Tocainide, mexiletine, flecainide, encainide, and amiodarone are antiarrhythmic agents that have recently been approved by the Food and Drug Administration for general use in the treatment of ventricular arrhythmias. All five agents are effective in the treatment of patients with ventricular arrhythmias, whereas encainide, flecainide, and amiodarone are also useful in patients with supraventricular arrhythmias and the Wolff-Parkinson-White syndrome (although not yet approved for these indications). Tocainide and mexiletine are similar to lidocaine and are as effective as quinidine in patients with ventricular arrhythmias. Encainide and flecainide are superior to quinidine for the control of ventricular ectopic beats and as effective as quinidine for patients with ventricular tachycardia. Amiodarone is the most effective agent available for treating patients with ventricular tachycardia, but it is also the most toxic antiarrhythmic agent and should be used only when other antiarrhythmic drugs have not been effective or tolerated.

Class I antiarrhythmic drugs are those that prolong the ventricular effective refractory period (ERP) by prolonging phase 2 of the action potential without significantly affecting the ventricular ERP. Class II drugs are those that decrease the slope of phase 4 diastolic depolarization or the rate of rise of phase 0 depolarization. Class III drugs are those that prolong the action potential duration (APD) and the effective refractory period (ERP). Class IV drugs are those that block calcium channels and decrease the inward sodium current.

Tocainide and mexiletine are similar to lidocaine and are as effective as quinidine in patients with ventricular arrhythmias. Encainide and flecainide are superior to quinidine for the control of ventricular ectopic beats and as effective as quinidine for patients with ventricular tachycardia. Amiodarone is the most effective agent available for treating patients with ventricular tachycardia, but it is also the most toxic antiarrhythmic agent and should be used only when other antiarrhythmic drugs have not been effective or tolerated.

Cardiac arrhythmias remain the leading cause of cardiac morbidity and mortality in patients with heart disease. Prompted by the need for more effective and less toxic drugs, considerable interest in the development of new antiarrhythmic agents exists. Several new antiarrhythmic drugs, previously available for only investigative purposes in the United States, have been approved for general use: (1) tocainide (Tonocard), (2) mexiletine (Mexitil), (3) flecainide (Tambocor), (4) encainide (Enkaid), and (5) amiodarone (Cordarone). In this discussion, we review the pharmacologic and electrophysiologic properties of these agents, the clinical indications for their use, and their adverse side effects. In addition, we comment on the role of each of these agents in the overall scheme of antiarrhythmic drug therapy.

Classification
In 1969, Vaughan Williams proposed a classification for antiarrhythmic drugs that has subsequently become widely accepted. His classification, based on the effect of such agents on cardiac action potentials or intracardiac conduction intervals, categorizes the drugs into four classes. In 1979, Harrison subdivided class I into IA, IB, and IC groups on the basis of electrophysiologic effects on the “fast sodium channels.” Table 1 lists the four classifications and the currently approved antiarrhythmic drugs in each class.

Half-life
When new steady-state blood levels are achieved during administration or discontinuation of any drug, assuming a first-order process, necessitates knowledge about the half-life of the drug (Table 2). The half-life is the amount of time needed for a 50% change in drug concentration. Figure 1 illustrates the effects of the half-life of a drug on elimination and accumulation.
As shown in Figure 1, four to five half-lives represent the time when a new steady state has been achieved. Therefore, when antiarrhythmic therapy is initiated, the full effectiveness or toxicity of a medication will not be apparent until four to five half-lives have elapsed. For drugs such as tocainide, mexiletine, encainide, and flecainide with 12- to 24-hour half-lives, steady state, peak effectiveness, and toxicity may not occur before 2 to 4 days.

In patients with disease states that decrease hepatic metabolism or renal clearance of an antiarrhythmic drug, the agent will have a prolonged half-life, and the time until a steady state is achieved will be delayed. For example, in patients with normal hepatic function, mexiletine (with 100% hepatic metabolism) has a half-life of 12 to 13 hours, and a steady state is achieved in 2 to 3 days. In patients with intrinsic hepatic disease or decreased hepatic perfusion due to congestive heart failure, the half-life may be prolonged to 24 hours, and a steady state will be achieved after 4 to 5 days. The prolonged half-life will delay the time when peak effectiveness or toxicity occurs.

**PROARRHYTHMIA**

Antiarrhythmic drugs have the potential to make a ventricular arrhythmia worse, a result that is known as a proarrhythmic effect. Proarrhythmia includes increasing the frequency of ventricular ectopic beats, a rapid ventricular tachycardia termed “torsades de pointes,” and the development of sustained ventricular tachycardia when only nonsustained ventricular tachycardia was present in the baseline state. In this review, proarrhythmia refers to the last-mentioned effect.

**TOCAINIDE**

Because of substantial first-pass hepatic metabolism that limits the oral use of lidocaine, a search for analogues with similar antiarrhythmic properties led to the development of tocainide and mexiletine. Tocainide (Table 3) is superior to lidocaine because it is able to avoid the first-pass metabolism and thus is almost 100% bioavailable.

**Clinical Indications.**—Tocainide has been shown to be effective in the prophylaxis and treatment of ventricular arrhythmias in both the short-term and the long-term setting after a myocardial infarction, the suppression of chronic complex ventricular ectopic beats, and the prevention of malignant ventricular tachyarrhythmias. Little or no effect on atrial fibrillation or flutter has been demonstrated with this drug. It is also useful in suppression of arrhythmias in the setting of a prolonged QT interval. In one study, the clinical response to lidocaine was concordant with and predictive of the response to tocainide in 71% of patients with malignant ven-

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**Table 1.—Classification of Antiarrhythmic Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Quinidine Disopyramide</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
</tr>
<tr>
<td>IB</td>
<td>Lidocaine Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Tocainide Mexiletine</td>
</tr>
<tr>
<td>IC</td>
<td>Flecainide Encainide</td>
</tr>
<tr>
<td>II</td>
<td>Propranolol</td>
</tr>
<tr>
<td>III</td>
<td>Bretylium Amiodarone</td>
</tr>
<tr>
<td>IV</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

**Table 2.—Recommended Dosage, Half-Life, and Therapeutic Levels of Five New Antiarrhythmic Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral dosage</th>
<th>Half-life (h)</th>
<th>Therapeutic range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocainide</td>
<td>400-600 mg every 6-8 h</td>
<td>9-20</td>
<td>5-12</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>150-400 mg every 6-8 h</td>
<td>12-13</td>
<td>1.2</td>
</tr>
<tr>
<td>Flecainide</td>
<td>100-200 mg every 12 h</td>
<td>12-27</td>
<td>0.2-1.0</td>
</tr>
<tr>
<td>Encainide</td>
<td>25-50 mg every 6-8 h</td>
<td>12</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Loading—800-1,200 mg/day for 10-14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance—200-400 mg/day (single dose)</td>
<td>50 days</td>
<td>1.5-2.5</td>
</tr>
</tbody>
</table>


