognized in antiarrhythmic therapy is the occurrence of arrhythmogenic activity. Such "proarrhythmic" effects may include increases in ectopic beat frequency or, of more concern, new or more frequent or longer episodes of sustained ventricular tachycardia (VT), torsade de pointes tachycardia, or ventricular fibrillation and sudden death.⁵

Flecainide acetate, one of the newest of approved antiarrhythmic agents, has been shown to possess favorable pharmacokinetic properties in clinical

studies⁶ (complete absorption after oral administration, no first-pass effect, no significant metabolites, and plasma elimination half-life of 20 hours), and to possess a high therapeutic ratio in suppressing ventricular arrhythmias.⁷⁻¹³ Its common noncardiac adverse effects include blurred vision, lightheadedness, and dizziness, which resolve with time or with reduction to smaller but often still effective doses.¹⁴ Cardiac adverse effects (provocation of conduction disturbances, heart failure, and proarrhythmia) remain a major area requiring additional observations. Only a few reports exist about the possible proarrhythmic effects of flecainide.¹⁵⁻¹⁸ We report herein our observations of wide complex tachycardia occurring either spontaneously or during exercise testing in a consecutive series of patients treated with flecainide for complex ventricular arrhythmias in our institutions.

METHODS

Patient characteristics. Over a 61-month period, flecainide was administered to a total of 55 patients, 38 men

From the University of Utah, LDS Hospital, and the University of Michigan.

Received for publication July 16, 1986; accepted Oct. 2, 1986.

Reprint requests: Jeffrey L. Anderson, M.D., Cardiology Division, LDS Hospital, Eighth Avenue and C St., Salt Lake City, UT 84143.

Table I. Selected patient characteristics

| Patient No. | Sex | Age (yr) | Cardiac diagnosis | Clinical arrhythmia diagnosis | Baseline EF | Baseline Holter TPVCs/RPVCs/hr | Treatment | Flecainide* dose (mg/day) | Duration of treatment at time of event (mo) |
|-------------|------------|---------------|-------------------|---|----------------|--|--|---------------------------|---|
| | | | | | | | Holter TPVCs/RPVCs/hr % Δ vs baseline | | |
| 1 | M | 71 | CAD | PVCs, VCs, VT _{NS} | 0.39† | 123/0.21 | 170/NA ↑38%/NA‡ | 200 | 0.9 |
| 2 | M | 68 | CAD | PVCs, VCs, VT _{NS} | 0.59† | 281/5.7 | 9/0.7 ↓97%/↓88% | 300 | 2.9 |
| 3 | M | 55 | CAD | AF, PVCs, VCs, VT _{NS} , VT/VF | 0.19§ | EPS-V flutter _{NS} (15 beats) | EPS-VT not induced | 400 | 0.3 |
| 4 | F | 63 | VHD | PVCs, VCs, VT _{NS} | 0.68§ | 147/12 | 28/0.45 ↓81%/↓96% | 400 | 28 |
| 5 | M | 60 | CAD | PVCs, VCs, VT _{NS} | 0.47§ | 156/6.3 | 0.09/0 ↓100%/↓100% | 600 | 1.9 |
| 6 | M | 69 | VHD | PVCs, VCs, VT _{NS} , VT _S | 0.55¶ | 1015/94.3 | 1.5/0.25 ↓100%/↓100% | 400 | 21.4 |
| 7 | F | 43 | VHD | PVCs, VCs, VT _{NS} , ?VT _S ** | 0.59§ | 1939/0 | 0.13/0 ↓100%/— | 500 | 3.7 |
| Totals | 5 M 2 F | 61 ± 10 yr | CAD=4 VHD=3 | | 0.49 ± 0.16 | | | 400 ± 129 | Median = 2.9 Range = 0.3-28 |

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; EF = ejection fraction; EPS = electrophysiologic study; PVCs = premature ventricular complexes; RPVCs = repetitive PVCs; TPVCs = total PVCs; VCs = ventricular couplets; VT_{NS} = nonsustained ventricular tachycardia; VHD = valvular heart disease; VT/VF = ventricular tachycardia/ventricular fibrillation; VT_S = sustained ventricular tachycardia; NA = not available.

