Ventricular Arrhythmias, Part III: Benefits And Risks Of Antiarrhythmic Therapy

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Abstract: In Parts I and II of this series, clinical significance, prevalence, and special concerns in the evaluation of patients with ventricular arrhythmias were reviewed. We now examine the categories of antiarrhythmic drugs and offer indications for their use. Reasons why a patient may not respond to antiarrhythmic therapy, end points of therapy, and the benefits and drawbacks of measuring serum drug levels are addressed. Use of newer drugs and additional treatment modalities are discussed in the final installment. (J Am Bd Fam Pract 1988; 1:255-66.)

In previous installments of this series, we classified ventricular arrhythmias as benign, potentially lethal, or lethal depending on their clinical significance. *Benign* ventricular arrhythmias occur in persons without underlying heart disease. They place the person at minimal increased risk of dying suddenly from an arrhythmia. Underlying heart disease is present in patients with both *potentially lethal* and *lethal* ventricular arrhythmias. The former is the largest group, and these persons have a moderate-to-high risk of dying suddenly from arrhythmias. The highest risk of sudden death is in the small group of patients with lethal ventricular arrhythmias and includes survivors of sudden cardiac death who have a 2-year, 50 percent recurrence rate unless effective treatment is instituted.

Potential benefits of antiarrhythmic therapy must always be balanced against the potential risks of such treatment (Table 1). This is especially true for asymptomatic patients who have benign or potentially lethal ventricular arrhythmias, because the benefit of treating such persons has never been proved.

Antiarrhythmic medications are associated with a high frequency of adverse effects with long-term use.[1,2] In addition to the common side effects noted in Table 2 is the reality that treatment is costly, long-term compliance is often poor, the benefit of therapy is questionable, and the drugs that are used may sometimes worsen the very arrhythmia that one is trying to suppress.[2-4]

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Classification of Antiarrhythmic Drugs

The most commonly used method for classifying antiarrhythmic drugs is the Vaughan-Williams system,[5] which divides the agents into four categories (Table 3). The largest group is made up of the local anesthetic agents (class I). These drugs exert a membrane-stabilizing effect and retard depolarization of the cardiac cell membrane by restricting entry of the fast sodium current (sodium-channel blockers). This results in a reduction of spontaneous automaticity. Class I agents are subdivided according to their effect on the action potential of cardiac cells.

Class IA drugs moderately slow the upstroke velocity of the action potential and significantly prolong repolarization. This latter effect is responsible for the Q-T interval prolongation characteristic of these agents. Conduction velocity is only slowed to a moderate degree. Included among the class IA drugs are quinidine, procainamide, and disopyramide.

In contrast, *class IC* drugs (flecainide, encainide) profoundly slow conduction and markedly depress the upstroke velocity of the action potential. They only exert a minimal effect on repolarization. As a result, the P-R and QRS duration may be significantly prolonged, but the Q-T interval per se is usually not greatly affected.

The lidocaine cogeners (tocainide, mexiletine) make up *class IB*. They may increase fibrillation

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Table 1. *Pros and Cons of Antiarrhythmic Therapy.*

Pros
Symptoms may be relieved
The risk of sudden cardiac death may be lessened
Cons
Cost
Need for follow-up monitoring
Poor long-term compliance in many patients
Questionable efficacy of treatment
Induction of a proarrhythmic effect in up to 10 percent of patients (especially with quinidine, procainamide, and disopyramide)
Adverse effects of antiarrhythmic drugs

threshold but have little effect on conduction velocity or repolarization. Consequently, they do not alter electrocardiographic intervals.

The other three classes in the Vaughan-Williams system are the beta-blockers (class II), antifibrillatory agents that also prolong repolarization (class III), and the calcium-channel blockers (class IV). Although calcium-channel blockers may be extremely useful in the treatment of supraventricular arrhythmias, they are not effective for ventricular arrhythmias.

Conventional Antiarrhythmic Agents

Quinidine and procainamide are two class IA antiarrhythmic agents that have withstood the test of time. Each was introduced more than 35 years ago. Despite development of newer agents, many clinicians continue to select one of these drugs as their first choice for antiarrhythmic therapy. With the introduction of disopyramide in 1977, a third drug with similar therapeutic properties became available in this class. All three of these agents are effective in the treatment of ventricular and supraventricular arrhythmias, and the