---
tricular tachyarrhythmias (sustained ventricular tachycardia or fibrillation), and lidocaine failure was associated with tocainide failure in 83% of patients.30

In open and controlled trials with use of continuous monitoring to assess therapy, complex ventricular ectopic beats or symptomatic recurrent ventricular tachycardia has been effectively suppressed by tocainide in 50 to 70% of patients.18,27,28,31,32 In patients with ventricular tachycardia induced at the time of electrophysiologic testing, however, the rate of response to tocainide has been low, ranging from 10 to 35% when programmed ventricular stimulation inducibility was used as the therapeutic endpoint.28,29 Although shown to be as effective as procainamide for chronic ventricular arrhythmias,30 particularly with QT interval prolongation with or without torsades de pointes, tocainide has not proved to be superior to traditional agents. During the first 24 hours of care in patients with an acute myocardial infarction, tocainide has demonstrated suppression of ventricular tachycardia and of premature ventricular complexes; in one report, 56% of patients had greater than 75% suppression of premature ventricular complexes.33

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Table 3.—Summary of Tocainide

A. Indication—ventricular arrhythmias
B. Therapeutic range—5–12 μg/ml
   Half-life—9–20 hours
   Metabolism—60% hepatic, 40% renal
C. Dosing: Intravenous—not available
   Oral—400–600 mg every 6–8 hours
D. Side effects—in 40%
   1. Drug discontinued in 10–20%
   2. Cardiac toxicity
      Proarrhythmia 1–8%
      Congestive heart failure 5%
      Heart block 1%
   3. Noncardiac toxicity
      Light-headedness, paresthesias, tremor, ataxia, confusion, loss of memory
      Nausea 15%
      Rash 12%
E. Problems
   High incidence of minor side effects
   Blood dyscrasia

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Fig. 1. Schematic representation of effect on blood concentration (Ct) of repeated doses of a drug administered at intervals equal to the elimination half-life. The light (fluctuating) line represents intermittent drug administration (oral or intravenous bolus). The heavier line represents continuous intravenous infusion. A steady-state level is achieved in four to five elimination half-lives. (From Mayer SE, Melmon KL, Gilman AG: Introduction; the dynamics of drug absorption, distribution, and elimination. In Goodman and Gilman's The Pharmacological Basis of Therapeutics. Sixth edition. Edited by AG Gilman, LS Goodman, A Gilman. New York, Macmillan Publishing Company, 1980, pp 1–27. By permission.)
Clinical Pharmacology.—Tocainide, with bioavailability approaching 100% after oral administration, is rapidly and completely absorbed. Primarily metabolized in the liver to glucuronides and other related conjugates (none pharmacologically active), 30 to 40% of the drug is excreted unchanged in the urine. Ten to 50% of the drug is protein-bound. The time to achievement of peak levels after oral administration is 1 to 1½ hours, and the ingestion of food slows the rate of absorption. The elimination half-life of tocainide is 9 to 20 hours, and therapeutic levels of the drug range from 5 to 12 μg/ml. Renal failure prolongs the half-life of tocainide to 27 hours, and the drug is removed during dialysis. Urinary acidification prolongs (and, conversely, urinary alkalinization shortens) the clearance of tocainide. Heart failure prolongs the half-life of the drug to 37 hours. Chronic liver disease does not seem to prolong the clearance of tocainide, and neither liver enzyme induction nor inhibitors seem to affect elimination of the drug. Questions still exist, however, about the impairment of nonrenal clearance of tocainide by allopurinol and cimetidine.

Electrophysiology.—Tocainide decreases the duration of the action potential, causes no change or decreases the rate of rise of phase 0 depolarization, and decreases automaticity. No changes are noted in the electrocardiographic intervals or QRS durations, although the QT interval may be slightly decreased. Little or no change is noted in sinus node recovery times or intra-atrial, atrioventricular nodal, or His-Purkinje conduction observed during therapy. Tocainide shortens or leaves unchanged atrial, atrioventricular nodal, and ventricular refractory periods. Tocainide may block the fast retrograde pathway of atrioventricular nodal re-entrant tachycardia and may prolong the antegrade and retrograde refractory periods of accessory pathways.

Cardiovascular Side Effects.—Variable depression of myocardial function occurs with administration of tocainide. Tocainide has been associated with an aggravation of congestive heart failure in 5% of patients. Proarrhythmic effects related to tocainide therapy occur in 1 to 8% of patients (4.8%, as assessed by electrophysiologic testing). Noncardiovascular Side Effects.—Tocainide predominantly causes neurologic or gastrointestinal side effects in about 40% of patients (some investigators have reported as high as 80%), necessitating discontinuation of use of the drug in 10 to 20%. Gastrointestinal side effects occur in 15% of patients and are less if the drug is administered with food or antacids. Nausea, vomiting, anorexia, abnormal results of liver function tests, light-headedness, vertigo, lethargy, tremors, paresthesias, impairment of speech, ataxia, decreased memory, and personality and sleep disorders have been described. Rashes develop in about 12% of patients. Rare but catastrophic side effects include fibrosing alveolitis and interstitial pneumonitis (0.11%), lupus erythematosus-like syndrome with positive antinuclear antibody (with the constellation of polyarthralgias, arthritis, pericarditis, and even immune complex glomerulonephritis), seizures, and blood dyscrasias (0.18%) with leukopenia, agranulocytosis, aplastic anemia, and thrombocytopenia. The indications for use of tocainide in the United Kingdom are limited because of the risks of hematologic problems. Investigators recommend that periodic complete blood cell counts be obtained during use of tocainide.

Drug Interactions.—Concomitant administration of tocainide and a β-blocker in the setting of sinus node dysfunction or impaired atrioventricular conduction may aggravate conduction problems or precipitate symptomatic bradycardias and even asystole. Tocainide alone is associated with a 1% incidence of heart block. The combination of tocainide and propranolol may cause paranoia and confusion.

Dosage.—Tocainide is available only in the oral form. The usual dosage of tocainide is 400 to 600 mg every 6 to 8 hours. For achievement of steady-state conditions, doses should not be changed for at least 3 to 4 days. The daily dose should be reduced in patients with renal or cardiac failure because of the associated prolongation of the half-life of the drug. Therapeutic levels are 5 to 12 μg/ml. The use of lidocaine should be discontinued 1 to 2 hours before initiation of tocainide therapy because side effects will be additive.

