Cardiac Arrhythmia Therapy

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Cardiac dysfunction is often manifested as arrhythmia, with disruption of the normal periodicity and regularity of electromechanical activity. The therapy for arrhythmia begins with proper diagnosis, since many pharmacological interventions are themselves arrhythmogenic. Intervention for acute arrhythmia involves correction of underlying systemic conditions by ensuring adequate oxygenation, ventilation, acid-base homeostasis, electrolyte balance, and fluid status. Classification of antiarrhythmic agents assists in a structured treatment approach that utilizes different agents based on the etiology of the arrhythmia and the drug's mechanism of action. A deliberate treatment strategy guided by the morphological criteria of the arrhythmia modified by the rate and duration of complexes, noting symptoms and hemodynamic stability, is desirable. (Am J Emerg Med 1995;13:459-470. Copyright © 1995 by W.B. Saunders)

Treatment strategies for cardiac arrhythmias are based on an understanding of the physiology of arrhythmia generation and the mechanisms of drug action. Proper therapy begins with a correct diagnosis of the arrhythmia, presence of associated symptoms, and a prognosis for patient outcome. If therapy is warranted, a goal-oriented strategy based on arrhythmia mechanism is matched to the mode of therapy of the pharmacological intervention. Thus, the proper antiarrhythmic agent is chosen from a classification scheme to ensure appropriate single agent therapy and to maximize the synergistic or additive effects of multiple drug regimens.

CLASSIFICATION

Antiarrhythmic agents are classified according to mechanism of action (Table 1).[1] The local anesthetics (Class I) usually slow conduction velocity by altering the fast sodium channel and decreasing the slope. The sympathetic antagonists (Class II) depress the spontaneous rest membrane potential. The antifibrillatory agents (Class III) achieve a homogeneous prolongation of the action potential duration (APD), whereas the calcium channel agents (Class IV) and anion antagonists (Class V) prolong both the effective refractory period (ERP) and the APD (Table 2).[1,2]

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Manuscript received May 18, 1994; revision accepted July 1, 1994.

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Key Words: Cardiac arrhythmia, antiarrhythmic agents, arrhythmia, arrhythmia therapy, dysrhythmia, ectopy.

0735-6757/95/1304-0021$5.00/0

Class I: Membrane Stabilizing Agents

These agents may be subdivided into types A, B, and C according to the rate of sodium channel dissociation and nature of receptor binding.[1,2] However, these agents are significant in arrhythmia therapy because of reproducible effects on the properties of automaticity, conduction, or recovery of myocardial tissue.

Class I, type A agents generally decrease automaticity, conduction, and recovery. *Quinidine,* a dextrostereoisomer of quinine, was the first antiarrhythmic agent pioneered and was originally used for malaria therapy. This Class I, type A agent decreases the rate of diastolic depolarization or automaticity (phase 4), slope or conduction (phase 0), and prolongs the APD or refractoriness (phase 3). Electrocardiographic effects include increased QT, QRS, and ST intervals. Quinidine has autonomic properties and an initial vagolytic effect on the atrioventricular (AV) node, followed by progressive conduction delay, and an α_1-antagonist activity resulting in vasodilation and dose-related hypotension.[1-3]

Quinidine may be used to treat atrial tachyarrhythmias, symptomatic premature atrial contractions, premature atrial tachycardia, atrial flutter, atrial fibrillation, AV nodal tachycardia, and ventricular arrhythmias such as symptomatic premature ventricular contraction (PVC) and chronic ventricular tachycardia.[3] Quinidine may also be synergistic when used in combination with Class II, type B agents for conditions of refractory arrhythmia.

Quinidine has a peak activity of one hour for sulfate and four hours for glucuronate preparations, with a half-life of six hours. The drug is predominantly protein-bound (95%) and undergoes hepatic degradation to active metabolites, 3-hydroxyquinidine or 2-oxyquinidine, and renal excretion as conjugated glucuronides. Quinidine sulfate is administered orally in a 200-mg to 300-mg dose every six to eight hours, and in extreme circumstances 600 mg in dextrose and water may be administered intravenously as a loading dose at 10 mg/min to 20 mg/min. Quinidine gluconate is administered orally in a 324-mg to 660-mg dose every six to 12 hours, whereas the intravenous formulation is administered in a 200-mg to 800-mg loading dose in dextrose and water, also at a rate of 10 mg/min to 20 mg/min. The latter agent may be used for specific refractory arrhythmias in patients who are prohibited from oral intake. The concentration of quinidine in the blood is maintained at 2 μg/mL to 6 μg/mL.[1-3]

The adverse effects of quinidine are those included in the classic description of cinchonism: tetanus, nausea, and vomiting. Cardiac side effects are manifested as sinoatrial (SA) or AV nodal block or decreased contractility. "Quinidine

TABLE 1. Classification of Antiarrhythmic Agents

I. Local anesthetics: Fast sodium channel antagonists
  A. Procainamide
    Quinidine
    Disopyramide
  B. Lidocaine
    Phenytoin
    Tocainide
    Mexiletine
  C. Encainide
    Flecainide
    Lorcainide
    Propafenone (III)
    Moricizine
II. Sympathetic antagonists: β-adrenergic antagonist
  Propranolol
  Esmolol
  Metoprolol
  Atenelal
  Acebutolol
III. Antifibrillatory agents
  Bretylium
  Amiodarone
  Sotalol (II)
  N-acetylprocainamide
IV. Calcium channel agents
  Verapamil
  Diltiazem
  Bepridil
V. Anion antagonist
  Alinidine

syncope" is an idiosyncratic prolongation of the QT interval, and patients are at risk for torsades de pointes as with any Class I, type A agent. Other adverse effects reported with quinidine use include hypersensitivity, thrombocytopenia, hepatitis, drug-induced lupus reactions associated with a positive antinuclear antibody test, and hemolysis linked with a direct Coomb's reaction.[1-3]

Procainamide was first formulated as a procaine congener in 1950. This agent decreases automaticity (phase 4) and conduction (phase 0) and prolongs refractoriness (APD, ERP) (phase 3). Electrocardiographic manifestations include prolonged QT, QRS, and ST intervals and less vagolytic effect than that seen with quinidine.[4] Procainamide is used to treat atrial tachyarrhythmias and features faster and more successful "chemical cardioversion" than quinidine. Procainamide is secondary therapy for ventricular tachycardia or fibrillation and should be avoided if a prolonged QT interval is suspected.