*At time of event.

†Contrast derived.

‡Repetitive beats not available; however, 24-hour Holter on flecainide 1 month previously showed 88% suppression of total PVCs.

§Echo derived.

||Dose begun or adjusted upward within 6 days.

¶Radionuclide derived.

**History of "tachyarrhythmia" but no documented VT on baseline Holters (x2) or exercise test.

and 17 women (average age 59.7 years; range 32 to 79 years). Patients were treated with the drug for a median of 6 months (range 0.07 to 61 months). Fourteen patients (25%) had a history of sustained ventricular tachyarrhythmia. Sixteen received oral flecainide after electrophysiologic study with programmed electrical stimulation for induction of VT. Thirty-nine were given oral flecainide guided by noninvasive methods, without electrophysiologic evaluation. Ventricular arrhythmias were associated with coronary artery disease in 29 patients, valvular heart disease in eight, dilated cardiomyopathy in three, primary rhythm disorder (without other evident heart disease) in 13, hypertension in one, and sick sinus syndrome (with a pacemaker) in one.

Study design. Records of all patients treated with flecainide were reviewed retrospectively for the occurrence of documented new or unexpected wide complex tachycardias. Tachycardias which were more frequent, more sustained, and/or less well tolerated were also included. The mechanism and morphology of tachycardia was confirmed by careful review of rhythm strips during tachycardia by one of us otherwise unfamiliar with the patient history (F.Y.). Patients in the electrophysiologic study group (n = 16) were subjected to continuous in-hospital monitoring and repeat programmed electrical stimulation to determine initial drug efficacy. Other patients underwent serial noninvasive monitoring. Clinical assessments were made initially monthly (for 2 to 3

months), then every 3 months, and ambulatory 24-hour monitor recordings were performed during initial and subsequent dose adjustments and at least every 6 months thereafter. Exercise testing was performed initially during therapy and repeated as clinically indicated during follow-up. Sustained VT was defined as that lasting for ≥ 15 seconds.¹⁹

Drug administration. Flecainide dosage ranged from 200 to 600 mg/day (median 200 mg/day initially, 300 mg/day at latest follow-up). Flecainide was given in two or (occasionally) three divided doses. Plasma concentration of flecainide was measured by gas-liquid chromatography.⁷

RESULTS

Of the 55 patients who were treated with oral flecainide, seven (13%) developed sustained (≥ 15 seconds) wide QRS complex tachycardia spontaneously (n = 2) or during exercise testing (n = 5). Relevant clinical information for these seven patients is presented in Table I. Entry characteristics did not readily distinguish this small group of patients from the other 48: four of seven had coronary artery disease, and three had experienced episodes of sustained VT or ventricular fibrillation; ejection fraction averaged 0.49 with a wide range (0.19 to 0.68). All seven patients had complex ven-

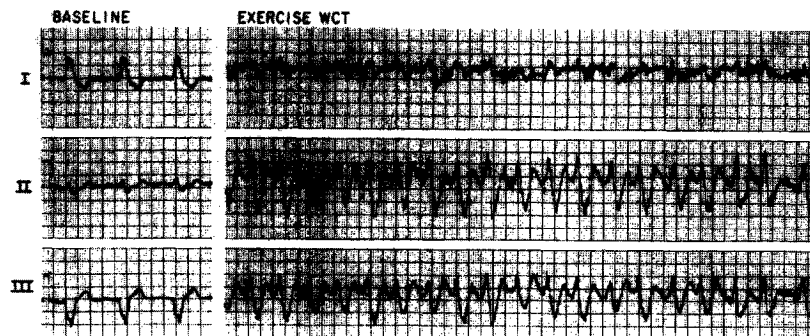


Fig. 1. Representative ECG strips from patient No. 1 at baseline and during wide complex tachycardia (WCT).