MEXILETINE

Mexiletine (Table 4) is an orally active lidocaine congener that was originally developed as an anorexic agent but found to have anticonvulsant and antiarrhythmic properties.
Table 4.—Summary of Mexiletine

- **A. Indication—ventricular arrhythmias**
- **B. Therapeutic range—1-2 μg/ml**
  - Half-life—12-13 hours
  - Metabolism—100% hepatic
- **C. Dosing:**
  - Intravenous—not available
  - Oral—150-400 mg every 6-8 hours
  - Side effects—in 50%
    - Drug discontinued in 30%
    - Cardiac toxicity
      - Proarrhythmia 10%
      - Congestive heart failure <3%
      - Heart block 1%
    - Noncardiac toxicity
      - Light-headedness, paresthesias, tremor, ataxia, confusion, loss of memory 20%
      - Nausea 39%
- **D. Problems**
  - High incidence of minor side effects

**Clinical Indications.**—Mexiletine suppresses premature ventricular complexes by 80% in 50 to 60% of patients tested and prevents reinduction of ventricular tachycardia during electrophysiological testing in 25 to 30% of patients. Stein and associates reported that in a group of 313 patients with medically refractory ventricular tachyarrhythmias, 30% had a favorable result of electrophysiological testing with mexiletine or mexiletine plus a second antiarrhythmic drug. Mexiletine has been used in the prophylactic treatment of arrhythmias after acute myocardial infarction but has not been shown to improve survival. Mexiletine has been ineffective in treating patients with supraventricular arrhythmias.

Mexiletine in combination therapy with class IA antiarrhythmic agents, propranolol, or amiodarone has been shown by some investigators to exert a synergistic beneficial response in treating patients with ventricular arrhythmias, although this finding is controversial. The combination of mexiletine and quinidine is more effective than either agent separately in suppressing complex ventricular ectopic beats or ventricular tachycardia induced during electrophysiological testing—either agent alone was effective in 20% of patients, whereas the combination prevented induction of ventricular tachycardia during electrophysiological testing in 35 to 65% of patients.

**Clinical Pharmacology.**—Absorption of mexiletine, a basic compound, occurs in the upper intestine; the drug has 80 to 90% bioavailability, and peak levels occur in 1 to 3 hours. Conditions and drugs that delay gastric emptying (for example, myocardial infarction, narcotics, sedatives, anticholinergic agents, ganglionic blockers, and aluminum hydroxide antacids) delay absorption of mexiletine, whereas absorption is increased when transit time is augmented by metoclopramide or when the gastric contents are alkalized. Almost 70% of the drug is protein-bound in the serum. It undergoes primarily hepatic metabolism (with 10% first-pass elimination), and 10 to 15% of the drug is excreted in the urine. Multiple nonantiarrhythmic, pharmacologically inactive metabolites are formed. The elimination half-life is 12 to 13 hours. Renal insufficiency does not substantially change the kinetics of elimination; however, end-stage renal disease, congestive heart failure, and cirrhosis decrease the clearance of mexiletine and necessitate a reduction in the dosage. Clearance of mexiletine is hastened by dialysis. Alkalization of the urine decreases renal clearance of the drug, whereas acidification of the urine accelerates excretion. Mexiletine has also been shown to be present in breast milk of nursing mothers who are taking the drug.

**Electrophysiology.**—The effects of mexiletine on conduction and refractoriness are similar to those described for tocainide. The duration of the action potential and rate of rise of phase 0 are decreased. The drug has little effect on sinus rate or atrial refractoriness, although preexistent His-Purkinje disease or sinus node dysfunction may be aggravated. Normally, no consistent atrioventricular nodal or His-Purkinje conduction effects are noted; however, some investigators have reported prolonged refractory periods of the atrioventricular node and His-Purkinje system in conjunction with prolongation of the HV intervals. Atrioventricular nodal block is rare, and the PR, QRS, or QT intervals remain unchanged.

**Cardiovascular Side Effects.**—Mexiletine is associated with a worsening of congestive heart failure in less than 3% of patients. Proarrhythmic effects occur in 10% of patients, and heart block occurs in 1%.

**Noncardiovascular Side Effects.**—Noncardiac side effects occur in 47 to 65% of patients taking mexiletine, necessitating discontinuation of the drug in up to 30%. Neurologic and gastrointestinal side effects are the most...
common. Typical neurologic complaints or observations are a fine intention hand tremor, light-headedness, ataxia, paresthesias or tingling of the extremities, throat numbness or oral cold sensation, blurred vision, nervous agitation, convulsions, and even a peculiar perception of a menthol taste. Gastrointestinal side effects include nausea (39%), vomiting, anorexia, and epigastric burning, which may be alleviated by coadministration with food or antacids. A macular erythematous rash is rare. Other rare (occurring in less than 1% of patients) reported side effects include abnormal results of liver function tests, positive antinuclear antibodies (lupus syndrome), thrombocytopenia, leukopenia (neutropenia and agranulocytosis), and impotence. Some authors suggest avoidance of mexiletine in patients with seizure disorders.

**Drug Interactions.**—Induction of hepatic enzymes by phenobarbital, primidone, rifampin, or phenoxytoin shortens the elimination half-life (up to 50%) of mexiletine. For maintenance of therapeutic blood levels of mexiletine, the dosage must be increased when it is administered concomitantly with any of these agents. Cimetidine, isoniazid, chloramphenicol, dicumarol, disulfiram, and methylphenidate have been shown to decrease the clearance of mexiletine and prolong the half-life.

**Dosage.**—Although mexiletine has been used intravenously, intramuscularly, and orally, only the oral form of the drug is available for clinical use. The recommended oral dosage is 150 to 400 mg every 6 to 8 hours, and peak concentrations occur in 1 to 3 hours. A starting dose of 150 to 200 mg every 8 hours with subsequent slow incrementation is associated with a lower frequency of side effects. The therapeutic range is 1 to 2 μg/ml. Caution is warranted when lidocaine is administered concurrently because the similar side effects may be additive. The use of lidocaine should be discontinued 1 to 2 hours before the initiation of mexiletine therapy. The dose of mexiletine should be reduced in patients with congestive heart failure because the half-life of the drug will be prolonged.

**FLECAINIDE**

Flecainide (Table 5) was the first class IC antiarrhythmic agent available for general use. Its unique properties allow flecainide to be effective in the treatment of both supraventricular and ventricular arrhythmias, although the drug has thus far been approved for only the treatment of ventricular arrhythmias.

**Clinical Indications.**—Flecainide has been shown to be effective in the treatment of nonsustained ventricular arrhythmias but not as effective in suppression of sustained ventricular tachyarrhythmias refractory to other agents. In addition, it is useful for conversion of atrial fibrillation and flutter and for termination of tachycardias associated with the Wolff-Parkinson-White syndrome and refractory junctional tachycardias in children.

Flecainide is particularly effective in suppression of premature ventricular complexes and nonsustained ventricular arrhythmias. In comparative trials, flecainide was more effective than quinidine, disopyramide, tocainide, propafenone, and mexiletine in suppression of simple and complex ventricular ectopic beats. Its use is less well defined in patients with sustained ventricular tachycardia or fibrillation, in 30% of whom it seems to be effective on the basis of electrophysiologic assessment.