Procainamide has an onset of action of one hour, is minimally protein-bound, and is excreted predominantly (60%) in unchanged form. However, it does undergo hepatic acetylation to *N*-acetylprocainamide (NAPA), retaining 33% of its activity. NAPA is excreted (40%) by the renal route, demonstrating a half-life of three hours, which is prolonged to 11 to 20 hours with renal failure.[1-4]

Oral administration of procainamide requires a 1000-mg to 1250-mg loading dose, followed by 500 mg every six hours for the slow-release preparation or 250 mg every three hours for the standard preparation. Intravenous administration requires a 500-mg to 1000-mg loading dose given at 20 mg/min, followed by a 1-mg/min to 4-mg/min infusion. The therapeutic concentration is between 4 μg/mL and 10 μg/mL.[1-3]

Adverse effects include cardiac dysfunction, AV block, depression of contractility, and QT prolongation, although less so than with quinidine. Drug-induced lupus is found in 50% to 80% of patients with a positive antinuclear antibody, whereas 10% to 15% of patients manifest a lupus-like syndrome with a positive anti-DNA antibody. Hematologic effects are also found, with agranulocytosis and pancytopenia reported occasionally.[3,4]

The active metabolite of procainamide is NAPA (P-amino-N-2-diethyl-amino-ethyl-benzamide), which is probably

TABLE 2. Mechanism of Antiarrhythmic Agents

Class	Automaticity Depolarization Rest Potential (phase 4)	Conduction Plateau Slope (phase 0)		Refractoriness Repolarization (phase 3)	
		Normal	Ischemia	APD	ERP
I. A. Slower conduction and repolarization	↓ ↓	↓	0	↑	↑
B. Faster repolarization	↓	0	↓	↓ ↓	↑ ↑
C. Slower conduction	↓	↓ ↓	0	0	0
II. Automaticity depression	↓	0	0	0	0
III. Homogeneous action potential prolongation	0	0	0	↑	↑
IV. Action potential prolongation	0	0	0	↑	↑
V. Action potential prolongation	0	0	0	↑	↑

NOTE: Arrows and zeros denote ranges of activity: Major decrease, ↓ ↓; minor decrease, ↓; no activity, 0; minor increase, ↑; major increase, ↑ ↑.
ABBREVIATIONS: APD, action potential duration; ERP, effective refractory period.

classified as a Class III agent.[4] NAPA has minimal effects on depolarization (phase 0), with normal SA and AV conduction, but it decreases automaticity (phase 4) and prolongs repolarization (ERP, APD). This investigational agent may be used for refractory ventricular arrhythmias; it undergoes renal elimination with a half-life of six to 12 hours. The oral dose is 1000 mg to 1500 mg administered every eight hours, and the intravenous dose is 18 mg/kg infused at a rate of 20 mg/min to 40 mg/min. Therapeutic concentrations are 8 μg/mL to 12 μg/mL or 12 μg/mL to 20 μg/mL for the combination of procainamide and NAPA.[2] This agent has minimal side effects and is advantageous in patients with myocardial depression.[1,2,4]

Last, *disopyramide phosphate* possesses a quinidine-like action causing decreased conduction (phase 0) and automaticity (phase 4) and prolonged refractoriness (phase 3) with increased ERP and APD. These effects are manifested as a prolonged QT interval on the electrocardiogram. This agent is used for chronic ventricular arrhythmias, symptomatic PVCs, couplets, or stable ventricular tachycardia.[5] Disopyramide is 50% protein bound, and its peak effect occurs at three hours. The drug is degraded to an active (25%) metabolite, Mono-*N* dialkyloisopyramide, which has an anticholinergic effect 25 times that of the original compound.[1,2,5]

Disopyramide is administered orally; the dose is based on body weight of 200 mg (<50 Kg) or 300 mg (>50 kg) daily and is administered at a rate of 100 mg every 8 to 12 hours. The therapeutic concentration is between 2 μg/mL and 5 μg/mL. Disopyramide is contraindicated in patients with an ejection fraction less than 30% because of significant myocardial depression and vasoconstriction. A slight anticholinergic effect is manifested as tachycardia.[1,2,5]

Class I, type B agents decrease automaticity and conduction; however, they hasten repolarization with a decreased APD, although ERP is increased. *Lidocaine* is the most widely used agent in acute ventricular arrhythmia because of its maximal efficacy and minimal side effects. Lidocaine has a dual mechanism of action, decreasing automaticity (phase 4) and subsequent ectopy, along with conduction (phase 0) and resulting reentry arrhythmia. Refractoriness (phase 3) is minimally affected, with a decrease in APD offset by an increase ERP.[1,2]

The effects of lidocaine on conduction velocity are selective to ischemic tissue, especially with an active fast sodium channel concentrated in the distal conduction system (bundle of His, Purkinje's fibers). Thus, lidocaine has little effect on conduction in nonischemic tissue and the proximal conduction system, including the SA and AV nodes. This selective effect allows efficacy for a wide variety of ventricular arrhythmias from isolated PVCs to ventricular fibrillation.

Lidocaine is highly protein-bound (70%) and undergoes extensive first-pass hepatic metabolism (90%), precluding oral efficacy. The agent undergoes renal excretion (10%) with a half-life of two hours and increased accumulation with hepatic dysfunction. Lidocaine is degraded to active metabolites mono-ethyl-glycinexylide with 85% potency and a half-life of two hours, and glycinexylide with 10% potency and a half-life of 10 hours.[1,2]

Lidocaine is administered as a bolus of 0.5 mg/kg to 1.0 mg/kg (maximum 300 mg), followed by a continuous infusion of 20 μg/kg/min to 50 μg/kg/min with a therapeutic concentration of 1.2 μg/mL to 6.0 μg/mL. Toxicity is seen predominantly in the cardiovascular system, with myocardial depression or accentuated AV conduction delay, or in the central nervous system, with overdose manifested as a change in mental status, nausea, or seizure.[1,2]

The clinical efficacy of lidocaine is debatable, but conclusions may be drawn by subgroup analysis. Lidocaine administration to patients with chest pain demonstrates no difference in malignant arrhythmias or outcome.[3-5] Prophylactic administration in patients with acute myocardial infarction demonstrates a decreased incidence (33%) of ventricular fibrillation but no difference in prehospital outcome and no improvement or worsened mortality in hospitalized patients.[6,7] Strategies suggesting the selective administration of lidocaine in patients with ventricular fibrillation in the setting of myocardial infarction or cardiac arrest similarly demonstrate no improvement in survival rates.[8,9]

Phenytoin sodium has an action similar to lidocaine, with decreased automaticity (phase 4) and conduction (phase 0) in ischemic tissue. Refractoriness is essentially unchanged, with prolonged APD and decreased ERP, a mechanism opposite to that seen with lidocaine. Phenytoin is useful as an arrhythmic agent in refractory ventricular tachycardia or in tricyclic antidepressant or digoxin toxicity because of its unique effect of increasing AV nodal conduction.[10]

Phenytoin is 90% protein-bound, with a peak effect in 1.5 to 3 hours, so it is not a primary agent for acute arrhythmia. Phenytoin is completely degraded by the liver to a conjugated glucuronide, and it has a half-life of six to 24 hours. Phenytoin may be administered orally in an aggressive loading schedule: day 1, 15 mg/kg for four doses; day 2, 7.5 mg/kg for three doses; day 3, 5 mg/kg for two doses; followed by standard maintenance dosing of 100 mg over eight hours. Acutely, phenytoin should be considered for refractory ventricular arrhythmias, tricyclic antidepressant or digoxin toxicity, or torsades de pointes.[10] This agent is administered intravenously as a 100-mg dose every five minutes until the desired effect has been obtained or 1000 to 1500 mg has been given.[10] Adverse reactions include hypotension caused by the phenol vehicle and occasional central nervous system toxicity after excessive (20 mg/mL) dosing.[1,2,10]