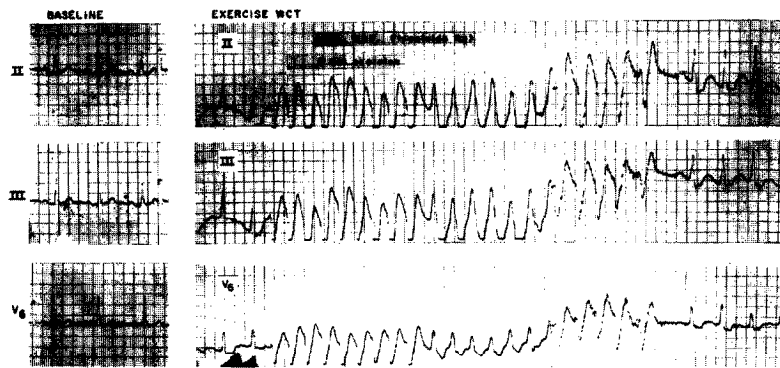


Fig. 2. Representative ECG strips from patient No. 2 at baseline and during wide complex tachycardia, (WCT).

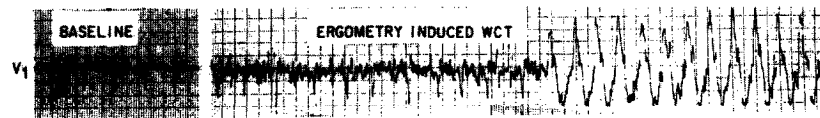


Fig. 3. Representative ECG strips from patient No. 3.

tricular arrhythmias including couplets and VT salvos (≥ 3 beats) at baseline. Representative ECG recordings before and during wide complex tachycardia are presented in Figs. 1 to 4. The tachycardia mechanism on careful review was thought to represent VT in all seven. Duration of tachycardia ranged from 15 seconds to 2 days (Table II). Tachycardia caused syncope in two, lightheadedness in two, and heart palpitations and chest discomfort in one each; it was asymptomatic in one. In our series, no patient died as a result of wide complex tachycardia. Tachycardia refractory to cardioversion was not encountered. Conversion was spontaneous in six and required overdriving with a pacemaker in one.

With respect to the possibility of ischemia-induced VT, no patient developed chest pain prior

to the arrhythmia induction; in two, the exercise test was read as suggestive of myocardial ischemia. Flecainide was discontinued in all patients. Subsequent exercise treadmill testing was performed in four patients during alternative antiarrhythmic therapy (one each on tocainide [patient No. 2], procainamide [patient No. 3], and amiodarone [patient No. 7] or no antiarrhythmic therapy [patient No. 1]) and did not reinduce VT.

Median flecainide acetate plasma concentration was $0.89 \mu\text{g/ml}$ (range 0.6 to >1.3) in the five patients in whom blood levels were available near to or at the time of the arrhythmia. Concurrent therapy included low-dose beta blockers in only two patients (Nos. 2 and 7). Arrhythmia during flecainide occurred in the absence of a clinical history of

Table II. Characteristics of flecainide-related wide complex tachycardia

| Patient No. | Activity during event | Minutes into exercise | Symptoms during event | Rate of WCT (bpm) | BP at or near time of event |
|-------------|---------------------------|-----------------------|-----------------------|-------------------|-----------------------------|
| 1 | ETT | 2.7 | Loss of consciousness | 125 | Imperceptible |
| 2 | ETT | 5.5 | Lightheaded | 150 | NA |
| 3 | Bicycle ergometry | 3 | Loss of consciousness | 167 | Imperceptible |
| 4 | Daily activity | — | Chest discomfort | 125 | 122/80 |
| 5 | ETT | 2 | Lightheaded | 167 | NA |
| 6 | Daily activity | — | Palpitations | 136 | 140/90 |
| 7 | ETT | 7.5 | Asymptomatic | 150 | 160/90 |
| Totals | Exercise = 5 Other = 2 | | | 146 ± 18 | |

Abbreviations: ETT = exercise treadmill test; LBBB = left bundle branch block; NA = not available (not measured at time of event); RBBB = right bundle branch block; WCT_S = sustained wide complex tachycardia.

