

A Proposal for the Clinical Use of Flecainide

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Effective antiarrhythmic therapy requires a carefully considered approach, including an understanding of the arrhythmia, the underlying cardiac disease and the drug's pharmacokinetics. Flecainide is a new antiarrhythmic drug that may soon be released for general use. Flecainide demonstrates unsurpassed efficacy in chronic ventricular arrhythmias in stable patients and may become a first-choice drug because of its ease of administration, efficacy and favorable tolerance. Twice-daily dosing with 100 to 200 mg usually provides effective therapy. Clinical experience suggests flecainide to be indicated in the treatment of uniform and multiform ventricular premature complexes, coupled ventricular premature complexes, and episodes of nonsustained ventricular tachycardia. A lower re-

sponse rate is observed in preventing induction of sustained ventricular tachycardia, and these patients should be carefully selected. Flecainide is promising in the treatment of supraventricular tachycardias using atrioventricular nodal or extra-nodal reentrant pathways, although this use is still investigational in the United States. The drug's use for arrhythmias during acute myocardial infarction requires further study. Flecainide possesses modest negative inotropic potential. Proarrhythmic or other adverse reactions have occurred primarily in settings of high drug level, poor ventricular function or refractory, malignant arrhythmias, suggesting caution in these groups.

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Effective therapy of cardiac arrhythmias requires a carefully considered approach.¹ The first step in arrhythmia management is an accurate cardiac diagnosis, which includes documentation and identification of the arrhythmia and evaluation of underlying heart disease. Specific initiating factors should be identified. Electrolyte, acid base and other metabolic derangements, neuroendocrine factors or adverse drug interactions should be addressed. Antiarrhythmic goals should be specified in advance and may include elimination of symptoms (palpitation), suppression of ectopic ventricular complexes, elimination of repetitive complexes or prevention of ventricular tachycardia and fibrillation. Drug administration should be based on sound clinical and pharmacologic principles. Disease states may alter drug effects and disposition. Once therapy has begun, careful follow-up should be undertaken, including documentation of antiarrhythmic effects, observation for adverse effects and, when appropriate, drug plasma concentration.

In association with organic heart disease, particularly

coronary artery disease, complex ventricular arrhythmias may be associated with an increased risk of mortality, particularly from sudden death due to ventricular fibrillation.^{2,3} Studies documenting the ability of antiarrhythmic therapy to reduce this excessive risk are incomplete. However, a carefully applied approach appears to hold promise.⁴ Therapy for ventricular arrhythmias is indicated in the following settings: (1) primary ventricular fibrillation unprovoked by myocardial infarction; (2) complex ventricular arrhythmias (pairs, runs, R-on-T complexes and high frequency arrhythmia) after myocardial infarction, particularly during the first year; (3) complex arrhythmias in association with ischemia; (4) ventricular tachycardia, particularly in coronary artery disease; (5) syncope ascribed to ventricular tachycardia of any origin; (6) arrhythmias causing significant clinical symptoms (palpitation, dyspnea, fatigue and dizziness).^{3,5}

An ideal antiarrhythmic drug should possess a high degree of effectiveness, a low level of toxicity with a wide therapeutic range and prolonged antiarrhythmic action.⁶ The clinical management of ventricular arrhythmias remains problematic, however, because of the frequent failure of standard drugs which may be attributable to inadequate antiarrhythmic activity, intolerable adverse effects or compliance problems. In this regard, flecainide acetate possesses several favorable properties compared with available antiarrhythmic agents: excellent antiarrhythmic potency per milligram, effectiveness against ventricular arrhythmias in a high

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percentage of patients, a low incidence of major adverse effects, and a long half-life, which favors patient compliance and continuous antiarrhythmic action.⁷

We are presenting a long-term patient experience, reviewing important investigative observations (many detailed in this symposium), and formulating guidelines for the initial clinical application of flecainide.

Application of Clinical Pharmacology

Only by applying a thorough understanding of a drug's unique pharmacologic characteristics can maximal therapeutic benefit be realized (Table I).