Mexiletine hydrochloride is a lidocaine congener demonstrating efficacy with oral administration. Mexiletine decreases conduction (phase 0) preferentially in ischemic tissue with a rapid fast sodium channel cycle. Membrane stabilization also occurs as a result of a more negative rest membrane potential, a unique feature, as well as an increased APD. Advantages of mexiletine include synergism with Class I, type A and Class II agents for combination therapy of difficult ventricular arrhythmias and minimal adverse cardiac effects, such as autonomic instability or myocardial depression, allowing its use in patients with cardiomyopathy.[2,11]

The drug is 70% protein-bound, with hepatic degradation (90%) to parahydroxymexiletine, an inactive metabolite. Renal excretion is 10%, so mexiletine is a preferable antiarrhythmic agent in renal failure. The drug is administered in a 200-mg to 800-mg oral dose every eight hours. An investigational preparation requires a loading dose of 300 mg/30 min, then 250 mg/30 min, followed by a maintenance dose of 250

to 500 mg every eight to 12 hours to achieve therapeutic concentrations of 0.7 μg/mL to 2.0 μg/mL.[2,11]

The major disadvantage of the drug is its prohibitive side-effect profile. The drug is poorly tolerated in 50% of patients and has only modest efficacy for ventricular arrhythmias when used for primary therapy (22%), or secondary therapy (12%) as a part of an antiarrhythmic combination.[11] Adverse effects include its arrhythmogenic effect, especially with multiple-drug regimens, and central nervous system toxicity manifested as tremor, gastrointestinal upset, thrombocytopenia, hepatitis, and seroconversion of antinuclear antibody.[11]

Tocainide hydrochloride, the first oral lidocaine analogue, is similar to Class I, type A agents, which cause decreased automaticity (phase 4) and conduction (phase 0) with specific sodium channel dependency and prolonged refractoriness (increased APD, constant ERP). The drug is useful in chronic ventricular ectopy and causes no myocardial hemodynamic depression or autonomic instability.[12]

The drug is minimally protein-bound (10%) and is renal-excreted (50%), with secondary hepatic glucuronidation to an active metabolite. Tocainide is administered orally in a 400-mg dose every eight hours. The therapeutic endpoint is a significant reduction (50% to 80%) in PVC at a serum concentration of 4 μg/mL to 10 μg/mL. Tocainide also has a significant (33% to 60%) side-effect profile, including central nervous system effects, arrhythmias in susceptible patients, and cardiac fibrosis.[2,12]

Class I, type C agents specifically slow automaticity (phase 4) and conduction (phase 0) in a nonselective fashion equivalent in normal and ischemic tissue, whereas refractoriness (APD, ERP) is unaffected. *Encainide* slows conduction velocity (slope 0) and diastolic depolarization (phase 4) or the Purkinje's fibers, without effect on the ERP.[13] This results in increased PR, QRS, and QT intervals. Encainide has demonstrated a 75% reduction of unifocal PVCs in 75% of patients, thus its designation as a "PVC killer." Furthermore, its use for ventricular tachycardia or atrial fibrillation is also successful (30% to 60%).[1,2,13]

Encainide is highly protein-bound (75%) and is processed by the liver to O-dimethyl-encainide (ODE), with fivefold the potency of the original compound, and 3-methoxy-O-dimethylencainide (MODE). The half-life of the parent drug is three to four hours, with that of the metabolites (ODE, MODE) more prolonged, from 12 to 24 hours. Encainide is administered as an oral dose of 25 to 50 mg every eight hours, with a maximum dose of 200 to 250 mg daily to attain a therapeutic concentration of 0.2 μg/mL to 1.0 μg/mL.[1,2,13] This drug has a prohibitive incidence of arrhythmia induction and is a myocardial depressant, and is no longer available.

Flecainide causes irreversible sodium channel inactivation, resulting in decreased diastolic depolarization (phase 0), slowed conduction, and refractoriness (phase 3). Electrocardiographic manifestations are increased PR, QRS, and QT intervals. This drug is as effective (80% to 90%) as encainide in eliminating single PVCs, but is less effective (30% to 40%) for complex arrhythmias such as ventricular tachycardia or fibrillation. Flecainide has selective use in Wolff-Parkinson-White syndrome because of its stabilizing depressant effect on the retrograde accessory pathway.[1,2,4]

The drug is moderately protein-bound (40%) and undergoes hepatic degradation to active metabolites, with a half-life of 14 hours, followed by renal excretion. Flecainide is a negative inotrope and chronotrope that is associated with congestive heart failure and SA arrest, and it has a significant pro-arrhythmic effect. Flecainide is administered in a 100-mg to 200-mg oral dose every 12 hours to achieve therapeutic concentrations of 0.6 ng/mL to 1.0 ng/mL.[1,2]

Earlier clinical trials suggested the efficacy of encainide and flecainide in atrial fibrillation (77%) and refractory ventricular tachycardia (69%), but they also cited a significant incidence of side effects such as congestive heart failure (9%).[13,14] Subsequent evaluation suggested that Class I, type C agents cause a proarrhythmic effect, with worsening of ventricular tachycardia after administration of encainide (31%) and flecainide (9%).[14,15] The more recent Cardiac Arrhythmia Suppression Trial (CAST) demonstrated higher nonarrhythmic mortality rates in the treatment population, resulting in limited use of these agents.[16]

Lorcainide also causes an irreversible sodium channel block that is typical of the Class I, type C antiarrhythmic agents. This block results in decreased diastolic depolarization (phase 0) slowing conduction and is manifested as prolonged PR, QRS, and QT intervals, but does not affect repolarization-ERP (phase 3). Lorcainide is used in the treatment of refractory ventricular tachycardia or accessory pathway arrhythmias. This agent is highly protein-bound (95%) and undergoes hepatic first-pass metabolism to norlorcainide, an active metabolite, with twice the half-life (15 to 30 hours) of the parent compound. Lorcainide may also result in arrhythmia generation from sinus node dysfunction, as well as neurological sequelae. The drug is administered as a 100-mg oral dose every 12 hours or a 100-mg intravenous dose at 2 mg/min.[1,2] A study performed in 1980, but reported only after the CAST I and II trials found that lorcainide administered in suspected acute myocardial infarction similarly reduced arrythmia incidence but increased mortality.[17]