Table 2. *Adverse Effects of Antiarrhythmic Drugs.*

Quinidine
Gastrointestinal side effects (nausea, vomiting, diarrhea, anorexia)
Fever
Skin rash
Increased tendency to bleeding (by causing thrombocytopenia, vitamin K antagonism, or by interfering with action of coumadin)
Cinchonism (dizziness, tinnitis, blurred vision, headache, tremor)
Procainamide
Drug-induced, lupus-like syndrome (fever, malaise, arthralgia or arthritis, pleural or pericardial effusions)
Gastrointestinal side effects (nausea, vomiting)
Neutropenia
Disopyramide
Significant anticholinergic side effects (constipation, dry mouth, blurred vision, urinary hesitancy or retention)
Negative inotropic effect
Propranolol and other B-blockers
May precipitate bronchospasm
Negative inotropic effect, bradycardia
May mask hypoglycemic effect in diabetics
Insomnia, nightmares
Weakness, fatigue
Tocainide
Gastrointestinal side effects (nausea, vomiting, anorexia, constipation)
Neurologic side effects (headache, dizziness, paresthesia, tremor)
Skin rash
Agranulocytosis
Pulmonary fibrosis
Mexiletine
Gastrointestinal side effects (nausea, vomiting)
Neurologic side effects (dizziness, tremor, blurred vision, coordination difficulties)
Flecainide
Neurologic side effects (dizziness, headache, blurred vision)
Nausea
Negative inotropic effect
Aggravation of conduction system disturbances
Encainide
Neurologic side effects (dizziness, headache, diplopia, ataxia, tremor)
Nausea
Metallic taste
Aggravation of conduction system disturbances
Amiodarone
Gastrointestinal side effects (nausea, vomiting, anorexia)
Neurologic side effects (ataxia, tremor, dizziness)
Photosensitivity
Blue-gray skin discoloration
Corneal microdeposits
Hyperthyroidism or hypothyroidism
Liver function abnormalities
Pulmonary fibrosis
Multiple drug interactions (with warfarin, digoxin, beta-blockers, quinidine, procainamide)
Bradyarrhythmias (sinus node dysfunction, AV block)

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choice among them is usually determined by their side-effect profile and the personal preference of the treating physician.

Quinidine

Gastrointestinal symptoms are the most common limiting feature of the various quinidine preparations. Lowering the dose, using the more expensive gluconate or polygalacturonate forms instead of quinidine sulfate, and taking the drug with an aluminum-containing antacid may reduce the frequency of diarrhea. Other noncardiac adverse reactions include fever, skin rash, clotting-factor abnormalities, and cinchonism. Although torsades de pointes may develop with any of the class IA agents, it is most likely to occur in patients receiving quinidine. Despite these shortcomings, quinidine has remained the most commonly used antiarrhythmic agent.

Table 3. *The Vaughan-Williams Classification of Antiarrhythmic Agents.*

Class I (local anesthetics)	
Subclass IA	
Quinidine*‡	
Procainamide*‡	
Disopyramide*‡	
Subclass IB	
Tocainide*	
Mexiletine*	
Subclass IC	
Flecainide*	
Encainide*	
Class II (beta-blockers)	
Acebutolol*‡	Nadolol
Atenolol	Pindolol
Esmolol‡	Propranolol*‡
Metoprolol	Timolol
Class III	
Bretylium*	
Amiodarone†	
Sotalol	
Class IV (calcium-channel blockers)	
Verapamil‡	
Diltiazem	
Nifedipine	

*Approved for treatment of ventricular arrhythmias.

†Approved for treatment of life-threatening ventricular arrhythmias that have not responded to adequate trial with other antiarrhythmic agents.

‡Approved for treatment of supraventicular arrhythmias.

Procainamide

Gastrointestinal symptoms may be prominent with procainamide. In addition, it may cause neutropenia. However, drug-induced systemic lupus erythematosus (SLE) appears to be the most frequent reason some clinicians avoid the drug. Others use procainamide almost exclusively for patients in need of short-term antiarrhythmic therapy, because the risk of developing antinuclear antibody (ANA) appears directly related to the length of treatment.[6] After 1 year of therapy, ANA titers will be positive for as many as 80 percent of patients.[7]

The meaning of positive ANA titers is unclear, and controversy still exists whether this indicates a need to discontinue the drug. Clinically, the syndrome of drug-induced SLE includes fever, myalgias, arthritis, pleurisy, and pericarditis. Fortunately, the renal vasculitis of systemic lupus erythematosis does not occur with the procainamide-induced form of the disease. Many patients with positive ANA titers never develop any of the above symptoms, and when symptoms do occur, they usually disappear after the drug is stopped. It may, therefore, be reasonable and cost-effective to use procainamide as long as patients remain well. ANA titers need not necessarily be checked routinely.[8]

Disopyramide

Many clinicians consider disopyramide as second-line therapy to quinidine and procainamide. Their reluctance to use the drug is probably from concern for its anticholinergic side effects and negative inotropic action. With careful patient selection, however, the drug is usually well tolerated by most patients. It should not be given to patients with obstructive uropathy or glaucoma or when there is any evidence of impaired left ventricular function.[9,10] Administration of a loading dose is no longer recommended because the cardiac output of otherwise normal persons may be depressed by this practice.[9] Instead, one should begin with a low dose and increase the amount in a very gradual manner. If these precautions are followed, the chances of precipitating heart failure or disabling anticholinergic side effects are greatly reduced. The sustained release form of this drug may further improve patient tolerance because it allows doses twice a day and eliminates the peaks and troughs inherent with more frequent administration.