**Clinical Pharmacology.**—Flecainide is 90 to 95% bioavailable, and peak serum levels occur in 3 to 4 hours during twice-daily dosing intervals. The ingestion of food seems to have no effect...
on the absorption of flecainide. Approximately 40% (range, 32 to 58%) of the drug is protein-bound; elimination is primarily by hepatic metabolism (70%), and 30% is excreted unchanged in the urine. Alkalization of the urine decreases flecainide elimination, whereas acidification of the urine shortens the half-life. Therapeutic levels are 0.2 to 1.0 µg/ml, and the half-life of the drug ranges from 12 to 27 hours. Renal dysfunction and congestive heart failure decrease the clearance of flecainide. Two major and two to three minor metabolites of the drug have little or no efficacy as antiarrhythmic agents. End-stage renal disease may prolong the half-life of flecainide to 51 to 58 hours; thus, the dosage should be reduced to 25 to 50% of the normal dose in patients with creatinine clearances of less than 20 ml/min per m².

Electrophysiology.—Flecainide slows the rate of rise of the action potential but does not prolong its duration. It slows atrial, atrioventricular nodal, and intranodal conduction and prolongs the refractory periods of the atrium, atrioventricular node, and ventricle. The drug has no effects on the automaticity of the sinus node or the duration of the sinus cycle, but preexisting sinus node dysfunction can be aggravated. The HV interval is prolonged 27 to 47% above control values. High doses of flecainide delay conduction throughout the entire conduction system, an effect that has implications for its cautious use in patients with preexisting bundle-branch block or bifascicular block. The QRS duration is prolonged 11 to 27%, as is the QT interval though to a lesser degree than with class IA agents. The prolongation of the QT interval is primarily a factor of QRS prolongation. The PR interval increases up to 25%. In patients with dual atrioventricular nodal pathways, flecainide increases the retrograde refractoriness of the “fast” atrioventricular nodal pathway.

Cardiovascular Side Effects.—Flecainide may depress left ventricular function. The frequency of congestive heart failure in association with use of this drug is 5%, and caution should be exercised in administering it to patients with previous episodes of congestive heart failure. Proarrhythmic effects occur in 7 to 26% of patients, particularly those taking more than 400 mg of flecainide daily or patients with reduced ventricular function or a history of sustained ventricular tachycardia. The proarrhythmic effects may make resuscitation efforts more difficult in comparison with previous resuscitations in the same patient.

In studies of endocardial pacing thresholds before and after administration of flecainide, acute thresholds rose 117% and chronic thresholds increased 83%. Therefore, it should be used with caution in patients with pacemakers, particularly those who are pacemaker-dependent.

Noncardiovascular Side Effects.—Multicenter trials have shown that 11 to 13% of patients had to discontinue flecainide therapy because of side effects. The effects include blurred vision, dizziness, headache, a bad taste, perioral paresthesias, sleeplessness, nausea, diarrhea, impaired sexual potency in men, nonischemic chest pain, digital warmth and tingling sensation, unsteady gait, and mild increases in alkaline phosphatase.

Drug Interactions.—Flecainide increases digitaloxin levels. Administration of flecainide in conjunction with propranolol may increase the hypertensive and negative inotropic effects as well as increase flecainide levels. Cimetidine has been shown to increase the elimination half-life of flecainide and decrease its clearance 13 to 27%. Dosage.—Flecainide is available only in the oral form. Dosages should not exceed 400 mg/day (200 mg twice daily) because of the concerns about the occurrence of major proarrhythmic side effects and the potential alteration in clearance of the drug in patients with poor cardiac function. With dosages that exceed 400 mg/day, proarrhythmic effects occur in 26% of patients (even though reports exist of 600 mg being given daily). The starting oral dosage is usually 100 mg every 12 hours, and dose changes can be made after 4 days of therapy to allow achievement of a steady state and to lessen the risk of proarrhythmia. Therapeutic levels are 0.2 to 1.0 µg/ml; levels in excess of 1.0 µg/ml are associated with an increased frequency of proarrhythmic effects.

Encaïnide

Encainide (Table 6) is a class IC antiarrhythmic drug that has been shown to be effective in the treatment of supraventricular and ventricular arrhythmias but has been approved by the Food and Drug Administration for only the treatment of ventricular arrhythmias. The potential advantage of this antiarrhythmic agent is its
Table 6.—Summary of Encainide

A. Indications
Ventricular arrhythmias
Supraventricular arrhythmias (not yet approved)

B. Therapeutic range—not helpful
Half-life—130 hours
Metabolism—100% hepatic
(90% are rapid metabolizers—2 metabolites with longer half-life and increased potency; 10% are slow metabolizers)

C. Dosing: Intravenous—not available
Oral—25 mg 3 times/day; change dose every 3-5 days*

D. Side effects—in 30%
1. Drug discontinued in 10%
2. Cardiac toxicity
   Proarrhythmia 5-20% (increased to 20% in patients with reduced ejection fraction and history of ventricular tachycardia or fibrillation)
   Congestive heart failure <1%
3. Noncardiac toxicity
   Dizziness 26%, blurred vision 19%, nausea 4%, tremor 4%, headache 4%

E. Problems
Close attention to dosing necessary to prevent proarrhythmia
Risk of proarrhythmia increases as ejection fraction decreases

*See text for details on incremental changes.

lack of important negative inotropic effects in patients with left ventricular dysfunction.67

Clinical Indications.—Encainide is effective in the treatment of supraventricular arrhythmias, particularly those associated with accessory pathways. The use of encainide results in complete antegrade and retrograde block in up to 50% of patients with accessory pathways, a prolongation of the tachycardia cycle length, a decrease in tachycardia inducibility on the basis of electrophysiologic testing, and the prevention of a rapid ventricular response in patients with the Wolff-Parkinson-White syndrome who have atrial fibrillation and an accessory pathway with a short refractory period.64,66-91 Prystowsky and associates61 showed that with encainide treatment (100 to 300 mg/day) induction of tachycardia was not possible during electrophysiologic testing in 53% of patients with the Wolff-Parkinson-White syndrome, and 8 of the 14 patients with prior evidence of preexcitation (delta wave on an electrocardiogram) lost preexcitation during treatment.98 Poole68 described the clinical effectiveness of long-term oral administration of encainide in 80% of 50 patients with supraventricular tachycardias associated with the Wolff-Parkinson-White syndrome. Encainide has also been effective in the suppression of previously refractory supraventricular tachycardias and rapid resolution of the associated arrhythmia-induced cardiomyopathy in children.92,93