Propafenone may be considered a combination agent featuring typical Class I, type C fast channel inactivation, decreasing the action potential slope (phase 0) while prolonging repolarization (ERP) Class III activity, with a slight (5%) Class II block, and Class IV calcium channel antagonism that provide inotropic protection. This agent is used to treat numerous atrial and ventricular tachycardia syndromes. Hepatic metabolism results in 5-hydroxypropafenone, an active byproduct. Adverse effects include conduction delay (PR-QRS) and a slight proarrhythmic potential (5%).[1,2] Propafenone is administered orally at 300 mg every eight hours or intravenously at 1 mg/kg to 2 mg/kg. Clinical effectiveness has been documented for oral therapy (80%) in chronic atrial arrhythmias and intravenous therapy (75%) in the acute setting.[18,19] Specifically, propafenone is more successful in patients with atrial fibrillation (62%) than in those with atrial flutter (33%), lasting less than 48 hours (71% *v* 26%) and with a left atrial size of less than 4.0 cm in diameter.[20]

Last, *moricizine,* a phenothiazine derivative, acts to prolong repolarization (phase 3) and increase the ERP and QRS interval. The dose is 200 mg every eight hours for oral administration. This agent is used only for ventricular arrhythmias and may be arrhythmogenic (5% to 27%), and has limited effectiveness (up to 12%) in sustained or recurrent episodes of ventricular tachycardia.[21,22] The Cardiac

Arrhythmia Suppression Trial II (CAST II) also demonstrated worsened outcome in the treatment group in the setting of myocardial infarction.[23]

Class II: Sympathetic Antagonists

This class of agents, isolated as isoproterenol antagonists in 1958, have a multitude of effects. Beta antagonists decrease all action potential phases such as automaticity (phase 4), conduction (phase 0), and refractoriness (phase 3) by their effect on exogenous autonomic stimuli and internal membrane stabilization.[24] Common characteristics of this group of agents include a decrease in sinus node discharge, AV conduction, and inotropic state, resulting in a reduction in myocardial oxygen consumption. Characteristics specific to each drug are lipid solubility proportional to the side effects in the central nervous system, quinidine-like membrane stabilization, intrinsic sympathetic activity with less hypotension, β_1 cardioselectivity, a nonselective β_2 effect causing bronchodilation and vasodilation, and metabolic effects such as decreased glycogenolysis.[25,26]

Beta antagonists have a diverse range of indications including supraventricular tachycardia, atrial fibrillation or flutter, catecholamine excess, ischemia, mitral valve prolapse, digitalis toxicity, hypertrophic cardiomyopathy, myocardial infarction, and withdrawal syndromes. Classification of these agents into cardiac-selective (β_1) and nonselective (β_1, β_2) categories facilitates analysis (Table 3).[2,24-27]

Propranolol is the prototype nonselective β-antagonist. This lipid-soluble agent provides good membrane stabilization with minimal intrinsic sympathetic activity. Propranolol is highly protein-bound (95%) and undergoes hepatic metabolism to 4-hydroxypropranolol, an active metabolite, with a half-life of 3 to 6 hours. The adverse effects include central nervous system depression, conduction system delay, inotropic suppression, and bronchoconstriction. The oral dose administered is 10 to 20 mg every six to eight hours (maximum, 320 mg/day), and the intravenous dose is 0.10 mg/kg to 0.15 mg/kg infused at a rate of 0.5 mg/min to 0.75 mg/min.[2,24-27]

Timolol has minimal lipid solubility, with subsequent effects of membrane stabilization and intrinsic sympathetic activity. It is minimally protein-bound (10%) and undergoes hepatic elimination with a half-life of four hours. Isolated side effects are central nervous system and cardiac toxicity. Although its use as an antiarrhythmic agent is not strongly supported, timolol may be administered in a 10-mg oral dose twice daily to a maximum dose of 20 mg/day.[2,24-27]

Pindolol also is poorly suited as an antiarrhythmic agent, having moderate lipid solubility and membrane stabilization, partial agonist activity, and minimal protein binding (10%). Its side effect profile is similar to other β-antagonists, with central nervous system sedation and minimal SA block. The therapeutic dose is 5 mg every 12 hours orally.[2,24-27]

Atenolol is a representative cardioselective agent featuring minimal solubility, membrane stabilization, and partial intrinsic sympathetic activity. The drug undergoes renal excretion (85%), with a half-life of six to seven hours, and it has adverse inotropic and chronotropic cardiac effects. The dose is 12.5 to 25 mg every six hours to a maximum dose of 100 mg/day. Atenolol, timolol, and pindolol have limited roles as antiarrhythmic agents and are best suited as antihypertensive medications.[2,24-27]

Metoprolol has been demonstrated to improve clinical outcome in patients with myocardial ischemia, and to decrease the incidence of arrhythmia caused by antagonism of a presumed increased level of basal norepinephrine in those with impaired ejection fraction.[28,29] The Thrombolysis In Myocardial Infarction Trial II (TIMI II) studied metoprolol administered intravenously in a 5-mg dose every five minutes for three doses, followed by 50 mg orally every 12 hours, then 100 mg orally as maintenance therapy.[30] This trial demonstrated a small decrease in the reinfarction rate (5.1%) compared with that seen in control patients (2.7%).

Acebutolol, a cardioselective agent with weak intrinsic sympathetic activity, may have a more pertinent role in the treatment of ventricular tachycardia in the setting of acute myocardial infarctions, and it has been shown to improve outcomes.[30] This short-acting agent undergoes hepatic degradation to an active diacetyl compound with a half-life of less than one hour. Side effects such as fatigue and hypotension are noted at doses of 200 to 1200 mg/day.[2,31]

Last, *esmolol,* the shortest acting compound, may have the most utility in the acutely ill patient. This cardioselective agent has poor lipid solubility and a membrane stabilizing effect, with no intrinsic sympathetic activity; these features are advantageous in the patient with a catecholamine-sensitive heart. Because of poor lipid solubility, esmolol has an ultrashort half-life of nine minutes, and elimination occurs by ester hydrolysis.[32] Beta antagonists may cause adverse effects such as hypotension in one third of patients, because

TABLE 3. β-Antagonists and Their Properties

Agent	Potency	Cardioselectivity	ISA	Lipid Solubility	Membrane Stabilization	Half-life
Esmolol	0.1	+	0	0	0	9 min
Acebutolol	0.3	+	+	0	+	15 min
Metoprolol	0.8	+	0	Weak	0	15 min
Atenolol	1.0	+	0	Weak	0	6-7 h
Labetalol	0.7	0	0	Weak	+	6-7 h
Nadolol	1.0	0	0	0	0	6-7 h
Propranolol	1.0	0	0	Strong	++	3-6 h
Pindolol	4.7	0	++	Weak	+	3-6 h
Timolol	6.0	0	0	0	0	4 h

NOTE: Ranges of activity denoted as follows: Inactive, 0; weak activity, +; strong activity, ++.
ABBREVIATIONS: ISA, intrinsic sympathetic activity.

these agents are administered to the most acutely ill patients. However, progression to acute congestive heart failure occurs in only 1%, specifically those with left ventricular dysfunction (ejection fraction 27 ± 2%). The drug administration strategy is complex: a loading dose of 50 μg/kg/min is administered incrementally every five minutes to a total of 500 μg/kg/min, followed by a continuous infusion of 25 μg/kg/min to 30 μg/kg/min.[32]

Class III: Antifibrillatory Agents

This diverse group of antiarrhythmic agents acts to restore automaticity (phase 4), convert multiple heterogeneous action potentials to a uniform morphology, and slow reentry recovery by prolonging the APD and ERP (phase 3).