Metabolism in humans⁸: After oral administration, the absorption of flecainide is nearly complete, and presystemic (first-pass) metabolism is negligible, resulting in systemic bioavailability of more than 90%. Peak plasma drug levels occur at about 3 hours (range 1 to 6). Food does not deter the rate or extent of flecainide absorption. Increases in oral dosage lead to increases in plasma level in a linear fashion.

The mean plasma elimination half-life in patients with ventricular arrhythmias as determined in several studies averages about 20 hours (range 12 to 27).^{7,9,10} This result is somewhat longer than the 14-hour mean half-life noted after single oral doses given to healthy persons.¹¹ Minimum therapeutic plasma concentrations associated with greater than 90% suppression of ventricular premature complexes (VPCs) in responding patients range from 200 to 1,000 ng/ml (mean 500). In patients with advanced cardiac disease, major adverse cardiac effects have usually occurred in association with plasma levels greater than 1,000 to 1,500 ng/ml. Because antiarrhythmic effects are related to parent drug, plasma determinations of flecainide may provide useful clinical information. Elimination of flecainide is primarily renal, consisting of unchanged drug and 2 major urinary metabolites with little or no antiarrhythmic activity. Plasma protein binding is low (about 40%) and independent of plasma drug levels. Drug interactions of consequence have not been observed. Despite the high percentage of flecainide circulating as free drug, its large volume of distribution (about 10 liters/kg) precludes effective removal of flecainide by hemodialysis.

Urinary excretion in moderate renal failure is only somewhat less than that in healthy subjects; in contrast, urinary elimination may be markedly lower with end-stage renal disease. Observation suggests a decrease of about 25% in the rate of flecainide elimination from plasma in patients with congestive heart failure (New York Heart Association class III or IV). Drug interactions with flecainide appear to be minor. The addition of flecainide in subjects receiving maintenance digoxin results in about a 15% increase in digoxin concentration, an insignificant change. Concurrent administration of flecainide and propranolol results in plasma increases in flecainide averaging 20% and propranolol of 30% in healthy subjects. Therefore, the pharmacokinetic profile of flecainide is favorable in many regards, and major anomalies of clinical significance have not been described.

Electrophysiologic implications: Flecainide

TABLE I Clinical Pharmacology of Oral Flecainide

Bioavailability: >90%
Minimum effective plasma concentration range: 200 to 1,000 ng/ml (mean 500)
Elimination half-life: 20 hours (range 12 to 27)
Elimination: Renal
Plasma protein binding: 40%
Active metabolites: None of significance

belongs to the membrane-stabilizing (class I) group of antiarrhythmic agents; however, it has its own characteristic electrophysiologic profile.^{12,13} In humans, flecainide depresses conduction in all parts of the heart, with greatest effects on the His-Purkinje system. Effects on refractory periods are less pronounced and primarily limited to the ventricle.¹³ Sinus node recovery times are usually unaffected except in certain patients with sick sinus syndrome, in whom flecainide occasionally may result in pronounced lengthening.¹⁴ Prolongation of PR and QRS intervals is greater during treatment with flecainide than with standard drugs,^{7,15,16} but effects on the QT interval are small¹⁵ (Table II). Increases in PR and QRS intervals of about 20% commonly occur at doses of 400 mg/day, and are usually not a cause for concern.^{7,13,15} Those with initially increased PR and QRS intervals are not disproportionately affected.¹³ Similar electrocardiographic changes also are noted with encainide.^{17,18} Clinically, an increase in electrocardiographic intervals of more than 50%, substantial increases in corrected QT interval¹⁹ or the development of new bundle branch block should raise a clinical concern, particularly in patients with advanced disease. The development of bifascicular block or second-degree or greater heart block is an indication for drug reduction or discontinuation unless a pacemaker is present to sustain rhythm.