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Special Considerations for the Use of β-Blocking Agents

A case may be made for considering β-blocking agents as the initial drug for therapy of ventricular arrhythmias.* Although not as effective as class IA antiarrhythmic agents for suppression of premature ventricular contractions (PVCs), β-blockers are usually better tolerated than other agents and less likely to produce a proarrhythmic effect. In addition, they are the treatment of choice for symptomatic patients with mitral valve prolapse (MVP), idiopathic hypertrophic subaortic stenosis (IHSS), and arrhythmias due to exercise or excessive sympathetic stimulation. When more than one drug is needed for control of an arrhythmia, β-blockers are excellent adjunctive agents to combine with class IA drugs. Moreover, β-blockers (propranolol,[11] timolol,[12] and others) have been shown to lower mortality following myocardial infarction. Whether this is due to reduction of myocardial oxygen demand, relief of ischemia, blunting of catecholamine effect, prevention of stress-induced hypokalemia, or their modest antiarrhythmic effect is not known.

Consideration should be given to Holter monitoring patients following acute myocardial infarction before they are sent home from the hospital. If PVC frequency on this predischarge Holter is moderate (between 3–10 PVCs per hour) and minimal complex forms are noted, one might elect to start β-blocker therapy with the dual aim of controlling the arrhythmia and reducing the risk of reinfarction. With more frequent ventricular ectopy (> 10 PVCs per hour) or a high prevalence of complex forms, consider substituting or adding another drug such as tocainide, mexiletine, or a class IA agent to the regimen.

A number of investigators have suggested that psychological stress is a risk factor for sudden cardiac death for persons with or without underlying structural heart disease.[13] The proposed mechanism predisposing to this risk is stimulation of the sympathetic nervous system. Solitary β-blocker therapy appears to be extremely effective for controlling symptoms in such persons and in reducing the frequency and severity of potentially lethal ventricular arrhythmias.[13]

*Propranolol is the prototype β-blocking drug for treatment of ventricular arrhythmias. Although other β-blockers are also effective, there is less experience with them, and few of these drugs have been approved in this country.

Tocainide and Mexiletine

Recently, tocainide and mexiletine have been added to the list of conventional antiarrhythmic drugs available for use in this country. These oral analogs of lidocaine belong to the type IB class of antiarrhythmic agents. As such, they have little effect on P-R, QRS, and Q-T intervals. Consequently, they may be safely used in patients with Q-T interval prolongation without fear of inducing torsades de pointes. Other proarrhythmic effects are also relatively uncommon.[14]

Both drugs are absorbed well, and peak serum concentrations are reached within several hours. Adverse effects are principally neurologic or gastrointestinal (Table 2). The former occur more frequently with tocainide, while the latter occur more often with mexiletine. Although neither tocainide nor mexiletine is active against supraventricular arrhythmias, both drugs are effective in suppressing ventricular arrhythmias that responded to therapy with intravenous lidocaine.[14-16] However, the response to one of these agents does *not* predict the antiarrhythmic response to the other.[17] Even though a patient fails to respond to one of these drugs, it may still be reasonable to try the other.

Treatment with tocainide is usually begun with a dose of 400 mg administered three times daily. This may be increased to 600 mg three times daily. When there is renal impairment, a dose twice a day suffices. Gastrointestinal and neurologic side effects occur in 30–40 percent of patients. The latter appear to be dose-related and often decrease with time.[18] When mild, gastrointestinal side effects may be minimized by taking the drug with food or antacid or by administering smaller doses more frequently.[15,16] Adverse effects are severe enough to warrant discontinuation of the drug in 10–20 percent of patients. Because case reports of agranulocytosis have been noted, it is prudent to monitor blood cell counts for the initial months of therapy.[15,16,19]

Mexiletine may be started with a dose of 150 or 200 mg administered three times daily. Most patients' arrhythmias are controlled with 600–900 mg per day; the maximum daily dosage is 1200 mg. Because of extensive hepatic metabolism, doses twice daily may suffice for patients with impaired liver function. The efficacy of this drug has been highly variable in studies to date, with satisfactory control of ventricular arrhythmias being achieved for 30–90 percent of patients.[20-23] The efficacy of mexiletine or tocainide