Amiodarone was first tested as an antianginal coronary artery vasodilator. This compound consists of a procainamide-lidocaine congener portion, a diethylamine group with noted electrophysiological effects, and an iodine group with thyroid function effects. Amiodarone decreases conduction (phase 0) by inhibiting calcium channels of the SA and AV nodes and the sodium channel of the Purkinje's fibers, although it has no effect on membrane potential. This action prolongs the APD and ERP, manifested as delayed atria-His bundle (AH) and His bundle-ventricle (HV) intervals correlating with increased PR and QT intervals on the electrocardiogram. An additional noncompetitive β- and a slight α-antagonist autonomic effect occurs as well.[1,2,33]

Amiodarone has a diverse group of indications for refractory arrhythmias including paroxysmal atrial tachycardia, rate control and conversion of atrial fibrillation, accessory bypass tract syndromes, and as "last resort" therapy for ventricular arrhythmias. The salvage rate for refractory ventricular arrhythmias is most successful with Class III (50%) and Class I, type C (30%) and type A (20%) agents.[2] Preliminary analysis of the European Myocardial Infarction Amiodarone Trial (EMIAT), in which 1,310 post–myocardial infarction patients have been enrolled, shows a 13.4% (130) mortality within the expected range, whereas 67% had VPBs <10 per hour and 27% had ventricular runs (>3 VPB).[34]

The absolute effectiveness of this drug is decreased by a prolonged onset of action and numerous side effects. Amiodarone has a peak onset of action of three to seven hours and undergoes hepatic degradation to an active metabolite *N*-des-ethylamiodarone with a half-life of 15 to 100 days. Thus, this agent requires a prolonged interval until a therapeutic effect is demonstrated using conventional drug administration strategies without loading (28 days) or with loading (10 days).[1,2,33]

Amiodarone has multiple adverse effects with significant morbidity, and therapy must be discontinued in 10% to 50% of patients. Side effects include cardiac inotropic and chronotropic inhibition, arrhythmogenesis (5%), idiosyncratic pulmonary fibrosis (3% to 10%) caused by phospholipidosis, corneal lipofuscin deposits, cutaneous blue-gray discoloration, hypothyroidism, and gastrointestinal and central nervous system symptomology.[1,2,33,35] The side-effect profile may not be predicted by serum drug or metabolite levels, and it seems to be related to cumulative dose and to be contingent on both amount and duration of therapy.[33]

The drug administration schedule offers many alternatives. Less acute intervention requires oral dosing of 600 mg every eight hours for one week, then 200 to 600 mg daily. Urgent oral dosing is achieved with 2000 mg during days 1 through 3, 1400 mg during days 4 through 7, 1000 mg/day during the 2nd week, 800 mg/day during the 3rd through 5th weeks, followed by 600 mg daily thereafter, with gradual adjustment to 200 to 600 mg for daily maintenance.[33] Although still undergoing clinical trials, emergency administration of amiodarone in life-threatening arrhythmias requires an intravenous dose of 5 mg/kg administered every five minutes to obtain a therapeutic concentration of 2.5 μg/mL. Daily maintenance therapy ranges from 200 to 400 mg for atrial and 400 to 600 mg for ventricular arrhythmias. Most important, amiodarone is efficacious in those with left ventricular dysfunction (93%), but occasionally with drug loading (15%) accompanied by cardioversion (90%).[1,2,33,36]

Bretylium increases the APD and ERP (phase 3) and reduces tissue disparity, almost a "chemical defibrillation." Systemic vascular effects include a biphasic hypotensive response or "chemical sympathectomy" followed by a hypertensive period resulting from norepinephrine release increasing the heart rate, systemic vascular resistance, and cardiac output, but ectopy is also more prominent. This agent is used for treatment of ventricular tachycardia and fibrillation and has an onset of action of one hour and 10 minutes, respectively.[1,2]

The drug undergoes renal excretion (100%) and has a half-life of 10 to 24 hours. The side-effect profile is caused by the adrenergic fluctuation, resulting in blood pressure lability accompanied by nausea and emesis. The dose of intravenous bretylium tosylate is 5 mg/kg to 10 mg/kg every 10 minutes followed by 1 mg/min to 2 mg/min for ventricular tachycardia or 5 mg/kg to a maximum of 30 mg/kg for ventricular fibrillation.[1,2]

Experimental and clinical trials have compared bretylium with other antiarrhythmic agents. Bretylium compared with flecainide and sotalol demonstrated an increased ERP and a variable increase in spontaneous ventricular fibrillation threshold.[37] A canine ventricular fibrillation model shows that bretylium and lidocaine may have equivalent initial effectiveness and hemodynamic effects, as well as a decreased recurrence rate after bretylium.[38] Results from a comparison of bretylium with lidocaine after coronary artery bypass reperfusion suggest a significant decrease in ventricular fibrillation incidence (36% to 64%).[39]

Sotalol is a nonselective β-antagonist with minimal intrinsic sympathetic activity and has a Class III antiarrhythmic effect. This combination agent increases the APD and ERP (phase 3), whereas conduction is unchanged. Sotalol is used for treatment of ventricular arrhythmias. This agent is eliminated by renal mechanisms (100%) and has a half-life of 7 to 15 hours. Sotalol is safe, with minimal adverse effects when administered at a 160-mg oral dose every 12 hours.[1,2,40] Electrophysiological evaluation of Wolff-Parkinson-White syndrome patients demonstrated 100% efficacy in a clinical trial.[41] Sotalol compared with lidocaine in a double-blinded crossover trial in patients with cardiac disease (EF 35%) was effective in treating ventricular tachycardia (69% to 18%) initially, as well as the sotalol salvage pathway for lidocaine failure (7% to 50%).[42] The Electrophysiology Study Versus

Electrocardiographic Monitoring (ESVEM) Trial conducted multivariate testing in 486 arrythmia patients and found that only sotalol therapy or absence of prior antiarrhythmic therapy was associated with a reduced risk of arrythmia recurrence.[43]

Class IV: Calcium Channel Antagonists

The calcium channel antagonists block calcium entry in a use-dependent fashion (verapamil > diltiazem > nifedipine) specific to the Supra-Hissian (SA and AV node) conduction syndrome. The cardiac effects are decreased diastolic depolarization, threshold potential (phase 4), and action potential slope and amplitude (phase 0). Cardiovascular sequelae are vascular relaxation (nifedipine > diltiazem > verapamil), depressed contractility proportional to intracellular calcium, and a negative chronotropic effect (AV > SA node). These agents are used to treat paroxysmal supraventricular tachycardia of the reentry type, with 90% conversion, and for atrial fibrillation rate control, with 10% conversion to normal sinus rhythm. However, a paradoxic rate acceleration may be noted with use in wide-complex Wolff-Parkinson-White syndrome.[1,2]