*Termination of VT was spontaneous in all except patient No. 6, who was converted with ventricular overdrive pacing. In patient No. 4, termination followed discontinuation of flecainide.

†Time from event, 1 day to 9.6 months (no change in flecainide dose over this period).

‡Mechanism proved to be VT by demonstration of AV dissociation on an intraatrial recording.

@Transient VT (60 sec) had occurred once previously and during therapy with procainamide after exercise.

§Exercise VT also induced on a second occasion lasting 1½ minutes and finally spontaneous VT lasting 3 hours noted on another occasion, converting after lidocaine therapy (flecainide then stopped).

previous sustained tachycardia in four patients (Nos. 1, 2, 4, and 5). In one patient (No. 3), cardiac arrest (ventricular fibrillation), probably related to ischemia, had occurred, but monomorphic sustained VT had not been subsequently documented. A summary of three representative cases is presented below.

Case 1. A 71-year-old man with a long-standing history of hypertension developed frequent complex premature ventricular complexes after an anterior wall myocardial infarction. Salvos but no sustained VT were noted on baseline monitoring. Flecainide, 200 mg/day, was prescribed. After treatment for 1 year, temporary discontinuation of the drug allowed documentation of drug effect (88% ectopic suppression). Because of complaints of left precordial discomfort, he underwent thallium exercise testing on a treadmill 1 month later. Of note, Holter recording near the time of exercise testing showed loss of arrhythmia control (Table I). Baseline ECG showed left bundle branch block (QRS = 170 msec). After exercise for 2¾ minutes into stage I of a standard Bruce protocol, he began to look gray and started to stagger. Blood pressure became imperceptible, and he lost consciousness. His ECG rhythm strip at that time showed a very wide complex tachycardia (QRS = 260 msec, rate 125 bpm) (Fig. 1). Clinical and rhythm recovery occurred spontaneously within 1 to 2 minutes after he was laid down in bed. (Thallium imaging was suggestive of a lateral wall defect; coronary angiography showed stenosis of a diagonal branch.) Repeat exercise testing on no antiarrhythmic therapy was performed 3 weeks lat-

er. Exercise treadmill testing was limited by chest pain; however, wide complex tachycardia did not occur.

Case 2. A 68-year-old man had a long-standing history of coronary artery disease manifested by a myocardial infarction 20 years ago. Coronary bypass graft surgery was performed 2 years previously because of worsening angina. His course was also complicated by complex (but unsustained) ventricular arrhythmias unresponsive to four conventional antiarrhythmic drugs (quinidine, procainamide, lidocaine, and β -blockers). Flecainide, 150 mg twice a day, was initiated with >90% suppression of ventricular ectopy. He subsequently underwent routine exercise treadmill testing. After exercising for 5½ minutes on a standard Bruce protocol, he suddenly developed wide complex tachycardia, rate 150 bpm, accompanied by lightheadedness (Fig. 2). Exercise was stopped and sinus rhythm was restored spontaneously after 15 seconds. Plasma flecainide level was 0.60 μ g/ml. Flecainide was discontinued and tocainide started. On repeat exercise treadmill testing 7 days later, VT did not occur.

