Ventricular Arrhythmias, Conclusion: New Agents, Additional Treatment Modalities, And Overall Approach To The Problem

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Abstract: In this final installment, we discuss use of the newer antiarrhythmic agents and indications for additional treatment modalities such as programmed electrophysiologic stimulation (PES), surgery, and implantation of the automatic cardioverter-defibrillator. We conclude with our approach for evaluating the efficacy of antiarrhythmic therapy. (J Am Bd Fam Pract 1988; 1:267-73.)

We have discussed in previous articles that persons with *benign* ventricular arrhythmias do not have underlying disease and are not in need of antiarrhythmic treatment unless they are symptomatic because their risk of dying from an arrhythmia is minimal.[1,2] Persons with *potentially lethal* ventricular arrhythmias have underlying heart disease and face a moderate-to-high risk of sudden death; however, benefit from therapy has not been proved, and treatment with antiarrhythmic drugs is controversial.

We now turn our attention to those patients with *lethal* ventricular arrhythmias who are prone to frequent and complex ventricular ectopy that often resists even the most vigorous attempt at antiarrhythmic therapy. Because the risk of sudden cardiac death is so high for this group, most investigators agree on the need for aggressive treatment when standard measures fail (Table 1).

The initial priority should be to correct or eliminate extracardiac or exacerbating factors. Then, conventional antiarrhythmic drug therapy may be tried, with the goal of achieving and maintaining therapeutic blood levels. In selected cases, combination therapy (using drugs from different classes or occasionally from within the same class) may be effective when a single agent is not.[3,4] If these measures are unsuccessful and facilities exist for additional treatment, consideration should be given to the use of more potent or investigational agents, programmed electrophysiologic stimulation (PES) studies, surgery, or implantation of an automatic cardioverter-defibrillator.

Newer Antiarrhythmic Drugs

Among the antiarrhythmic agents listed in Table 1, flecainide and encainide deserve special mention. These drugs belong to class IC of the Vaughan-Williams system, and they markedly depress upstroke velocity of the action potential and profoundly slow conduction. Both P-R and QRS intervals may be significantly prolonged. However, unlike class IA agents, neither flecainide nor encainide exerts much effect on repolarization, and Q-T interval prolongation is minimal.*

Flecainide

Flecainide received approval from the U.S. Food and Drug Administration for treatment of ventricular arrhythmias in 1986. Although initially restricted to the use of the specialist, we believe that the drug merits consideration for use by the primary care physician. Flecainide exhibits many attractive features; it is extremely potent, and greater than 90 percent premature ventricular contraction (PVC) suppression is achieved in most patients, even when other agents have failed.[5,7] It also appears to be effective against supraventricular arrhythmias.[8-10] Doses may be administered

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*Although the Q-T interval may appear to widen, this is due principally to the drug's effect on depolarization (i.e., QRS duration) rather than to prolongation of repolarization per se.

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Table 1. *Modalties for Treating Lethal Arrhythmias.*

1. Treatment and/or elimination of extracardiac factors or exacerbating factors
2. Conventional antiarrhythmic agents (alone or in combination)
   - Quinidine
   - Procainamide
   - Disopyramide
   - Propranolol (and other β-blockers)
   - Tocainide
   - Mexiletine
3. More potent and investigational antiarrhythmic agents
   - Flecainide
   - Lorcainide
   - Encainide
   - Aprindine
   - Amiodarone
   - Propafenone
4. Programmed electrophysiologic stimulation studies
5. Surgery
   - Coronary artery bypass grafting
   - Cardiac transplantation
   - Aneurysectomy
   - Endocardial mapping with ablative surgery of arrhythmogenic focus
6. Automatic implantable cardioverter-defibrillator

twice a day because the drug has a long duration of action (half-life averages 20 hours). Monitoring antiarrhythmic blood levels is extremely useful, and the results are easy to interpret because there are no significant active metabolites. Patient tolerance of the drug is generally good, and adverse effects—nausea, headache, dizziness, and blurred vision—are usually not severe enough to warrant discontinuation.