DiBianco and colleagues94 prospectively investigated the oral use of encainide in 21 patients with chronic complex ventricular ectopy by using 24-hour ambulatory monitoring. Encainide produced a 96% overall decrease in the mean hourly frequency of ectopic beats and more than a 99% suppression of more complex ventricular ectopy (pairs and runs of ventricular tachycardia). In a single-blind, crossover trial with quinidine in 20 patients with chronic ischemic heart disease and ventricular ectopy, encainide was better tolerated and yielded total suppression of ectopic beats in 44% of the patients in comparison with an absence of total suppression during quinidine therapy.84

Different dosing regimens and intervals have been used in the reported studies of encainide. With the treatment goal defined as achievement of at least a 75% decrease in premature ventricular complexes, doses of 25 mg three times a day achieved a 40% response rate whereas 50 mg three times a day attained a 58 to 72% response rate.95 In a review of several multicenter, placebo-controlled trials of encainide therapy for ventricular arrhythmias, Morganroth96 concluded that 80% of the patients will have at least a 70% reduction in frequency of premature ventricular complexes (judged by ambulatory monitoring) and 75% of patients will have elimination of all nonsustained ventricular tachycardia. This review represented pooled data with variable encainide doses ranging from the lowest effective dose of 25 mg three times daily to 75 mg four times daily.

In a review of encainide treatment of lethal ventricular arrhythmias evaluated by electrophysiologic testing, Horowitz97 found that oral doses prevented inducibility of arrhythmias in 23% of the patients. He used dosages of 150 to 250 mg/day divided into three or four doses. Similar to tocainide, mexiletine, and flecainide, the encainide response rate is substantially lower when electrophysiologic techniques are used to assess efficacy.98,99

Clinical Pharmacology.—Encainide is completely absorbed from the gastrointestinal tract, has considerable variability in its volume of distribution, is extensively metabolized by the liver,100 and is 70 to 78% protein-bound. Inter-
individual variability in response to encainide therapy is based primarily on the phenotypic mode of metabolism. Ninety percent of the population are extensive metabolizers, whereas 10% are poor metabolizers. In extensive metabolizers, encainide undergoes first-pass hepatic metabolism and has a short elimination half-life of 1.9 ± 0.1 hours (range, 1 to 3 hours). It is primarily metabolized to two active metabolites: O-demethyl encainide (ODE), which is the primary metabolite and has a half-life of 4 ± 0.5 hours to 11.4 ± 9.6 hours, and 3-methoxy-O-demethyl encainide (3-MODE). ODE accumulates during long-term treatment and is primarily responsible for the effects of the drug observed in extensive metabolizers; in contrast, the parent drug (encainide) is primarily responsible for the effects of the drug noted in poor metabolizers.

In poor metabolizers, encainide has a longer half-life (5.8 to 13.8 hours) and plasma levels are more than 20 times higher than those present in extensive metabolizers. Approximately 21 to 50% of the dose of encainide is excreted in the urine as ODE and 5% is excreted as encainide and 3-MODE in extensive metabolizers, whereas more than 50% of the drug is eliminated in the urine unchanged (as encainide) in poor metabolizers.

**Electrophysiology.**—The variations in electrophysiologic effects of encainide depend on the route and duration of administration. Encainide, as a class IC antiarrhythmic agent, decreases the rate of rise of phase 0 of the action potential but has little effect on the duration or amplitude of the action potential. It depresses the fast sodium channel and decreases myocardial conduction velocity. Within 30 minutes after a single intravenous infusion (thus, primarily parent-drug effects), the QRS duration and HV interval (His-Purkinje conduction time) increase, but no changes are observed in atrioventricular nodal conduction or atrial or ventricular refractory periods.

Long-term oral encainide therapy brings the effects of the metabolites to the forefront, including prolonged atrial, atrioventricular nodal, and His-Purkinje conduction, lengthened atrial and ventricular refractory periods, and prolonged AH intervals (the PR interval increases 30%). No major effects have been noted on sinus automaticity or the normal sinoatrial node. An insignificant or small increase occurs in the corrected QT interval. The effects of the metabolites may be increased in ischemic tissue, with reductions or paradoxical increases in excitability evident at low concentrations. In patients with accessory pathways, encainide abolishes antegrade conduction, increases retrograde refractoriness, and suppresses ectopic atrial activity.

**Cardiovascular Side Effects.**—In comparison with other antiarrhythmic agents, encainide lacks important negative inotropic properties—a potential advantage for patients with severe left ventricular dysfunction. Sami performed radionuclide ventriculography before and 6 weeks after encainide treatment in patients with baseline ejection fractions of less than 45%. At a mean dosage of 170 ± 65 mg/day, he found no significant short-term or long-term changes in mean heart rate, blood pressure, stroke volume, end-diastolic volume, or ejection fraction. These findings were consistent with those of DiBianco and associates. Similar to flecainide and lorcainide, encainide lacks anticholinergic effects.

Important concerns have been raised about the occurrence of proarrhythmia during encainide therapy. Patients with ejection fractions of less than 35% and sustained ventricular tachycardia seem to have an increased incidence of proarrhythmia. Tordjman and colleagues reported aggravation of arrhythmia in 4% of patients who had nonsustained ventricular tachycardia but in 25% of patients who had sustained ventricular tachycardia or ventricular fibrillation (particularly if the ejection fraction was less than 35%). DiBianco and co-workers found that 15% of patients had conversion from nonsustained to sustained ventricular tachycardia during encainide treatment. In a study of 1,245 patients, Soyka found a 9.2% incidence of proarrhythmia, with new sustained ventricular tachycardia in 1.8%. This 9 to 15% range is similar to that with other antiarrhythmic agents. Bradycardia and sinus pauses occurred in 8 to 14% of patients, and those with preexisting infranodal conduction abnormalities were more susceptible to further His-Purkinje depression by encainide. Defibrillation energy requirements are also increased by encainide treatment.

**Noncardiovascular Side Effects.**—The incidence of minor, transient adverse effects associated with encainide therapy has been reported as 30 to 60%. Tordjman and associates described nausea, vomiting, headache, and tremors.
in 38% of their patients. In a review of 1,245 patients by Soyka, noncardiac side effects attributable to encainide included dizziness (26%), abnormal or blurred vision (19%), taste alterations (metallic taste) (4%), and tremor (3%). The visual symptoms and dizziness occurred more frequently with daily doses of 200 mg or more.

**Drug Interactions.**—Concomitant administration of cimetidine and encainide increases encainide blood levels by 30 to 40%. Insignificant interactions occur between encainide and digoxin, calcium blockers, diuretics, anticoagulants, oral hypoglycemic agents, antipsychotic agents, amiodarone, and other antiarrhythmic agents (other than the expected additive pharmacologic antiarrhythmic effects). The combination of \( \beta \)-blockers and encainide increases the frequency of dizziness and paresthesias over the occurrence of these symptoms with use of either drug alone.