Hemodynamic considerations: Flecainide has been well tolerated hemodynamically. Blood pressure is typically unchanged. Small increases have occasionally been noted, and rarely increases in antihypertensive therapy are needed. Heart rate is unchanged, although rarely bradycardia or tachycardia may be seen. Among antiarrhythmic drugs, flecainide appears to have intermediate negative inotropic potential. In stable pa-

TABLE II Cardiovascular Effects of Oral Flecainide

Blood pressure: → (±↑)
Heart rate: →
Electrocardiographic intervals*:
ΔPR: 0.04 s (↑23%), p < 0.01
ΔQRS: 0.02 s (↑20%), p < 0.01
ΔQT: 0.03 s (↑7%), p < 0.05
ΔJT†: 0.01 s (↑4%), p = NS
Worsening heart failure:
Overall: 2.1% (8/373)
Previous failure: 9.0% (6/67)
Proarrhythmic effect: treatment groups
Chronic stable arrhythmias: 4%
Unstable arrhythmia patients: 12%
Overall: 7.5% (44/588)

* During doses of 400 to 600 mg/day.¹⁵

† ΔJT = ΔQT - ΔQRS; a measure of independent effects on QT.^{7,15}

NS = not significant.

TABLE III Efficacy of Oral Flecainide

Study (n)	Summary of Representative Trials			
	% Responders (>80% VPC Suppression)	% VPC Suppression (Mean Frequency Reduction)	% Suppression Couplets, Runs	Mean Dose (mg/day) (Range)
Multicenter dose ranging (n = 33) ^{7,9,10}	97 (32/33)	97%	>99%	400 (200-600)
Flecainide-quinidine comparison (n = 233) ¹⁵	85	95%, mean (99.5%, median)	100% reduction in 75% 80% reduction in 90%	440 (400-600)
Flecainide, mexiletine, propafenone comparison (n = 12) ²²	82 (9/11)	94.2%	98.8%	400

VPC = ventricular premature complexes.

tients, electrocardiographic ejection fraction does not change during maintenance therapy.^{7,9,10} Twelve patients with compromised left ventricular function were studied by radionuclide ventriculography before and during maintenance therapy: ejection fraction averaged 42% before and 38% after therapy; this decrease was not associated with clinical failure.²⁰ In a retrospective analysis of 373 patients treated with flecainide, in 4.3% (16 patients), signs or symptoms developed that might be indicative of heart failure, possibly related to flecainide therapy. In a subgroup with previous heart failure, symptoms developed in 15% (10 of 67). However, a closer examination of each patient's clinical history indicated that only 2.1% (8 patients) and 9% (6 of 67), respectively, had evidence of heart failure possibly attributable to flecainide therapy. These figures suggest that flecainide is better tolerated hemodynamically than disopyramide²¹ or propafenone.²² In conclusion, flecainide may be used without concern in those with normal or moderately depressed left ventricular function, but caution should be used in those with more advanced dysfunction with preexistent heart failure.

Review of Clinical Experience and Use

Clinical studies: Flecainide has been administered to approximately 1,000 American patients during clinical investigative studies (Table III). European experience is broader; flecainide has rapidly achieved a position among the most commonly prescribed antiarrhythmic drugs in areas where it is now generally available.

Clinical efficacy of the oral drug was initially demonstrated in the United States in a 3-center dose-finding and short-term efficacy trial.^{7,9,10} Flecainide therapy resulted in suppression of ventricular premature complexes averaging 97% in the 33 patients studied. The average dose was 400 mg/day. Repetitive ventricular activity was essentially eliminated.

More recently, the efficacy of flecainide (200 to 300 mg b.i.d.) has been compared with that of quinidine (300 to 400 mg q.i.d.) in a large multicenter trial.¹⁵ Both drugs were effective in arrhythmia suppression, but the response to flecainide was substantially greater, resulting in 95% VPC suppression, vs 70% during quinidine. Seventy-five percent of patients achieved more than 95% suppression with flecainide, as opposed to 35% in the parallel group treated with quinidine ($p < 0.001$).

Couplets were eliminated in 70% of patients treated with flecainide; quinidine eliminated the couplets in only 41% ($p < 0.001$). Similarly, ventricular runs were eliminated in 80% treated with flecainide, vs 55% with quinidine.