Verapamil was the first calcium channel antagonist used, and it has a significant negative chronotropic effect. Verapamil administered in the acute setting for paroxysmal supraventricular tachycardia, multifocal atrial tachycardia, or atrial fibrillation has 75% to 100% efficacy, with a mean decrease in heart rate of 21%.[44-46] This agent is 90% protein-bound and undergoes hepatic *N*-dialkylation to norverapamil, which has 20% activity and a half-life of 5 to 10 hours. Adverse effects include AV block and hypotension, which are somewhat blunted by prior administration of calcium chloride (1 g intravenously) in the unstable patient. The oral dose is 80 mg every six hours to a maximum of 480 mg. Acutely, verapamil may be administered in a 0.05-mg/kg to 0.10-mg/kg dose every five minutes followed by a 0.005-mg/kg/min infusion as tolerated.[1,2]

Diltiazem has moderate depressant effects on both chronotropic and inotropic function. This agent may offer some cardioprotective effect in selected vasospasm-related ischemic states while affording significant rate control, minimizing hypotensive side effects. Diltiazem administered to patients with myocardial infarction resulted in unchanged mortality, but it worsened pulmonary congestion in those with left ventricular dysfunction (40%).[47] In patients with subendocardial myocardial infarction, diltiazem administration resulted in a decreased reinfarction rate (9.3% *v* 5.2%), but a similar mortality rate was noted.[48]

Diltiazem undergoes hepatic elimination and has a half-life of three to five hours, with AV block and hypotension noted with drug accumulation. This agent is administered orally at 30 mg every six hours to a maximum of 360 mg per day. Acutely, an intravenous formulation administered as a 0.25-mg/kg loading dose, followed by a 0.35-mg/kg repeat load if the arrhythmia condition is refractory, followed by a 10-mg/h to 15-mg/h continuous infusion. This regimen, when used for atrial fibrillation/flutter rhythms, demonstrates 75% success rate with the initial loading dose and 93% with a repeat loading dose compared with placebo (12%) with a mean decrease in heart rate of 20%.[49,50]

Bepridil is an antianginal preparation that decreases sodium, calcium influx, and potassium efflux through potential dependent and receptor-operated channels. This results in prolonged APD, ERP, AV, AH, and QT intervals and has characteristics of Class I_B, III, and IV agents. The drug is highly protein-bound and renally excreted with prolonged half-life of 42 hours. The drug is administered in a dose of 200 to 600 mg/day. Caution is warranted in the setting of myocardial depression, conduction delay, whereas the presence of ischemia may actually improve function, slowing fast sodium channel conduction in acidemia.[51] Electrophysiological evaluation of bepridil administration to 38 patients in a 2-mg/kg intravenous dose prevented inducible ventricular tachycardia in 21% of cases, and conversion to oral therapy required a 900-mg daily dose, whereas 500 mg daily was only effective in 1% of cases.[52]

Class V: Anion Antagonists

This experimental therapeutic class (such as alinidine, restricting chronic influx) will be explored in the near future as antiarrhythmic agents.[1]

UNCLASSIFIED MISCELLANEOUS AGENTS

Digitalis, the first and most widely utilized cardiac agent, inhibits the sodium-potassium ATPase pump, decreasing sodium efflux and potassium influx and affecting membrane integrity. The net effect is to increase automaticity (phase 4), reduce conduction velocity (phase 0), prolong repolarization-APD and ERP (phase 3), and increase the vagal effect. Electrocardiographic manifestations include an increased PR interval, a downward sloping ST depression, and a shortened QT interval. Indications for use include supraventricular rate control and some inotropic stabilization. Adverse effects include a wide variety of gastrointestinal and central nervous system toxicities. The oral or intravenous digitalizing dose is 0.125 to 0.5 mg to a total of 1.0 mg, followed by 0.125 to 0.5 mg for daily maintenance.[1,2]

Recent investigation has suggested that digoxin may not provide effective rate control and arrythmia termination capability, and may in fact aggravate paroxysmal atrial fibrillation.[53] Rate control has been achieved in the setting of acute and chronic atrial flutter/fibrillation using digoxin in contrast to diltiazem as a single agent or in combination therapy with adjunct agents such as sotalol.[54,55] Conversion of acute atrial flutter/fibrillation in 87 patients was achieved in 62% to 83% of those receiving propafenone (IC), 38% of those receiving digoxin, 48% of those receiving digoxin and quinidine (IA), and 17% to 34% for placebo at 6 to 12 hours respectively.[56,57]

Adenosine is analogous to the prototype adrenergic agonist ATP and has dose-dependent negative chronotropic and dromotropic effects. This agent decreases calcium influx and potassium efflux, inhibiting automaticity (phase 4) and conduction (phase 0) in the SA and AV nodes and bundle of His. Cardiac effects of adenosine are both direct and indirect, relying on the cyclic adenosine monophosphate (cAMP) system for cardiac-specific (A_1) and vascular smooth muscle (A_2) effects.[58] Adenosine is used for reentry AV nodal and junctional arrhythmias to slow the antegrade

loop. Adverse reactions are sinus arrest and vagal-related gastrointestinal symptoms. The dosing protocol is 6 mg, 12 mg, and 12 mg administered intravenously in a repetitive fashion to a total of 0.05 mg/kg to 0.25 mg/kg. Adenosine has a better and faster response rate (93%) than verapamil.[59,60] This response is dose-related from 3 mg (35%) to 12 mg (91%), improves with experimental dosing from 6 mg (52%) to 12 mg (93%), and is successful when patients are refractory to verapamil (81% to 91%).[60]

MANAGEMENT STRATEGIES

Therapy of arrhythmias encompasses a multifactorial approach to confirm the nature of the arrhythmia, past and present cardiac condition, respiratory influence, electrolyte effects, drugs administered, and systemic conditions such as temperature extremes, altered autonomic activity, and endocrine or neurological dysfunction. Fluid status should also be evaluated, with rapid crystalloid administration or fluid removal if necessary.

Electrolyte stability should be confirmed early in the management of arrhythmia. The association between hypokalemia and ventricular ectopy has been proven, with the effect being exacerbated by vasopressor administration.[61] A 1.0-mEq/L serum change in potassium corresponds to a 380-mEq to 400-mEq change in tissue stores.