**Dosage.**—The variations in plasma drug levels and in phenotypic modes of metabolism have made monitoring of encainide therapy with blood levels difficult and misleading. Limiting dosages to less than 200 mg/day divided into two to four doses has been recommended. Administration every 8 to 12 hours is reasonable during encainide treatment because of the accumulation and slow elimination of active metabolites in patients with extensive metabolism and the slow elimination of the parent drug (encainide) in patients with slow metabolism. Treatment should be initiated in a hospital setting where the patient can be monitored continuously. Dosage changes can be made after 2 to 3 days, and a stable dose should be maintained for 48 hours before dismissal because of the potential occurrence of proarrhythmia attributable to accumulation of metabolites. The initial dosage should be 25 mg three times a day; this amount can be increased to 35 mg three times daily, 50 mg three times daily, 50 mg four times daily, and then 75 mg four times daily. Changes can be made every 3 to 5 days, and the goal should be the lowest effective dose. Extreme caution should be exercised in patients with preexisting conduction defects. Discontinuing or reducing the dose is recommended with QRS prolongation beyond 0.18 second or a PR interval in excess of 0.28 second.

Advanced liver disease (cirrhosis) impairs the elimination of encainide though the production of active metabolites is unchanged. In patients with this disorder, plasma encaainide concentrations may be 2 to 3 times higher and the half-life of encainide may be prolonged up to 13 to 14 hours; however, dosage changes are generally not necessary. Renal disease substantially decreases the clearance of encaainide and metabolites such that major dosage adjustments are needed in patients with renal insufficiency. Initial dosages in such patients should be 25 mg daily or 25 mg twice a day, and the dosage can be changed every 5 to 7 days if necessary as the half-life is prolonged to 19 hours or more.

**AMIODARONE**

The wide spectrum of the antiarrhythmic effectiveness of amiodarone was recognized years after its introduction in 1962. The drug is effective for treating patients with one of several rhythm disorders; however, the high incidence of side effects limits the usefulness of amiodarone. It is recommended as therapy for hemodynamically unstable ventricular tachycardia or fibrillation refractory to other medication.

**Clinical Indications.**—Amiodarone (Table 7) is effective in the treatment of ventricular tachycardia and fibrillation, supraventricular tachy-

<table>
<thead>
<tr>
<th>Table 7.—Summary of Amiodarone</th>
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<tbody>
<tr>
<td>A. Indication—ventricular arrhythmias in patients with severe symptoms not effectively treated by other agents</td>
</tr>
<tr>
<td>B. Therapeutic range—1.5-2.5 ( \mu )g/ml</td>
</tr>
<tr>
<td>Half-life—approximately 30 days (range, 25-100 days)</td>
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<tr>
<td>Metabolism—unknown</td>
</tr>
<tr>
<td>C. Dosing: Intravenous—research only</td>
</tr>
<tr>
<td>Oral: Loading—800-1,200 mg/day for 10-14 days</td>
</tr>
<tr>
<td>Rapid loading—800-2,000 mg 2 or 3 times/day*</td>
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<tr>
<td>Maintenance—200-400 mg/day</td>
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<tr>
<td>D. Side effects—in 50%</td>
</tr>
<tr>
<td>1. Drug discontinued in 10%</td>
</tr>
<tr>
<td>2. Cardiac toxicity</td>
</tr>
<tr>
<td>Proarrhythmia 2%</td>
</tr>
<tr>
<td>Bradycardia (necessitating pacing) 4%</td>
</tr>
<tr>
<td>Congestive heart failure 4%</td>
</tr>
<tr>
<td>3. Noncardiac toxicity</td>
</tr>
<tr>
<td>Photosensitivity 20%; sleep disturbance 10%; nausea and anorexia 10%; tremor, ataxia, neuropathy 10%; headache 5%; pulmonary toxicity 5%; thyroid disorder 5%; hepatotoxicity 1%</td>
</tr>
<tr>
<td>4. Drug interactions</td>
</tr>
<tr>
<td>Need to reduce concurrent dose of warfarin, digoxin, procaainamide, quinidine, phenytoin, flecaainide, mexiletine</td>
</tr>
<tr>
<td>E. Problems</td>
</tr>
<tr>
<td>High incidence of minor and major side effects</td>
</tr>
</tbody>
</table>

*See text.
cardia with and without preexcitation, conversion of atrial fibrillation to sinus rhythm, control of recurrent refractory paroxysmal atrial fibrillation and flutter, the tachycardia of the tachycardia-bradycardia syndrome, and the supraventricular and ventricular arrhythmias associated with hypertrophic cardiomyopathy.\textsuperscript{107,110,112-114}
The drug, however, has been approved only for the treatment of life-threatening ventricular arrhythmias and is associated with a considerable incidence of toxicity.

Pioneering work in the 1970s reported the excellent antiarrhythmic responses to amiodarone—suppression of ventricular arrhythmias in up to 82% of patients and suppression of supraventricular arrhythmias in 90 to 100%; the subgroup of patients with atrial fibrillation with a rapid ventricular response due to an accessory pathway had only a 54% response rate.\textsuperscript{115-118} Subsequent studies of amiodarone showed lower but still favorable effectiveness in controlling supraventricular and ventricular arrhythmias. Intravenously administered amiodarone (for investigational use only) has immediate effects on atrioventricular node conductivity for rapid treatment of atrial fibrillation and is useful for the rapid suppression of complex ventricular arrhythmias.\textsuperscript{31,119-121}

In patients with symptomatic ventricular tachycardia with or without syncope, amiodarone is 64 to 74% successful in preventing recurrence.\textsuperscript{122} As shown by Waxman and associates,\textsuperscript{122} electrophysiologic inducibility of ventricular tachycardia or fibrillation was still possible after amiodarone loading in 38 of 43 patients (88%) with medically refractory ventricular tachycardia or fibrillation. Nonetheless, beneficial responses were seen in the prevention of spontaneous recurrences of ventricular tachycardia or fibrillation, even in the group of patients in whom arrhythmias were inducible during amiodarone therapy. This discrepancy between the frequency of inducible arrhythmias and the low incidence of spontaneous recurrences during amiodarone therapy has been confirmed by others.\textsuperscript{111,121-126} Although inducibility, by programmed ventricular stimulation, of ventricular tachycardia or fibrillation during serial drug testing of class I agents is highly predictive of poor long-term control of arrhythmia,\textsuperscript{111,123} lack of suppression of inducible ventricular tachycardia during amiodarone therapy does not preclude a favorable response.\textsuperscript{31,123,125,126}