Case 3. A 55-year-old man had coronary artery disease manifested by two myocardial infarctions. He had also undergone five-graft coronary artery bypass surgery. He subsequently experienced cardiac arrest after which he was treated with procainamide for complex ventricular arrhythmias on ambulatory monitoring, with only partial suppression but without recurrence of arrest. Baseline electrophysiologic testing induced nonsustained polymorphic VT. Oral flecainide, 200 mg twice a day,

| Duration* of WCT | Morphology of WCT | Closest† flecainide level (ng/ml) |
|--------------------------------|----------------------|--------------------------------------|
| 60 sec | Undetermined | NA |
| 15 sec | Polymorphous | 0.60 |
| >15 sec | RBBB | 0.80 |
| 1-2 days | LBBB | NA |
| ≤30 sec | Undetermined | >1.3 |
| >1 hr‡, @ | LBBB | 0.89 |
| 2 min§ | LBBB | 0.96 |
| WCT _s (≥15 sec) = 7 | | 0.91 ± 0.26 |

was prescribed. On the fourth day of therapy, he experienced a syncopal episode during a hot shower. On repeat electrophysiologic study, no VT was induced. Because of continued suspicion of spontaneous VT, he underwent bicycle ergometry, which induced wide complex tachycardia, rate 167 bpm, with loss of consciousness (Fig. 3). Spontaneous conversion to his usual rhythm (atrial fibrillation) occurred before electrocardioversion could be applied. Flecainide level was 0.80 µg/ml. Flecainide was stopped and he was restarted on procainamide. On repeat exercise (treadmill) testing (on procainamide), wide complex tachycardia was not induced.

DISCUSSION

The distinction between arrhythmogenic effects and therapeutic failure of antiarrhythmic drugs is difficult. Thus, we evaluated a consecutive series of 55 patients treated with flecainide by one group of investigators and reported on all occurrences of paroxysmal wide complex tachycardia that were unexpected or more frequent. We observed seven instances (13% incidence). Of interest, in five of these, tachycardia induction occurred during exercise testing. This observation suggests the possibility of a sympathoadrenal, ischemic, and/or other exercise or rate-related factor in arrhythmia occurrence.

Explanations for wide complex tachycardia occurrence other than flecainide induction should also be considered. Flecainide substantially slows cardiac conduction as part of its therapeutic effects, causing increases in QRS intervals which may average 20% to 25% at therapeutic blood levels and which may be as great as 30% to 50% in some patients.^{10,15} The possibility that wide complex tachycardia during exercise might represent a rate-related increase in intraventricular conduction delay must therefore be strongly considered. However, more bizarre QRS changes were observed during tachycardia than

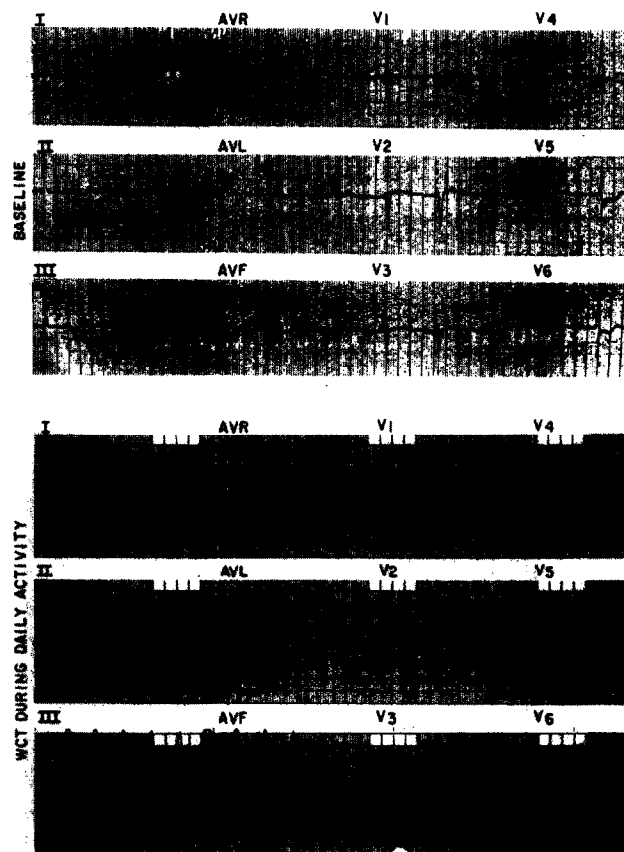


Fig. 4. Representative ECG strips from patient No. 6.