Magnesium is essential to maintain membrane stability. Hypomagnesemia has an incidence of 20% to 30% in intensive care and coronary care patient populations, respectively.[62,63] Most investigators have reported a decrease in tachyarrhythmias in patients with equivalent potassium levels with magnesium administration in the acute myocardial infarction population.[64,65] However, smaller differences may be noted in patients with advanced congestive heart failure.[66]

Calcium is likely to be involved in disorders of automaticity or impulse conduction. Hypocalcemia often results in partial depolarization manifested as early afterdepolarization, whereas hypercalcemia is associated with delayed afterdepolarizations, with the former often associated with prolonged QT interval and torsades des pointes.[67]

Arrhythmias should be interpreted according to clinical circumstance, morphology, and symptomology. Relatively regular narrow complex rhythms that include sinus arrhythmia, wandering atrial pacemaker, and premature atrial contractions (<6/min) usually require no treatment without significant symptomology.

Sinus bradycardia should be treated if there is evidence of hypotension, a change in mental status, or the heart rate decreases below 50 beats/min. Therapy includes atropine (0.01 mg/kg) in a total dose range of 0.5 mg/kg to 2.0 mg/kg or isoproterenol, a balanced β_1- and β_2-agonist at 1 μg/min to 2 μg/min or 0.01 μg/kg/min, which increases myocardial oxygen consumption. Therefore, cardiac pacing is preferable to isoproterenol administration. Dopamine, a combined β_1- and α-adrenergic agent, may increase heart rate and improve blood pressure, avoiding the systemic hypotensive effects that result from isoproterenol's β_2 vasodilatory action.[68] Chronic bradycardia has been recently treated with albuterol, a β_2-agonist, or scopolamine, an anticholinergic agent. Comprehensive treatment requires discontinuing medication that causes bradycardia such as digoxin, narcotics, and β-antagonists, as well as monitoring for hyperkalemia.

Sinus tachycardia with a heart rate of 150 beats/min and evidence of hypoperfusion should be addressed by examining for fever, pain, anxiety, thyrotoxicosis, or withdrawal from drugs, alcohol, β-blockers, and central α-agonists. Specifically, *multifocal atrial tachycardia* and *paroxysmal atrial tachycardia* may be associated with theophylline or digoxin toxicity, respectively. Therapy includes beta blockade with propranolol (0.05 mg/kg to 0.1 mg/kg) at 0.5 mg/min to 1.0 mg/min or the calcium antagonist verapamil (0.05 mg/kg) at 0.5 mg/min to 1.0 mg/min.

Supraventricular tachycardia most commonly results from a reentry mechanism and should be addressed in a systematic sequence based on acuity. A vagal maneuver such as carotid sinus massage, the Valsalva maneuver in adults or "diving" maneuver and facial ice application in pediatric patients, both of which prolong AV nodal refractoriness, should be attempted initially and after each pharmacological intervention.

Urgent intervention includes adenosine, which has a 95% success rate when administered in a dose regimen of 6 mg, 6 mg, and 12 mg peripherally, or half of that dose centrally. Verapamil (2.5 to 5.0 mg intravenously) is probably slightly less efficacious (90%) than adenosine, but there is more clinical experience with its use. Beta blockade with propranolol (0.5 mg/kg to 0.1 mg/kg) administered in 0.5-mg to 1.0-mg doses every minute to a total dose of 3 to 7 mg is helpful in hyperadrenergic or withdrawal states. Digitalization with digoxin administered in a 0.125-mg to 0.5-mg dose to a total of 1.0 mg should be attempted only if some irregular rhythm components suggest atrial flutter or fibrillation.

Historically, anticholinesterase agents such as edrophonium, 0.05 mg/kg, were used in 2.5-mg to 5.0-mg dosing increments to a total of 10.0 mg to induce vagal suppression, and α-antagonists such as phenylephrine, 0.5 to 1.0 mg, were used to induce a systematic hypertensive state and baroreceptor-mediator reflex tachycardia. These drugs, because of a prohibitive side-effect profile, have been replaced by newer safer antiarrhythmic agents, and should not be used today.

Emergent management requires overdrive cardiac pacing by transcutaneous or transvenous routes.[69] As a last resort, synchronized cardioversion is attempted using 25 to 200 *j*, or 5 to 100 *j* if digoxin toxicity is present, progressing to synchronized cardioversion at 200 to 360 *j* in states of cardiac arrest.

Irregular, narrow complex rhythms such as *atrial flutter* often require component therapy. Rate control is attempted initially using digoxin, verapamil, and β-blockers, in order of effectiveness, avoiding the paradoxic rate acceleration noted in the setting of Class I, type A antiarrhythmic agents. Second, chemical cardioversion is attempted using procainamide (1000 mg followed by 1 mg/min to 4 mg/min) or quinidine orally in the less acute setting. Electrical intervention progressing from synchronized cardioversion (25 to 360 *j*) to defibrillation (100 to 360 *j*) is required in the emergent setting.

Atrial fibrillation is associated with a decreased cardiac output (30%) because of a loss of atrial systole and a 5% incidence of an embolic event, usually occurring with con-

version. Atrial fibrillation most commonly results from ischemia (55%), rheumatic heart disease (23%), chronic obstructive pulmonary disease (2.8%), Wolff-Parkinson-White syndrome (2.6%), thyrotoxicosis (2.6%), or idiopathic conditions (4.5%) that are associated with the most successful conversion rate (94%).[70] Therapy should be instituted to avoid the risk of embolism (2% to 7%).[71] Rate control is required with an enlarged left atrium (>4 cm), using digoxin to minimize hypotension, verapamil (which has more adverse hemodynamic effects but allows safer cardioversion), and β-blockers (25 μg/kg/min to 200 μg/kg/min). This therapy may be followed by cardioversion, if warranted by the clinical scenario. Adjunct therapy for refractory arrhythmias includes Class I, type A agents (procainamide, quinidine, disopyramide), Class I, type C agents (propafenone, flecainide), and Class III combination agents (amiodarone, sotalol).

Wolf-Parkinson-White syndrome typifies arrhythmias of the accessory bypass tract and is characterized into two groups based on QRS morphology. The less common orthodromic variant involves conduction antegrade down the normal conduction pathway, with the normal AV delay, and retrograde up the accessory tract. This results in a regular, narrow complex rhythm at a rate of 220 to 360 beats/min, resembling paroxysmal atrial tachycardia that responds to treatment with calcium channel agents, β-antagonists, or digoxin. The more common antidromic variant involves conduction antegrade down the accessory tract and retrograde up the normal conduction pathway, without AV delay. This results in an irregular, wide complex rhythm at a rate of 300 to 400 beats/min, resembling atrial fibrillation that responds to treatment with digoxin and procainamide. The hazard of treating the wide complex variant with verapamil is that this agent causes rate acceleration rather than reduction.[72]

Arrhythmias caused by an accessory atrial bypass tract generally are categorized by anatomic area and direction. Atrial tracts that bypass the SA and AV nodes that are anterograde (narrow complex) are treated with digoxin, β-blockers, verapamil, or vagal stimuli, whereas retrograde (wide complex) variants are treated with quinidine, procainamide, disopyramide, or encainide.[73] Ventricular tracts that bypass the AV-Purkinje system that are anterograde are treated with flecainide, whereas the retrograde version requires amiodarone or flecainide. Thus, chronic therapy of accessory bypass tracts suggests a remaining niche for flecainide.