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may be enhanced when used in combination with other antiarrhythmic agents such as quinidine. In addition to improving antiarrhythmic effect, combining class IA and class IB drugs may allow a lower dose of each drug and therefore result in a reduction of side effects.[21,22,24] Adverse reactions to mexiletine may be reduced by taking the drug with food or antacid or by lowering the dose. Drug discontinuation is necessary for 10–40 percent of patients.[14,25]

The two class IB agents represent an important addition to the antiarrhythmic repertoire. The drugs are well tolerated in many patients and show moderate efficacy against ventricular arrhythmias that are not life threatening, especially those suppressed by lidocaine. Proarrhythmic effects are relatively uncommon, and the Q-T interval prolongation seen with the class IA agents does not occur. Because of the potential for tocainide to produce agranulocytosis, selection of mexiletine should be favored when the decision is made to choose an agent in this class.

Newer Antiarrhythmic Agents

Three extremely potent agents that have recently been approved for antiarrhythmic therapy are flecainide, encainide, and amiodarone. In general, their use has been reserved for patients who have not responded to the drugs discussed above. Each of these agents is examined in detail in the final installment of this series.

Reasons Why a Patient May Not Respond to Antiarrhythmic Therapy

Once the decision is made to institute antiarrhythmic therapy, it is important to keep in mind the reasons why patients may not respond favorably to treatment (Table 4). It is often assumed that if a patient is receiving a therapeutic dose of an antiarrhythmic agent and is tolerating the drug, the arrhythmia will be suppressed. Unfortunately, this is not necessarily the case. Under the best of circumstances, conventional antiarrhythmic agents are no more than 70 percent effective in achieving a statistically significant decrease in PVC frequency when used to treat patients with chronic ventricular arrhythmias.[18] Success rates are significantly less for treatment of more unstable patients with lethal ventricular arrhythmias or impaired left ventricular function or both. In addition, the risk of inducing a proarrhythmic effect becomes correspondingly greater for this latter group of patients.[18]

Table 4. *Reasons for an Inadequate Response to Antiarrhythmic Therapy.*

- Wrong Drug
  - Proarrhythmic effect
  - Inefficacy of drug
    - Quinidine, procainamide ≈ 50–70 percent efficacy
    - Disopyramide ≈ 50–60 percent efficacy
    - Tocainide, mexiletine ≈ 50 percent efficacy
    - Propranolol ≈ 30–50 percent efficacy
      - BUT — the above figures are for *chronic* ventricular arrhythmias! (For unstable patients with impaired LV function and lethal ventricular arrhythmias, the success rates of these drugs are considerably lower [only in the range of 10–25 percent success]).
- Right drug — wrong dose
  - Subtherapeutic dose prescribed
  - Drug interaction
- Right drug — poor compliance due to
  - Undesirable side effects
  - High cost of medication
  - Inconvenient (i.e., too frequent) dosing
  - Inadequate patient motivation to take the drug
  - Lack of patient conviction about the need for therapy and the benefits of treatment
- Right drug — other problem causing PVCs
  - Extracardiac factors
    - Stimulants — smoking, alcohol, caffeine, diet pills, over-the-counter sympathomimetics (i.e., cough/cold remedies)
    - Stress
    - Insufficient sleep
  - Metabolic abnormality (i.e., decreased K^+, Mg^{++})
  - Acute ischemia (i.e., angina pectoris, coronary spasm, silent myocardial ischemia)
  - Congestive heart failure
- Dissociation between dysrhythmic and antifibrillatory effect
  - A decrease in PVCs does *not* necessarily result in protection againt VT/VF

Even if the "right" drug is chosen for therapy, there are still a number of reasons why an antiarrhythmic agent may not be effective. These include inadequate doses, the interaction of one drug with another, poor compliance, persistence of unrecognized extracardiac factors, uncorrected metabolic abnormalities, and coexistent ischemia or congestive heart failure (Table 4).

Drug interactions are often subtle. For example, phenytoin, phenobarbital, and rifampin may enhance hepatic metabolism of quinidine, resulting in decreased serum concentrations of this agent.[7] Conversely, increases in serum concentrations of

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quinidine have been reported when either cimetidine or nifedipine are used concomitantly.[26,27]

Quinidine may markedly increase serum digoxin concentrations. On the average, the addition of quinidine results in a doubling of the serum digoxin level. In some patients, however, no effect is seen, while in others up to a sixfold increase in serum digoxin levels may occur.[28] The effect is believed to be due to displacement of digoxin from tissue-binding sites or from impaired renal clearance of the drug or both.[7,29] Unfortunately, it is impossible to predict how quinidine will affect the serum digoxin level in any given patient. Many clinicians routinely halve the digoxin dose when quinidine is added. Others prefer not to alter the dose but to monitor serum drug concentrations closely. Regardless of which tack is chosen, unless there is awareness of the digoxin-quinidine interaction, ventricular arrhythmias may be precipitated by the development of digitalis toxicity.