would be expected from classic rate-related bundle branch block alone, Atrioventricular dissociation was frequently suggested (and proved with an intraatrial wire in patient No. 6), and hemodynamic deterioration (presyncope or syncope, hypotension) was often noted. On careful review of rhythm strips during wide complex tachycardia, the mechanism appeared to be VT in all seven. Four of our patients had ischemic heart disease; exercise-induced ischemia might also lead to bundle branch block as a manifestation. However, either wide complex tachycardia occurred in the absence of chest pain or preceding ST segment depression or repeat exercise testing on alternative therapy failed to reproduce wide complex tachycardia. Only in patients Nos. 1 and 2 was an ischemic response noted and might be considered as a cofactor.

Clues to risks of clinical proarrhythmias may be provided by animal models. In a canine postinfarction model of sustained VT, Zimmerman et al.²⁰ found high-dose flecainide (3 to 10 mg/kg intravenously) to be arrhythmogenic. In a series of 15 dogs, flecainide infusions caused arrhythmias in five, consisting of spontaneous VT in four (after 10 mg/kg drug) and new electrophysiologic induction of VT in

one (nonsustained VT converted to sustained VT). VT was resistant to cardioversion in three animals. Proarrhythmia was dependent on drug concentration with adverse rhythms occurring in five of five with plasma levels $>3 \mu\text{g/ml}$ vs one of ten with lower levels. Proarrhythmia also correlated with ventricular dysfunction, occurring in four of six with large vs one of eight with small infarctions. Much lower flecainide doses and associated plasma levels pertain in clinical practice, however.

During clinical investigational administration of flecainide, an overall incidence of proarrhythmia, as judged by the individual investigating physician, has averaged 7%, of which three fourths have taken the form of sustained tachyarrhythmia (primarily ventricular), an incidence of 5%.^{15,21} However, the risk of proarrhythmia has not been uniform across patient subgroups. Substantial increments in risk have been noted in the presence of significant organic heart disease (ventricular dysfunction) and more malignant baseline arrhythmias (nonsustained and especially sustained VT).²¹ Any proarrhythmic event was reported in 1.7% of patients treated for symptomatic premature ventricular complexes only vs 16.4% in those with prior sustained VT events. Moreover, proarrhythmia risk was twice as great in those with structural heart disease as in those without it (7.4% vs 3.6%). Clinical proarrhythmia also appears to be dose related especially in patients with underlying sustained VT: the incidence of a significant proarrhythmic event was 26% in a high-initial-dose (400 mg/day) compassionate use trial vs 13% in a low-initial-dose (200 mg/day) study.²¹ In our study, patients Nos. 5 and 7 appear to fulfill the risk criteria of high dosage ($>400 \text{ mg/day}$) and high plasma drug levels (1.0 and $>1.3 \mu\text{g/ml}$). Patient No. 3 was at high risk because of a history of cardiac arrest and markedly depressed ventricular function. Patients Nos. 1, 2, and 4 were perceived to be at intermediate or lower risk of an adverse rhythm event, given the previous history of nonsustained VT with or without ventricular dysfunction.