In another clinical trial, the antiarrhythmic efficacy of flecainide was compared with that of mexiletine, a lidocaine congener, and propafenone, another potent type I agent.²² Response to flecainide was superior in terms of efficacy and tolerance. Arrhythmia (VPC) reduction averaged 94% after flecainide (400 mg/day), 80% after propafenone (900 mg/day) and only 53% after mexiletine (600 mg/day) in 12 patients with coronary artery disease. Repetitive extrasystoles were reduced by 99, 97 and 83% by the 3 drugs, respectively, in this blinded, crossover study. Side effects led to discontinuation of propafenone and mexiletine in 2 patients each.

Experience has been more limited in patients with inducible ventricular tachycardia by programmed electrical stimulation.¹³ In 15 consecutive patients studied in our laboratory, oral flecainide prevented tachycardia induction in 9 (60%) and improved the response in 2 others, a 73% overall favorable response. Higher response rates have not been reported for other class I agents. However, response in these patients is evidently less than that in stable patients without ventricular tachycardia and depends on patient selection and stimulation protocol.^{23,24}

Long-Term Experience in Treating Complex Arrhythmias

Antiarrhythmic experience extending over several years is important in assessing clinical safety and efficacy. Such experience with flecainide is still limited and will require further observation. Our own experience with a small group of patients presenting initially with complex ventricular arrhythmias follows.

Ten consecutive patients entered into long-term flecainide therapy on the basis of an initial successful response (80% suppression) (Table IV).^{7,25} At the end of a short-term study (14 days), geometric mean VPC frequency had been reduced by 99.5% ($p < 0.001$) (Table V). The effective drug dose averaged 420 mg/day (range 300 to 600), given in divided doses every 12 hours. Median plasma flecainide concentration was 837 ng/ml (range 357 to 1,615) (Table V). Patients were continued

TABLE IV Experience with Long-Term Therapy

Pt	Age (yr) & Sex	Cardiac Diagnosis	Arrhythmia Complexity	No. of Previous Drugs*	Follow-Up (mo)	Outcome
1	62F	ASD	Couplets	2	28	Successful (X28 mo); late failure (see text)
2	56F	MVP, MR	Runs	1	37	Successful
3	49F	Normal	Couplets	2	36	Successful
4	55F	AVD	Multiform	3	35	Successful
5	52F	Normal	Runs	5	32	Successful
6	61M	CAD, old MI	Runs	3	3	Failure (exercise VT)
7	43F	Normal	Runs	3	10	Failure (exercise VT)
8	69M	AS, CM	Runs	3	21	Successful (X21 mo); late failure (VT)
9	70F	Normal	Runs	5	16	Successful
10	67M	CAD, old MI	Runs (sustained VT)	3	9	Successful

* Includes disopyramide (5 patients), lidocaine (1 patient), phenytoin (2 patients), procainamide (6 patients), propranolol (6 patients), quinidine (8 patients) and tocainide (1 patient).

AS = aortic stenosis; ASD = atrial septal defect; AVD = aortic valve disease (bicuspid); CAD = coronary artery disease; CM = cardiomyopathy; MI = myocardial infarction; MR = mitral regurgitation; MVP = mitral valve prolapse.

TABLE V Experience with Long-Term Therapy

Pt	Dose (mg/day)	Average VPCs/Hour				Plasma Flecainide (ng/ml)		
		Baseline	14 Days	4-8 Mo	18-36 Mo	14 Days [†]	6 Mo [§]	30 Mo [§]
1	400	125	0	1	16	921	1,160	...
2	400	2,544	0	0	0	544	892	603
3	600	636	6	258	74	1,291	1,589	1,444
4	400	264	108	0	2	357	1,284	1,476
5	400	3,468	18	0	0	777	967	727
6	500	144	0	1,615
7	400	1,854	0	0	...	743	1,421	...
8	400	1,302	6	110	2	897	1,047	...
9	300	1,478	0	129*	1,012	...
10	400	8,100 [†]	127	33	845	...

* After attempted dosage reduction.

[†] Sustained ventricular tachycardia, 136 beats/min.

[‡] Predose (trough).