Digoxin levels may also be increased with concomitant use of calcium-channel blockers. The greatest effect seems to occur with verapamil. Up to a 70 percent increase in steady-state serum digoxin concentrations is seen when this drug is added to digoxin.[30] A lesser effect is seen with nifedipine, while diltiazem has the least effect and probably does not increase serum digoxin concentrations greatly.[30,31]

In the acute care setting, the high first-pass metabolism of lidocaine makes this drug susceptible to interactions with agents that impair hepatic blood flow. Concomitant use of either cimetidine or propranolol may markedly increase the half-life of lidocaine and lead to toxicity.[7,32]

The final reason for an inadequate response to antiarrhythmic therapy is due to the potential discrepancy that may exist between *dysrhythmic* and *antifibrillatory* effects of antiarrhythmic medications. Decreasing both the frequency and complexity of ventricular ectopy does *not* necessarily reduce the risk of dying from a cardiac arrhythmia. This disturbing finding was reported by Ruskin, et al. in a study where a small subset of patients developed an increased susceptibility to ventricular tachycardia/fibrillation despite a greater than 90 percent reduction in PVC frequency.[4] Similar findings have been noted by others.[33] Thus, the usual methods of monitoring may sometimes deceive one into thinking that a good clinical response is being achieved (i.e., the number of PVCs dramatically decreases), when in fact the opposite may be occurring (i.e., the patient becomes more susceptible to developing ventricular tachycardia/fibrillation). How frequently this discrepancy between the dysrhythmic and antifibrillatory effect occurs in clinical practice is unknown. In the Ruskin study in which survivors of sudden cardiac death were examined, it was seen in less than 5 percent of patients. It probably occurs even less often in patients who are treated for arrhythmias that are not life threatening. Nevertheless, the fact remains that antiarrhythmic medications (particularly class IA antiarrhythmic agents) may actually *cause* cardiac arrest in a small number of predisposed persons. Use of antiarrhythmic drugs must never be taken lightly.

End Points of Therapy

Because antiarrhythmic agents have the potential for exacerbating ventricular arrhythmias, the clinician is left with the dilemma of determining a suitable end point of therapy (Table 5). Severity of the arrhythmia, its effect on the patient, cost, compliance with and tolerance of antiarrhythmic treatment, and availability of other therapeutic modalities are factors that influence this decision.

For example, control of symptoms would not be an acceptable end point of therapy for a patient who has sustained an out-of-hospital cardiac arrest, because subjective relief of symptoms is not necessarily correlated with control of this life-threatening arrhythmia. On the other hand, control of symptoms might be a perfectly appropriate and cost-effective end point for the management of a benign ventricular arrhythmia that was merely bothersome to the patient.

The ideal goal of antiarrhythmic therapy would seem to be total elimination of PVCs. Although this end point may be attainable when ventricular ectopy is infrequent, it is much more difficult (if

Table 5. *Potential End Points of Antiarrhythmic Therapy.*

Control of symptoms
Total elimination of PVCs
Partial suppression of ventricular arrhythmias, especially of the most worrisome forms
Maintenance of consistently therapeutic antiarrhythmic blood levels
Prevention of ventricular tachycardia induction by PES studies
Implantation of an automatic cardioverter-defibrillator

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not impossible) to achieve for most patients with lethal ventricular arrhythmias. The overwhelming majority of these persons show extremely frequent and complex ventricular ectopy that cannot be completely suppressed by any antiarrhythmic therapy. Considering the discrepancy that may exist between dysrhythmic and antifibrillatory effects of antiarrhythmic medications, even if significant suppression of PVCs could be achieved, protection from sudden cardiac death would *not* necessarily be assured.

Optimal management of high-risk patients with lethal ventricular arrhythmias should probably include invasive evaluation with programmed electrophysiologic stimulation (PES) studies or with implantation of an automatic cardioverter-defibrillator (AICD) or both. Unfortunately, implementation of these modalities is expensive and requires facilities that are not available in many parts of the country. An alternative for management that we have found attractive is the empiric approach proposed by Myerburg.[34,35] His data suggest patients with ventricular arrhythmias have improved long-term survival when consistently therapeutic antiarrhythmic blood levels are maintained regardless of whether PVC frequency is significantly reduced. Although far from optimal, partial reduction in PVC frequency with elimination of the most worrisome forms and maintenance of therapeutic antiarrhythmic drug levels may be a realistic and reasonable end point when sophisticated alternatives are not available.[36]

Benefits and Drawbacks of Monitoring Antiarrhythmic Drug Levels

In general, antiarrhythmic agents operate within a fairly narrow range of serum drug concentrations where a favorable balance exists between antiarrhythmic activity and adverse effects. Serum drug levels have been empirically defined as subtherapeutic, therapeutic, or toxic depending on whether they are below, within, or beyond this "therapeutic window." A major advantage of measuring serum drug levels, therefore, is to provide an indication of whether the amount of antiarrhythmic drug in the circulation is adequate (Table 6).