In a study conducted by Horowitz and colleagues,\textsuperscript{125} patients with sustained ventricular tachyarrhythmias before amiodarone treatment and no inducible arrhythmias at the time of electrophysiologic testing after amiodarone loading subsequently had no recurrence of ventricular tachycardia or fibrillation for 8 months to 2 years. In contrast, patients with ventricular tachycardia or fibrillation induced during electrophysiologic testing after amiodarone loading had a 48% recurrence rate during a period of 3 to 21 months. Elimination or reduction of the initiating premature beats and elimination of ventricular tachycardia detected by Holter monitoring have been linked to the prevention by amiodarone of recurrent spontaneous ventricular tachycardia or fibrillation.\textsuperscript{121} Although one could conclude that the usefulness of electrophysiologic testing to determine the clinical outcome regarding amiodarone therapy is uncertain,\textsuperscript{31,120,125} several features of the test help predict successful control of ventricular tachycardia despite inducibility of ventricular tachycardia during amiodarone therapy; (1) increased difficulty in the mode of ventricular tachycardia inducibility and (2) longer tachycardia cycle length (slower ventricular tachycardia) with improved hemodynamic stability during the tachycardia.\textsuperscript{125,126} Patients with the Wolff-Parkinson-White syndrome and atrial fibrillation are usually responsive to amiodarone with a reduction in the episodes of tachycardia and a slower ventricular rate should tachycardia occur.\textsuperscript{121} Amiodarone treatment of patients with a short antegrade refractory period of the accessory pathway, however, may produce too small an effect on the refractoriness of the pathway to allow adequate protection from rapid ventricular conduction during atrial fibrillation. Effective refractory periods of 280 ms or less identify a group of patients\textsuperscript{127} with the Wolff-Parkinson-White syndrome who continue to have tachycardias during amiodarone therapy and who thus should be considered for surgical ablation. The long-term side effects of amiodarone limit its usefulness in patients with the Wolff-Parkinson-White syndrome. The drug should be reserved for patients with supraventricular arrhythmias associated with pronounced symptoms refractory to other medications and not for candidates for surgical ablation of the accessory pathway.
Persistent or paroxysmal rapid atrial fibrillation resistant to conventional therapeutic agents such as quinidine has also been amenable to amiodarone treatment, response rates being 70 to 97%. Long-term atrial fibrillation (more than 1 year in duration) was an adverse factor in maintenance of sinus rhythm, yet 57% were successful in conversion after amiodarone alone or after a month on drug therapy followed by cardioversion. Numerous articles have recounted the efficacy of amiodarone therapy in patients with ventricular tachycardia and hypertrophic cardiomyopathy in improving survival and reducing the frequency of sudden death.

Clinical Pharmacology.—Amiodarone is a benzofuran with a ringed iodine-containing portion thought to be responsible for its thyroid interactions. Gastrointestinal absorption of the drug is poor and variable (bioavailability of 22 to 50%); the onset of action occurs 5 to 10 minutes after amiodarone is given intravenously and 4 to 6 hours after oral administration. It is highly protein-bound. After cessation of amiodarone therapy, antiarrhythmic action may persist for 30 to 45 days. The full effects of the drug necessitate several weeks of use because of the prolonged loading period to achieve adequate tissue concentrations. There is avid tissue binding. Renal elimination of the drug and its metabolite is negligible. The drug undergoes predominantly hepatic metabolism, and the mean terminal elimination half-life is 53 to 61 days (range, 25 to 100 days) after long-term therapy. The drug exhibits noncompetitive α- and β-receptor antagonism without parasympathetic effects.

Electrophysiology.—The electrophysiologic profile of amiodarone, a class III agent, is divergent from previously known antiarrhythmic drugs. It prolongs the duration of the action potential 50 to 90% in all cardiac tissues and also prolongs the effective refractory period and decreases phase 4 depolarization. It causes little or no depression of phase 0. Sinus node and junctional automaticity are decreased and PR, QT, and QRS durations are prolonged. Amiodarone also prolongs the effective refractory periods in bypass tracts in patients with the Wolff-Parkinson-White syndrome.

Cardiovascular Side Effects.—Amiodarone is generally recognized as a safe antiarrhythmic agent in patients with severe left ventricular dysfunction. The proarrhythmic effect of amiodarone (occurring in 1 to 2% of patients) is less than that associated with other antiarrhythmic agents. Amiodarone may result in symptomatic heart block or bradycardia that necessitates permanent pacing (in 4% of patients). Transient arrhythmic exacerbation during the early stages of therapy need not prompt discontinuation of the amiodarone regimen during the loading phase because continued administration of the drug will usually yield control.

Noncardiovascular Side Effects.—Adverse side effects seem to correlate with the dosage of amiodarone. (Maintenance doses should be kept in the 200 to 400 mg/day range to minimize side effects.) Numerous side effects have been reported, and only the most frequent or serious complications will be discussed here. Photosensitivity dermatitis (sensitivity to sunlight) occurs in 20% of patients. In 1 to 2% of patients, a slate or bluish gray discoloration of the skin develops, which may appear purplish and ecchymotic on the extremities. Avoidance of sunlight or use of products that block the rays of the sun is recommended to prevent burns but may not be entirely helpful. Corneal microdeposits (yellow-brown granules) occur in at least 98% of patients taking amiodarone, sometimes in association with visual blue-green halos, although only 6% of patients have symptoms and these generally resolve after discontinuation of use of the drug.

The molecular weight of amiodarone is 37% iodine from the two iodine molecules. This translates into the presence of 75 mg of organic iodine in each 200-mg dose. Hyperthyroidism (in 1 to 2% of patients) and hypothyroidism (in 1 to 5%) have been described. Mild elevation of thyroxine and reduced triiodothyronine (reduced conversion) have been noted, and thyroid releasing hormone stimulation testing or a “sensitive thyroid-stimulating hormone” assay may be necessary to identify hyperthyroidism. Recurrent arrhythmias that were previously controlled with amiodarone therapy should suggest hyperthyroidism. Both hypothyroidism and hyperthyroidism may be masked by the α- and β-blocking effects of the drug.

Pulmonary side effects, which occur in 4 to 6% of patients, are the most serious extracardiac complication of amiodarone therapy. Pulmonary abnormalities may become manifest as soon as 2 weeks after the onset of treatment,
the mean interval being 8.6 months. Signs and symptoms include a cough that is usually nonproductive, low-grade fever, dyspnea on exertion, leukocytosis, rales, and bilateral pulmonary interstitial infiltrates, usually peripheral and in the lower lung fields. The pulmonary disorder may mimic congestive heart failure or infection, the distinguishing features being low to normal pulmonary artery wedge pressures, no response to diuretics and antibiotics, and negative cultures for bacteria. Decreased diffusion capacity and total lung capacity or deterioration from previous values (or both) may help identify but are not pathognomonic of amiodarone pulmonary toxicity. Bronchoalveolar lavage with microscopic evidence of foamy macrophages and lymphocyte predominance helps identify toxicity but is not diagnostic in itself. The spectrum of alveolitis and lipoidal pneumonitis may be a direct toxic effect or a hypersensitivity (immunologic) reaction to the drug; the condition may progress to pulmonary fibrosis and respiratory failure if amiodarone therapy is not discontinued. Early pulmonary toxicity may be reversible in many cases after drug discontinuation. Although corticosteroids are often used in this setting, their role remains uncertain. Pulmonary angiography may precipitate acute respiratory distress syndrome and even death in patients suffering from amiodarone pulmonary toxicity.