[§] Random.

on the same dose of medication and were followed monthly for 4 months and bimonthly thereafter. History, examination, 12-lead electrocardiography with 1-minute rhythm strip and blood chemistry tests were performed at each visit and 24-hour ambulatory (Holter) electrocardiographic recordings at 4-month intervals.

The follow-up period ranged from 3 months in a patient with early treatment failure to 37 months, with a median of 25 months (Tables IV and V). In the 9 patients successfully treated at 6 months, geometric mean VPC frequency was 8.0/hour (range 0 to 258), representing 99% suppression with respect to baseline. An additional treatment failure occurred between 6 and 12 months, and 1 each during the second and third treatment years. During successful treatment at 18 to 36 months ($n = 7$), geometric mean VPC frequency was 6.2/hour (range 0 to 78), representing 99.6% continued VPC suppression.

Treatment failures included ventricular tachycardia in 3 instances and supraventricular arrhythmia in 1. In Patients 6, 7 and 8, spontaneous episodes of more sustained ventricular tachycardia developed despite continued reduction of VPC frequency. In Patients 6 and

7 ventricular tachycardia also occurred during treadmill exercise. Most recent levels in the 4 patients in whom tachyarrhythmias developed were in excess of 1,000 ng/ml (mean 1,300).

Side effects were minor. Symptoms occurred early in the course of treatment and did not progress during follow-up. Seven patients complained of intermittent visual blurring and 2 noted a metallic taste. No hematologic or blood biochemistry abnormalities were observed. Electrocardiographic changes, including moderate increases in PR and QRS intervals of 10 to 20%, remained stable.

In summary, flecainide has remained highly effective in reducing VPC frequency in these patients for as long as 37 months (median 25) and is symptomatically well tolerated.²⁵ However, spontaneous ventricular tachycardia may still occur in some patients. Disease progression or high plasma levels may have contributed to these failures. Exercise testing was useful in assessing proarrhythmic potential.

Granrud et al²⁶ reported preliminary results of long-term follow-up in 27 patients treated with flecainide. Treatment was stopped in 4 patients, because of sudden death in 1, heart failure in 1, right bundle

TABLE VI Dosage Recommendations for Oral Flecainide Therapy

Usual dosage: 200–400 mg/day
Initial dose: 200 mg
Initial maintenance dose: 100 mg every 12 hours
Dose increments: 50 mg every 12 hours, every 4 days as needed
Usual effective regimens:
100, 150, and 200 mg every 12 hours
Alternative: 100 mg every 8 hours
Maximum dosage: 300 mg every 12 hours (600 mg/day)
Conditions of altered dosage:
1. End-stage renal disease (creatinine clearance ≤ 20 ml/min/ m^2)
2. Advanced ventricular dysfunction, heart failure and unstable rhythms
3. Recommend: Schedule hospital administration: begin 100 mg every 12 hours; increments \geq every 4 to 7 days, maximum 200 mg every 12 hours; follow plasma levels if possible.

branch block in 1 and inadequate efficacy in 1. Side effects were minor. At 18 to 20 months, mean percent suppression of VPCs and ventricular pairs was 88% and suppression of ventricular tachycardia 83% (23 patients). The average dose of flecainide was reduced to a mean of 320 mg/day during chronic therapy, resulting in an average plasma drug level of 577 ng/ml. Flecainide was well tolerated.

Drug Dosage

Dosing recommendations (Table VI): Most studies with flecainide have used an average starting dose of 200 mg every 12 hours, and this dose has been effective and well tolerated in most patients. Because of the long half-life of flecainide, it is likely that even smaller doses (100 to 150 mg every 12 hours) will provide antiarrhythmic efficacy in many patients. Therefore, it is recommended that after a loading dose (200 mg), therapy be initiated at 100 mg every 12 hours. This dose may be increased in increments of 50 mg twice daily every 4 days until efficacy has been achieved or until 400 mg/day (200 mg twice daily) has been reached. A few