The therapeutic range for any given drug is a statistical calculation of the *average* range of serum concentrations at which a drug is effective and its side effects are minimal. It provides only rough guidelines for treatment and does not give definitive information for a particular patient. Marked differences in tolerance and response to a drug make individualization of antiarrhythmic therapy essential.[7,36]

Table 6. *Benefits and Drawbacks of Monitoring Antiarrhythmic Drug Levels.*

Benefits
Allows correlation of peak drug activity to antiarrhythmic effect
May suggest toxicity, proarrhythmic effect, or both
Achievement of therapeutic drug levels may serve as a desirable end point of antiarrhythmic therapy
Detects noncompliance
Drawbacks
Cost
Inappropriately timed drug level may give misleading results (trough levels drawn before next dose are preferred)
Potential misinterpretation of actual drug level obtained
Quinidine
Active metabolites are frequently not measured
Lower doses are required in the presence of congestive heart failure, liver or renal disease, and for the elderly
Procainamide
Peak rather than trough levels are sometimes obtained when blood is sampled just before the next dose
Potentially active metabolite NAPA has unusual pharmacokinetics
Disopyramide
Protein binding (and amount of free "active" drug) varies depending on dose of drug

Monitoring serum drug levels allows correlation of peak drug activity with antiarrhythmic effect on Holter monitoring. For example, if drug levels are subtherapeutic at a time when arrhythmia suppression is unsatisfactory, the dose may be increased until a therapeutic level is attained or satisfactory control of the arrhythmia is achieved. If, on the other hand, the arrhythmia is worsened despite therapeutic levels of a drug, a proarrhythmic effect may be suspected. Maintenance of therapeutic antiarrhythmic blood levels may be a desired end point of therapy for selected patients in whom total suppression of ventricular ectopy is not feasible. Because different drug levels may be needed to control different arrhythmias, a greater dosage is usually required for total abolition of ventricular ectopic activity than for reduction of complex forms.[36]

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Table 7. *Practical Pharmacokinetic Information on Approved Antiarrhythmic Agents.*

Generic Drug (Class)	Trade Name	Available Oral Dose (mg)	Usual Starting Dose & Frequency	Usual Range of Oral Dose (mg/day)	Suggested Therapeutic Serum Level[1]
Quinidine (IA)	Quinidine Sulfate	200, 300 (The 300 mg tablet contains 249 mg of active quinidine)	200–300 mg q6–8 hr	800–1800	2–6 μg/mL[3]
	Quinidex Extentabs (Sulfate)	300 (= 249 mg of active quinidine)	1–2 tabs q8–12 hr	900–1800	same
	Quinaglute Dura-tabs (Gluconate)	324 (= 202 mg of active quinidine	same	648–2000	same
	Duraquin (Gluconate)	330 (= 206 mg of active quinidine)	same	660–2000	same
	Cardioquin (Polygalacturonate)	275 (= 200 mg of active quinidine)	same	550–1700	same
Procainamide (IA)	Procainamide or Pronestyl	250, 375, 500	375–500 mg q3–4 hr	1500–4000	Procainamide level = 4–10 μg/mL
	Procan SR	250, 375, 500, 1000	500–750 mg q6–8 hr	same	NAPA + procainamide level = 10–30 μg/mL
	Pronestyl-SR	500	500–1000 mg q6–8 hr	same	
Disopyramide (IA)	Norpace	100,150	100 mg q6 hr	200–600	2–6 μg/mL
	Norpace CR	100,150	100–300 mg q12 hr	same	same
Tocainide (IB)	Tonocard	400, 600 scored tablets	400 mg q8 hr	900–1800	4–10 μg/mL
Mexiletine (IB)	Mexitil	150, 200, 250	150–200 mg q8 hr	450–900	0.5–2.0 μg/mL
Flecainide (IC)	Tambocor	100 mg (scored) tablets	100 mg q12 hr	200–400	0.2–1.0 μg/mL
Encainide (IC)	Enkaid	25, 35, 50	25 mg q8 hr	75–200	100–400 μg/mL
Propranolol (II)	Inderal[6]	10, 20, 40, 60, 80[7]	20 mg q6–8 hr	60–320	Not usually measured

[1]For optimal monitoring, *trough* rather than peak levels of antiarrhythmic agents should be followed and maintained within the therapeutic range. The therapeutic range may vary slightly from one laboratory to the next.