The junctional arrhythmia is intermediate in morphology between atrial narrow complex and ventricular wide complex rhythms. Symptomatic *junctional bradycardia* (<60 beats/min) may require atropine therapy and monitoring for digoxin toxicity or hyperkalemia. Symptomatic *junctional tachycardia* (>100 beats/min) often requires therapy with procainamide or lidocaine, followed by cardioversion if warranted.

Idioventricular rhythm may be the transition between junctional and ventricular origins of myocardial activity. Thus, *slow idioventricular rhythm* should be treated with atropine to increase the rate, and in select circumstances cautious use of lidocaine may be warranted, but not in such a way that the remaining automatic rate is eliminated. Patients with *accelerated idioventricular rhythm* become symptomatic because of the loss of atrial kick, and it is probably best to avoid the use of antiarrhythmic agents such as lidocaine, which may eliminate the baseline perfusing rhythm.

Therapy of wide complex arrhythmias begins with a discussion of the premature ventricular complex (PVC), or ventricular premature beat (VPB), and examination of the consequences of marker arrhythmias. A grading scale can be assigned to progressively note increasing morbidity and mortality: 0 = normal, 1 = occasional VPB, 2 = frequent VPB (1/min), 3 = multiformed VPB, 4 = repetitive VPB (a = couplets, b = salvos), 5 = early VPB or the "R-on-T" phenomenon.[74] Primary therapy for these complexes is lidocaine or procainamide, followed by oral lidocaine congeners, or in specific circumstances, flecainide, encainide, or amiodarone, depending on electrophysiological testing (Table 4).[1,2]

Ventricular tachycardia is the prototype wide complex arrhythmia. Ventricular tachycardia is the most common (81% to 85%) cause of wide complex tachycardia, followed by supraventricular tachycardia with aberrancy (14%) and accessory bypass tracts (5%).[75,76] Although diagnosis is paramount, ventricular tachycardia is documented correctly in only 61% of cases, with atrioventricular dissociation (73%) as the most reliable criterion.[77] This distinction is important because therapy of ventricular tachycardia using verapamil results in hemodynamic deterioration in 85% of cases and in poor outcome in 59%. Sustained ventricular tachycardia with acute myocardial infarction carries a 14% versus 2% rate of early sudden death in those without myocardial ischemia, although the one-year survival rates are equivalent.[78]

Ventricular fibrillation is the most disorganized of arrhythmias. Those with primary ventricular fibrillation with myocardial ischemia have been documented to have poorer outcomes than those without this arrhythmia, with a mortality rate of 11% versus 6%.[79] Controlled trials of Class I, type A antiarrhythmic agents show that those at risk for early ventricular fibrillation (within 72 hours of cardiac arrest) were those with left ventricular dysfunction (EF 29%), a prolonged QT interval, and multiple drug regimens including digoxin and diuretics (31%), with a mortality of 20%.[80]

Therapy of ventricular tachycardia and fibrillation begins with lidocaine as primary therapy. Procainamide may be substituted unless a prolonged QT interval is present. Bretylium is sometimes helpful, especially in the setting of hypothermia. Experimental models suggest that moderate to severe hypothermia (T 25-30°C) decreases spontaneous ventricular fibrillation threshold, whereas bretylium reverses this adverse effect.[81] Phenytoin may be of benefit with digoxin or tricyclic antidepressant toxicity, whereas lidocaine may be ineffective, and cardioversion may result in further degeneration. Beta antagonists are useful in hyperadrenergic states, ischemia, or polymorphic ventricular tachycardia. Torsades de pointes is often refractory to standard modalities and may benefit from magnesium or dilantin administration or cardiac pacing, because Class I, type A agents can be detrimental.[82] Amiodarone is a last-resort antiarrhythmic, but it may be effective in an aggressive loading strategy if the arrhythmia is refractory to conventional therapy. Last, ventricular tachycardia warrants synchronized cardioversion (50 to 200 *j*), and ventricular fibrillation requires unsynchronized defibrillation (100 to 360 *j*) if refractory to antiarrhythmic agents or if severe symptoms occur.

Conduction delay in the form of *first-degree AV block*

TABLE 4. Therapy for Ventricular Arrhythmias

Agent	Chronic-oral	Dose (mg)	Initial (h)	Cumulative (mg)	Level (μg/mL)
Class I	A. Procainamide	375-500	4	2250-3000	4-8
	Quinidine	200-400	6	800-1200	2-6
	Disopyramide	100-250	6	400-1000	2-5
	B. Tocainide	400-600	12	800-1200	4-10
	Mexiletine	250-400	8	750-1200	1-2
	C. Flecainide	100-200	12	200-400	0.6-1.0
	Encainide	25-50	8	75-150	0.2-1.0
	Propafenone	300	8	900	
Class III	Amiodarone	600-800	8	1200-1800	1-3
		200-300	12	200-600	
	Sotalol	160	12	320	

	Acute-intravenous	Loading Dose	Continuous Infusion (mg/min)	Maximum Dose	Level (μg/mL)
Class I	A. Procainamide	15 mg/kg	1-4	1000 mg	4-8
	Quinidine	200-800 mg	1-4		2-6
	Lidocaine	1 mg/kg	1-4	3 mg/kg	1.2-6.0
	Phenytoin	15 mg/kg			10-20
Class III	B. Bretylium	5-10 mg/kg	1-4	30 mg/kg	
	Amiodarone	5 mg/kg			2.5

requires no therapy unless symptomatic. This condition has an incidence of 1% congenitally, with a minimal chance of progression to more advanced block or change in mortality if chronic ischemia is absent.[83] Atropine is the therapy for first-degree block and *Mobitz type I second-degree block* if symptomatic. Cardiac pacing should be utilized in addition to atropine for *Mobitz type II second-degree block* and *complete heart block*, which are associated with ineffective perfusion resulting in increased morbidity and mortality. Isoproterenol may be used in select nonischemic cases as a temporizing measure.

The use of electrophysiological testing has allowed significant advances in the diagnosis and treatment of complex arrhythmias. Electrophysiological testing has been used to identify appropriate drug therapy in 50% of refractory patients, allowing 84% one-year and 75% two-year survival rates.[84] The basis of therapy is the use of empirical treatment trials, resulting in fewer drugs used (3.2 *v* 5.5) and a decreased length of hospital stay.[85] Although the electrophysiological regimen resulted in a decreased recurrence of arrhythmia, the overall mortality rate was unchanged.[84]

CONCLUSION

The diagnosis and treatment of cardiac arrhythmia entails recognition of the clinical scenario, nature of the arrhythmia, symptomatology, associated factors, effects of administering or withholding therapy, side effects, and effect on clinical outcome and survival. Doses of pharmacological agents should always be verified before use. All drug dosing information should be verified before administration.

The author thanks Christine Henderson for manuscript preparation and Nancy Arora for editorial review.

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