TABLE VII Adverse Reaction Profile

Neurocirculatory:
Common: Dizziness, blurred vision ($\approx 30\%$)
Comment: Usually minor; may decrease with time; usually responds to dosage reduction if needed
Occasional: Headache and nausea (5 to 10%); asymptomatic 1° atrioventricular block
Uncommon: Flushing, chest pain, anxiety, tremor, palpitation, altered taste, paresthesia, fatigue, asthenia and hypertension
Proarrhythmic:
Increased VPCs: <5 to 10% of patients
Comment: More common at subtherapeutic dosage; if so, may decrease with therapeutic dosage
Facilitation of VT: (1) on ambulatory monitoring (may be independent of total VPC response), (2) at electrophysiologic induction, and (3) exercise-induced spontaneous.
Incessant VT or VF (difficult to resuscitate): Very rare.
Comment: Associated with high plasma drug levels ($>1,000$ ng/ml), poor ventricular function (ejection fraction $<30\%$), history of malignant arrhythmias and \pm concurrent antiarrhythmic use; avoid, by careful patient selection and dosage increments, careful monitoring

VF = ventricular fibrillation; VPC = ventricular premature complexes; VT = ventricular tachycardia.

patients have required higher doses, but a dose of 600 mg/day should not be exceeded.

Dosage increases greater than 400 mg/day should not be made in patients at higher risk for toxicity (heart failure, renal failure with creatinine clearance ≤ 20 ml/min/ m^2 , the very elderly and weight less than 50 kg) unless guided by plasma drug concentrations. Again, initial dosage should not exceed 100 mg every 12 hours and increments should be made cautiously, at 4- to 7-day intervals, allowing for steady-state plasma levels to be reached. Studies to determine the effect of hepatic impairment on flecainide elimination have not been completed.

Some patients may be intolerant to or not adequately controlled by a dose given every 12 hours. In these cases, the daily dose may be divided into 8-hour intervals. The long half-life of flecainide suggests the possibility of once-daily dosing in certain patients, but this possibility has not been studied.

Recognizing and Dealing with Adverse Reactions (Table VII)

Flecainide is well tolerated, although minor adverse effects may be seen. About 30% of patients receiving an average dose of 400 mg/day or greater have visual disturbance (blurred vision and difficulty in accommodation, particularly on lateral gaze) or dizziness (lightheadedness and unsteadiness).^{7,9,10,13,15} These effects most often occur after dosing, during the period of expected drug peak. Complaints of nausea and headache may occur in 5 to 10% on larger doses. Infrequent effects (incidence of less than 5%) include flushing, chest pain, dyspnea, nervousness, palpitation, tremor, paresthesia, fatigue, asthenia and metallic taste. These effects are minor, transient and well tolerated in most patients. In 1 large study,¹⁵ 13% of patients discontinued flecainide because of adverse effects. However, dosages of 400 to 600 mg/day were used, and down-titration was not allowed. Experience in chronic studies indicates that adverse effects may be relieved while efficacy is maintained by downward dose adjustments.²⁶ Intolerance should force discontinuation in less than 10%. Flecainide has not caused biochemical or hematologic abnormalities.

Hemodynamic and rhythm effects form the other basis for potential adverse reactions. Worsening of heart failure may occur in approximately 2% of the patients. First-degree atrioventricular (AV) block is seen frequently, but is usually benign. QRS widening may rarely progress to bundle branch block, usually asymptomatic. Sinus bradycardia, sinus pause, sinus arrest or more advanced AV block is rare, but may occur with preexistent conduction system disease. Proarrhythmic effects are discussed herein.

Precautions: Important drug interactions with flecainide have not been apparent. There has been no experience with co-administration of flecainide and either disopyramide or verapamil. There is little rationale to co-administer disopyramide, particularly in view of the negative inotropic properties of each drug. In appropriate patients, co-administration of verapamil and flecainide may be indicated when the potential benefit

outweighs the risk (negative inotropy and decreased AV conduction).