[2]Ideally, serum drug levels should not be drawn until steady-state conditions have become established (i.e., until at least 5 half-lives of drug have passed). If blood is sampled before this time, misleadingly low levels may be seen.

[3]A number of cardioactive quinidine metabolites are not detected by standard assay techniques. Because these metabolites are most likely to accumulate in the elderly and in those with renal impairment, therapeutic serum trough levels may be as low as 0.08 μg/mL in these persons.

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Table 7. *Practical Pharmacokinetic Information. (Continued from previous page.)*

Time to Peak Concentration	Half-Life	Time to Steady-State Concentration[2]	Special Points	
1 hr	Average ≈ 6 hrs (1.6–16 hr range)	30–45 hrs	*Short-acting form* Less expensive; quick peak effect compared to other preparations	Absorption more complete with sulfate forms All dosages of quinidine preparations should be decreased in presence of congestive failure, liver or renal disease, and in the elderly Gluconate and polygalacturonate forms have a lower incidence of GI side effects
3–5hrs	same	same	*Sustained-release forms*[4] Allow bid dose Diarrhea may be lessened by taking an aluminum-containing antacid (i.e., Amphogel™, Alternagel™	
5 hrs	same	same		
same	same	same		
same	same	same		
1–1.5 hrs	Procainamide ≈ 3–5 hrs	30–60 hrs[5]	*Short-acting forms* Less expensive	NAPA levels are increased in fast acetylators and in those with renal impairment Drug-induced lupus is less likely when NAPA level is high
2–4 hrs	NAPA ≈ 6–10 hrs	same	*Sustained-release forms* Allow tid, qid dose Breaking, crushing or chewing tablets will interfere with sustained release effect	
same		same		
2–3 hrs	Average ≈ 7 hrs (4–10 hr range)	30–45 hrs		With higher doses, protein binding is less, and the amount of free (i.e., active) drug increases
2.5–4.5 hrs	same	same	*Sustained-release form* Allows for bid dose Adverse effects minimized by beginning at a low dose	Contraindicated in congestive heart failure
0.5–2 hrs	Average ≈ 15 hrs (11–17 hr range)	75–90 hrs	GI side effects may be lessened by taking the drug with food and antacids and/or by lowering the dose and giving the drug more frequently Half-life with renal failure increases to as much as 30 hrs (i.e., bid dose should be used in these patients)	
1–3 hrs	Average ≈ 11 hrs (8–14 hr range)	48–72 hrs	GI side effects may be lessened by taking the drug with food and antacids, by lowering the dose and giving the drug frequently, or both The drug undergoes extensive hepatic metabolism, so doses are needed less frequently with liver impairment	
3 hrs	Average ≈ 13 hrs (up to 24 hrs)	72–120 hrs	Almost completely absorbed following oral administration Drug dose increases should be made slowly (not more often than every 72–96 hrs) A lower starting dose (50 mg qd or bid) should be used for patients with significantly impaired renal function Plasma monitoring is effective because there are no significant active metabolites	
1–2 hrs	1.6–4 hrs	72–120 hrs	Usually well absorbed following oral administration Drug dose increases should be made slowly (not more often than every 72–96 hrs) A lower starting dose (25 mg qd or bid) should be used in patients with significantly impaired renal function Plasma drug levels are difficult to interpret due to the antiarrhythmic activity of encainide metabolites	
1–1.5 hrs	3–6 hrs	15–40 hrs	β-blockers tend to have the most favorable side effect profile among the antiarrhythmic agents	

[4]Quiniday™, a sustained-release preparation of quinidine sulfate (A.H. Robins Co.) with the potential for a once-a-day dose has become available for study. It should be released for general use in the near future.[40]

[5]The time to reach steady-state conditions becomes closer to the upper limit of this range as the amount of NAPA increases.

[6]Although a sustained-release form of propranolol is available (Inderal LA™), it has not been approved for the treatment of cardiac arrythmias.

[7]The patent for propranolol expired in 1985, so that a number of generic forms have become available.

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One of the most important benefits of monitoring serum drug levels is that the results indicate whether a patient is actually taking the drug. Squire, et al. studied 98 consecutive patients receiving long-term oral antiarrhythmic therapy in an ambulatory cardiology clinic.[37] Despite adequate doses, more than 75 percent of the patients treated with quinidine or procainamide had serum drug concentrations that were *less* than 50 percent of the recommended minimal therapeutic level. Even among patients who claimed to have taken their last dose of medication within 6 hours of blood sampling, a majority still had subtherapeutic levels. These results suggest that noncompliance with long-term antiarrhythmic therapy is probably more common than is generally appreciated. It may be the *most* frequent explanation for an inadequate response to antiarrhythmic therapy.