Other side effects are a fine tremor, ataxia, dizziness, sleep disturbances (vivid dreams, nightmares), loss of memory, vertigo, headaches, myoclonus, hemiballismus, peripheral neuropathy, myopathy with proximal muscle weakness, epidermitis, constipation, nausea, anorexia, and ageusia (a lack or impairment of the sense of taste). Abnormal results of liver function tests (alkaline phosphatase, serum glutamic-oxaloacetic transaminase and pyruvic transaminase, and lactic dehydrogenase without bilirubin changes) occur in up to 55% of patients on amiodarone therapy. Discontinuation of therapy is not warranted by elevation of liver function tests alone. Hepatitis has been reported in 4% of patients, with or without hepatic infiltration with foamy cell infiltrates.

Drug Interactions.—Drug interactions with amiodarone are numerous, including warfarin, digoxin, quinidine, procainamide, mexiletine, propafenone, flecainide, and β-blockers. Amiodarone potentiates the effects of warfarin (the prothrombin time may double). Torsades de pointes, heart block, and atropine-resistant bradycardias have been noted when amiodarone is used in combination with class I antiarrhythmic agents. Amiodarone has been shown to increase serum digoxin levels as well as concentrations of quinidine and procainamide. Investigators recommend that the digoxin dose be halved when the two drugs are administered together.

Dosage.—Amiodarone is available for general use only in the oral form. Because of its unusually long half-life, delays in suppression of arrhythmia may occur. In urgent situations such as refractory life-threatening ventricular tachycardia, the use of high-dose orally administered amiodarone has been reported as a method of achieving rapid control of the arrhythmia. In this circumstance, the recommended dosage is 800 to 2,000 mg two to three times daily for 24 to 48 hours, and the blood level should be maintained in the 2 to 3 μg/ml range. Generally, loading regimens are 800 to 1,200 mg/day divided into three doses and given for 10 to 14 days. Therapeutic levels are 1.5 to 2.5 μg/ml after several weeks of therapy. Patients are then maintained on 200 to 400 mg daily. Lower maintenance doses in the 200 mg/day range seem favorable for control of supraventricular tachycardias. Even in cases of treatment of ventricular arrhythmias, it is prudent to reduce the dose to the minimal effective level because of the high incidence of side effects. The extremely long half-life of amiodarone makes dosage adjustments more difficult than with other antiarrhythmic drugs. During the loading phase, occurrence of toxicity is rare, except for sleep disturbances. From multicenter controlled observations, 400 mg/day seemed effective in severe ventricular arrhythmias in 73% of cases and 200 mg/day was effective in 68% of cases, an indication that substantially smaller doses than the 600 to 800 mg/day used previously can achieve antiarrhythmic efficacy.

Selection of Antiarrhythmic Agents and Conclusions
Effective antiarrhythmic drug therapy remains important for managing patients who have serious cardiac arrhythmias. This need is not diminished, even in the face of new advances
such as the automatic implantable defibrillator/cardioverter or ablation of tachycardia foci with use of operative or catheter techniques. The new antiarrhythmic medications have been substantiated as effective treatment of ventricular arrhythmias, many of which have been refractory to other conventional antiarrhythmic agents such as quinidine, procainamide, disopyramide, and lidocaine. Although these new drugs have not been approved for treatment of supraventricular arrhythmias, studies indicate that flecainide, encainide, and amiodarone are promising agents for the treatment of selected patients with supraventricular rhythm disturbances.

Important differences exist among the new drugs and their effectiveness in preventing arrhythmias. Tocainide and mexiletine are not substantially more effective than quinidine in treating patients with ventricular arrhythmias but may be useful because of their different side-effect profile and lack of QT prolongation. Neither drug has been demonstrated to be effective for treating patients with supraventricular arrhythmias. Flecainide and encainide are more effective than quinidine for the treatment of premature ventricular complexes, but their role in preventing ventricular tachycardia has not been fully studied. As first-line therapy, other potentially less proarrhythmic drugs than flecainide or encainide warrant trial first. The proarrhythmic effects of flecainide and encainide are increased in patients with reduced left ventricular function and a history of sustained ventricular tachycardia; thus, these drugs should be used with caution in such patients. Amiodarone is the most effective antiarrhythmic agent for the treatment of rhythm disturbances, but the drug is associated with a high incidence of toxicity. The adverse effects of amiodarone must be weighed in the decisions and may have to be accepted as a compromise for controlling life-threatening rhythm problems such as recurrent ventricular tachycardia or ventricular fibrillation. Proceeding directly to administration of drugs with dangerous adverse effects such as amiodarone is discouraged. In all cases, decisions should be tempered by awareness of clinical experiences with the particular antiarrhythmic agent in controlling the rhythm disturbance in question. Information should be available about the kinetics, metabolic mechanisms, and electrophysiologic effects desired, the adverse hemodynamic, conduction, and extracardiac effects, and the potential drug interactions. Finally, dosages should be carefully selected for effective control of the arrhythmia without exaggerated risks of adverse or detrimental effects.

REFERENCES

NEW ANTIARRHYTHMIC DRUGS


22. Grant AO, Starmer CF, Strauss HC: Antiarrhythmic 20. Grant AO, Starmer CF, Strauss HC: Antiarrhythmic


18. RF, Talbot RG, Dolder MA, Murray A, 17. Anderson JL: Rationale of combination antiarrhythmic

17. Anderson JL: Rationale of combination antiarrhythmic 16. Charlier R: Cardiac actions in the dog of a new antag-


15. Ruskin JN: Oral mexiletine in the treatment of refrac-


3. Ruskin JN: Oral mexiletine in the treatment of refrac-

2. Federman J, Vlietstra RE: Antiarrhythmic drug ther-

2. Federman J, Vlietstra RE: Antiarrhythmic drug ther-

1. Federman J, Vlietstra RE: Antiarrhythmic drug ther-

0. Federman J, Vlietstra RE: Antiarrhythmic drug ther-

0. Federman J, Vlietstra RE: Antiarrhythmic drug ther-

93. Horowitz LN: Encainide in lethal ventricular arrhythmias evaluated by electrophysiologic testing and decrease in symptoms. Am J Cardiol 58:89C-96C, 1986
100. Gomoll AW, Byrne JE, Antonaccio MJ: Electrophysiology, hemodynamic and arrhythmia efficacy model studies on encainide. Am J Cardiol 58:10C-17C, 1986

NEW ANTIARRHYTHMIC DRUGS 1049