Flecainide has not been shown to be carcinogenic in animal studies.²⁷ There are no adequate and well-controlled studies in pregnancy. Therefore, the drug should be used in pregnancy only if benefit justifies the unknown risk to the fetus. Teratogenic effects were noted in large doses in 1, but not another, strain of rabbit. Effects on human labor and delivery, and excretion in human milk of flecainide have not been studied. Safety and effectiveness of flecainide have not been established in children younger than 18 years of age. In view of flecainide's modest negative inotropic effects, it should be used cautiously in patients with a history of congestive heart failure.

Contraindications: As with other class I antiarrhythmic drugs, flecainide should be considered contraindicated in patients with preexisting second- or third-degree AV block or with bifascicular or trifascicular bundle branch block unless a pacemaker is present that can sustain cardiac rhythm should complete AV block occur. Flecainide is contraindicated in the presence of cardiogenic shock.

Proarrhythmic effects: a clinical caution: A clear understanding of the potential of antiarrhythmic agents to produce proarrhythmic effects is essential to their safe and rational administration²⁸; such is also the case for flecainide.²⁹ Substantial proarrhythmic effects have been observed with all antiarrhythmic drugs, with an incidence of about 5 to 15% using ambulatory electrocardiographic recording²⁸ and about 10 to 30% during programmed stimulation.³⁰ There is also concern with class IC agents.^{17,18,31} The risk of proarrhythmic effects from flecainide appears to be similar: In a survey of 588 patients, 8% (44 patients) were believed to have such effects. In studies in which only stable patients were recruited, proarrhythmic effects were noted in about 4%, whereas in studies in which unstable patients with advanced disease were recruited, the percentage was 12% (personal communication, Riker Laboratories). Arrhythmias associated with a long QT syndrome, noted commonly with quinidine,³² appear to be rare with flecainide and are associated with toxic doses.¹⁹ Proarrhythmic effects may take the form of an increased frequency of VPC. If facilitation is mild and occurs in stable patients at subtherapeutic levels, a dosage increase may be considered. Otherwise, alternative therapy should be used. An increase in repetitive beats (pairs and runs) irrespective of effects on total VPC should be a stronger indication for alternative therapy. Inducibility of ventricular tachycardia at electrophysiologic study in nonresponding patients is unpredictable and may be better, worse or unchanged.¹³ The most serious arrhythmogenic effects have included rare instances of unresuscitable ventricular tachycardia or fibrillation. A recent review among flecainide investigators pointed to a potential role of excessive drug levels (>1,000 ng/ml) in patients with advanced disease (left ventricular ejection fraction <30%, previous infarction, history of sustained ventricular tachycardia or concomitant treatment with other class I antiarrhythmic drugs). In these very ill patients with a frequent re-

TABLE VIII Indications for Clinical Use

Highly effective:*
1. Uniform and multiform VPC
2. Coupled VPC
3. Runs of VPC (nonsustained VT)
Selected [†] prophylactic efficacy:
Sustained VT, VF (includes electrophysiologic guided therapy)
Investigational applications:
1. Supraventricular tachycardias [‡]
A. AV nodal reentry
B. AV bypass tract reentry (concealed or overt WPW syndrome)
2. Arrhythmias during myocardial infarction

* May be agent of choice for chronic VPCs; little experience to date with acute VPCs during myocardial infarction.

[†] Younger patients without advanced ischemic heart disease or ventricular dysfunction may do better.

[‡] Little experience for atrial flutter or fibrillation.

AV = atrioventricular; VF = ventricular fibrillation; VPC = ventricular premature complex; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

fractory condition, an extremely cautious approach, or alternative therapy, is indicated.

Clinical Proposal for Initial Drug Use

Flecainide's safety, unsurpassed efficacy and near-ideal pharmacokinetics in patients with chronic stable ventricular arrhythmias suggest that it will frequently be the drug of choice when medical treatment is indicated. Studies summarized herein indicate that flecainide will result in greater suppression of ventricular ectopy, including pairs and runs in these patients, than will the standard drugs (quinidine and disopyramide), and the newer lidocaine congeners (i.e., mexiletine and tocainide) soon due for general release in the United States. Convenience of dosing (twice-daily schedule) exceeds that of these other drugs, and adverse effects jeopardizing continued therapy are low.