Monitoring serum drug levels of antiarrhythmic agents is not without drawbacks (Table 6). The cost is appreciable (approximately $30 per level); multiple determinations are often required; and the actual level obtained may be misinterpreted.

Appropriate timing for blood sampling is critical. Monitoring is best accomplished during steady-state conditions. *Trough levels* (obtained just before the next dose) are ideal, because they indicate the lowest level of medication during a particular interval. Concentrations obtained 1 to several hours after the patient receives the dose are much more difficult to interpret because sampling during the time of peak absorption may have little to do with the steady-state concentration of a drug.

For unknown reasons, some patients on procainamide have peak rather than trough levels when blood is sampled before the next dose.[38] Multiple sampling techniques are occasionally needed to avoid inappropriate interpretations of drug concentrations in these patients.

Other vagaries in interpreting serum drug levels include alterations in protein binding and the pharmacologically active metabolites of the drugs. For example, hepatic metabolism of quinidine produces several cardioactive metabolites.[7] Because different types of assays for quinidine drug concentrations vary in their sensitivity for detecting the active metabolites, the recommended therapeutic serum level for quinidine may vary from one laboratory to the next. In general, active metabolites of quinidine tend to accumulate more in elderly patients and in those with renal impairment.[7,39] For these persons, a level of 0.8μg/mL may be therapeutic even though standard recommended serum concentrations are usually higher (i.e., on the order of 2–6 μg/L).

The important metabolite of procainamide is N-acetylprocainamide (NAPA). At one time, consideration was given to marketing NAPA as a separate antiarrhythmic agent, but recent data suggest that its antiarrhythmic activity is of little clinical significance. NAPA has a much longer half-life than the parent compound, and it accumulates more in people who are fast acetylators, a genetically determined trait. It also accumulates in patients with impaired renal function. Antiarrhythmic activity of NAPA may become clinically significant at high levels, and for this reason both procainamide and NAPA levels should be monitored.[8]

The final factor in interpreting antiarrhythmic blood levels is the degree of protein binding of the drugs. This is particularly important for disopyramide, because the amount of free (active) drug varies with protein binding and dose. With higher doses, there is less protein binding and greater amounts of free drug in circulation.[6] Because serum levels indicate total circulating drug (but not *free* drug), patients may conceivably become toxic despite having "therapeutic" concentrations of disopyramide. Similarly, protein binding may be important when quinidine is used. In the presence of liver disease, protein binding decreases,[39] and lower than usual blood levels should be sought.

Pharmacokinetic information to consider when prescribing oral antiarrhythmic agents is summarized in Table 7. Included are the dose forms available, usual initial and maintenance doses, suggested therapeutic drug levels, serum half-lives, the time to peak and steady-state concentration, and special points of interest.

In general, serum levels should not be obtained until steady-state conditions have been reached. This requires approximately 5 half-lives of the drug. Serum levels obtained before this time may be misleadingly low and deceive the clinician into thinking that the dose needs to be increased. For example, the average half-life of tocainide is 15 hours, so a serum level should not be obtained for *at least* 75 hours. With procainamide and its potentially cardioactive metabolite, NAPA, the half-life of the parent compound is shorter (3–5 hours) than that of NAPA (6–10 hours). Patients who are likely to accumulate NAPA (fast acetylators and those with

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renal impairment) will require a longer time to achieve equilibrium (up to 60 hours).

A final point shown in Table 7 is the required dose frequencies for the agents. The more frequently the drug must be given, the less likely a patient is going to be compliant in taking the medication.

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GLEANINGS FROM A COMMONPLACE BOOK — *NJP*

"The true aim of medicine is not to make men virtuous; it is to safeguard and rescue them from the consequences of their vices. The physician does not preach repentance; he offers absolution."
H.L. Mencken

"I hold it to be one of the distinguishing excellences of elective over hereditary succession, that the talents, which nature has provided in sufficient proportion, should be selected by the society for the government of their affairs, rather than this should be transmitted through the loins of knaves and fools, passing from the debauches of the table to those of the bed."
T. Jefferson

"Do you not know that disease and death must needs overtake us, no matter what we are doing, [or] what you wish to be doing, when it overtakes you. If you have anything better to be doing when you are so overtaken, get to work on that."
Epictetus

"An ideal cannot wait for its realization to prove its validity."
G. Santayana

"Much of the leadership of our profession seems to have been transumed from physicians of pride and clinical experience to those meretricious phrase-mongers and uplifters whose only baggage is voluminous but vacuous reports of 'task forces'."
N. Pisacano

Re Antibiotics: "The Lord hath created medicines out of the earth; and he that is wise will not abhor them."
Apocrypha (Ecclesiaticus)

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