The distinction between drug failure and proarrhythmia is often difficult to make. However, concern can be raised about the possibility of underestimating the incidence of proarrhythmia in large data base reviews because of investigator bias or initial inexperience with unexpected types of proarrhythmic events. Thus, in our series, all patients with documented wide complex tachycardia from a single investigator group series, excluding patients who initially failed therapy, are described. Our approach, if anything, might overestimate the role of flecainide by including all suspicious tachycardias. Our obser-

vations about proarrhythmia risk, however, are consistent with previous laboratory and clinical observations and also emphasize the potential for the combination of flecainide therapy and exercise to convert nonsustained to sustained VT. Previous sustained, monomorphic VT had occurred in one or possibly two patients; in both of these patients (Nos. 6 and 7), VT during increasing doses of flecainide became more frequent and more sustained (e.g., patient No. 6, lasting >1 hour; patient No. 7, induced on multiple treadmill tests and occurring spontaneously, lasting up to 3 hours, despite reduction in isolated ectopic events).

No directly comparable studies of the proarrhythmic effects of various other antiarrhythmic drugs in the same patient population have been reported. However, the overall reported incidence of 7% with flecainide^{15,21} compares favorably with the range of 5% to 15% reported for various other agents in the experience of one large arrhythmia treatment center.⁵ Of concern, however, is the form of proarrhythmia observed with class IC agents, that is, sustained VT.²¹ Cases of difficult to resuscitate VT, including fatal cases, have also been observed rarely with flecainide.^{15,21} We did not observe this form in our series of patients. Our patient population as a whole may be considered to be at intermediate rather than higher risk of proarrhythmia, as defined by the severity of presenting clinical arrhythmias and ventricular dysfunction.²¹ Although the wide complex tachyarrhythmias observed in our group were not of the lethal variety (incessant or conversion resistant), which has occasionally been observed in very high-risk patient groups, they were nonetheless regarded as serious and unexpected and may be of the type more frequently observed in clinical practice.

The observation in our series that wide complex tachycardia was frequently induced by treadmill or ergometric testing, even in the face of suppression of ambient ventricular ectopy (patients Nos. 2 and 4 to 7) or electrophysiologically noninducible VT (patient No. 3), has suggested to us an exercise-related mechanism. In this regard, it would be of interest to test the hypothesis that concurrent beta blocker therapy might influence the risk of exercise-stimulated wide complex tachycardia (VT) by limiting the heart rate and sympathetic response to exercise. Hirsowitz et al.²² evaluated the role of beta-blocking agents as adjunct therapy to membrane-stabilizing drugs (including some class IC agents) in malignant ventricular arrhythmias by means of ambulatory monitoring and exercise testing.²² The major contribution of beta blocker therapy was the reduction of the incidence of runs of VT during exercise testing

(from 39% to 7% of exercise tests). In our study, two patients were on beta blockers (Nos. 2 and 7), and five were not. Flecainide has been combined with beta blockers in therapy of postmyocardial infarct arrhythmias in the Cardiac Arrhythmia Pilot Study (CAPS)²³ with a low incidence (3%) of proarrhythmic events.

In conclusion, wide complex tachycardia with features of VT occurred as the principal adverse rhythm manifestation during flecainide therapy of patients with complex ventricular arrhythmias and occurred independently of the response of isolated ectopic beats during ambulatory recording. Our observations, coupled with other reports, are consistent with an increased propensity for proarrhythmia in those with structural heart disease (especially coronary artery disease with left ventricular dysfunction) and with more malignant underlying arrhythmias (nonsustained and sustained VT). Our experience suggests exercise testing to be a potentially arrhythmogenic stimulus in several patients. Other factors (rate-related conduction delay, exercise ischemia) might be considered as cofactors in individual patients. This leads to the proposal that routine exercise testing be used to evaluate the propensity for activity-related proarrhythmia risk in patients treated with flecainide, especially in those at high risk (i.e., preexistent nonsustained or sustained VT and/or ventricular dysfunction). Future trials should use a prospective design with routine pre- and post-therapy exercise testing. These trials might also test the interaction of beta blockers in the exercise induction of arrhythmias during flecainide. Improved prediction and detection of the proarrhythmic potential of flecainide is important for the safe and effective use of this important new agent.

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