Proposed indications for clinical use (Table VIII): Flecainide is proposed for suppression and prevention of uniform and multiform ventricular premature complexes, coupled ventricular premature complexes, and runs of ventricular tachycardia. If the tachycardia is nonsustained, response is followed primarily by ambulatory monitoring; if sustained, therapy may also be directed by programmed electrical stimulation. The response rate of sustained VT is lower and dependent on patient selection; younger patients without coronary disease or, if they have coronary disease, with reasonably well-preserved ventricular function respond most favorably.¹³ The same may be said for other antiarrhythmic drugs.^{23,24} Experience to date is greatest for chronic arrhythmias. Class I antiarrhythmics are usually not effective in treating arrhythmias associated with digitalis intoxication; therefore, flecainide is not recommended for such cases. Although effects of the QT interval are less than those after quinidine, flecainide has not been determined to be useful in the treatment of arrhythmias associated with a long QT interval. Effects of flecainide in patients with supraventricular arrhythmias or acute myocardial infarction have not been adequately studied to provide usage recommendations at this time. In patients with advanced heart disease, including multiple arrhythmia mechanisms, conduction system disease or advanced ventricular

dysfunction, the increased risks of flecainide's mild negative inotropic effects and potential proarrhythmic effects should be carefully weighed against those of other therapeutic alternatives.³³⁻³⁶

Clinical approach: Flecainide, like other antiarrhythmic drugs, should be started during in-hospital observation. Most adverse effects of drug occur within a few days of initial administration. In patients with stable arrhythmias without a history of sustained tachycardia, a carefully designed outpatient plan forms an alternative approach. Weekly outpatient visits including ambulatory electrocardiographic recording and symptom assessment may be undertaken until a successful regimen is obtained. Thereafter, the patient may be seen at monthly intervals for 3 months, and 3-month intervals during the first year or as otherwise indicated by the patient's condition. Ambulatory electrocardiographic recordings are obtained until an effective response has been achieved, in the presence of recurrent symptoms or dose adjustment or at about 6-month intervals during at least the first 1 to 2 years.

For patients with a history of, or who have potential for, malignant arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, poor ventricular function and advanced age), in-hospital titration (beginning with 100 mg every 12 hours) should be obligatory. Continuous in-hospital ambulatory electrocardiographic recording and pre-discharge exercise testing to a symptomatic end point by treadmill or bicycle ergometry are performed. Patients with a history of sustained ventricular tachycardia are usually tested with programmed electrical stimulation, particularly if spontaneous arrhythmia episodes are infrequent. Blood level monitoring is encouraged when doses of 400 mg/day or greater are administered and for patients with compromised physiologic findings.

Investigational Use (Table VIII)

Flecainide is 1 of 4 new antiarrhythmic drugs being tested in the National Institutes of Health-sponsored Cardiac Arrhythmia Pilot Study (CAPS), which began in July 1983. This study in patients with complex arrhythmias in the early period after myocardial infarction will compare the effectiveness of selected antiarrhythmic drugs in suppressing complex ventricular arrhythmias and evaluate their safety. If the results of CAPS are promising, a full-scale trial is proposed to test the hypothesis that elimination of ventricular arrhythmias may reduce the excessive risk of sudden death in this patient group. On the basis of current assessment, flecainide appears to be an excellent candidate drug for such an application.

Another application of great interest includes the use of flecainide for treatment of reentrant supraventricular arrhythmias, including those associated with AV bypass tracts as seen in the Wolff-Parkinson-White syndrome. Preliminary indications suggest that flecainide is an excellent drug in these applications. Hellestrand et al³⁷ found flecainide to be effective in treating 12 of 14 cases of AV bypass tract reentrant tachycardia and 8 of 9 cases of AV nodal reentrant tachycardia evaluated by

electrophysiologic study. Flecainide may also be useful in other supraventricular arrhythmias, but further documentation will be required. There is little experience in the prevention or treatment of atrial fibrillation or flutter with flecainide. The therapeutic use of combining flecainide with other antiarrhythmic drugs or nondrug management (pacemakers and internal defibrillators) requires exploration.

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