Despite these advantages, flecainide has the potential to exacerbate ventricular arrhythmias. Although the risk of a proarrhythmic effect appears to be much less for stable patients without life-threatening ventricular arrhythmias, it approaches 10–15 percent for patients with hemodynamically significant ventricular arrhythmias or poor left ventricular function.[9,11] Unfortunately, this is the subset of patients most likely to receive the drug. In addition, flecainide may aggravate sinus node dysfunction, atrioventricular conduction disturbances, or congestive failure in predisposed persons. Careful patient selection and monitoring is therefore essential.

In the presence of normal renal function, treatment is begun with a dose of 100 mg twice daily. This may be increased by 50 mg twice daily every 4 days until efficacy is achieved. In general, one should aim for serum drug concentrations between 200–1,000 ng/mL and not exceed a daily dosage of 400 mg. Adverse effects increase markedly once the upper limit of this range has been surpassed. With renal failure, dosage must be markedly reduced, and therapy should be initiated with no more than 50 mg once or twice daily.

Encainide

Encainide is the most recently approved agent in the United States for treatment of ventricular arrhythmias. Like flecainide, this class IC drug is extremely potent, and its efficacy appears to be superior to that of quinidine; however, its potential for producing a proarrhythmic effect may also be greater.[12]

Encainide is well absorbed orally. The drug undergoes extensive hepatic metabolism to form a number of active metabolites that exert more antiarrhythmic activity than the parent drug in most patients. Because great variability exists among patients in their ability to metabolize the drug, serum drug levels are difficult to interpret.

Treatment with encainide is usually begun with a dose of 25 mg three times a day.[13,14] If necessary, this may be safely increased in several days to 35 mg and, eventually, to 50 mg three times daily. Because of the extremely long half-life of encainide metabolites, dosage adjustments should not be made more often than every 3–5 days. With renal impairment, the 25 mg initial dose needs to be given only once or twice daily.

In patients with normal renal function, 25 mg three times daily appears to be the lowest effective dose.[15] Clinical efficacy of the drug has been shown to improve when this dose is increased.[15] Although maximum dosages of 300 mg have been used to treat life-threatening ventricular arrhythmias, it is probably prudent to maintain daily dosages below 200 mg because adverse effects tend to occur when this amount is exceeded.[14]

Adverse effects of encainide include dizziness, visual disturbances, headache, nausea, and an 8–10 percent risk of a proarrhythmic effect. In many patients, noncardiac side effects are mild and abate with continued therapy or dose reduction.[16] The risk of arrhythmia exacerbation appears to be much less for patients with normal ventricular function and without life-threatening arrhythmias.[16] In addition, the use of more gradual dose titration and lower amounts of the drug have resulted in a reduced risk of the proarrhythmic effect.[17] Compared with flecainide, encainide's metabolism is more complex, making the drug more difficult to monitor. In addition, more

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frequent doses are needed. However, it offers a potential advantage over flecainide: it is much less likely to aggravate congestive heart failure.[14,17]

Until recently, the use of flecainide and encainide has been largely restricted to patients with lethal ventricular arrhythmias who have not responded to trials with other antiarrhythmic agents. This trend appears to be changing. As we have noted, the risk of developing a proarrhythmic effect from these two IC agents is greatest for patients with impaired left ventricular function or with hemodynamically significant ventricular arrhythmias. For these persons, it is probably most appropriate to initiate therapy with either a class IA or IB antiarrhythmic agent. Hospitalization for continuous electrocardiographic monitoring during drug titration may be needed. For ventricular arrhythmias that remain refractory to this approach, combination therapy or a trial with a IC agent is warranted.

In contrast, for outpatient management of symptomatic patients with benign or potentially lethal ventricular arrhythmias, many authorities now consider selection of a β-blocker or a class IC agent the preferred approach when ventricular function is normal. In general, for this subset of patients, both flecainide and encainide are better tolerated, more effective, and less likely to induce a proarrhythmic effect than are standard type IA agents such as quinidine.[11,18]

Some degree of QRS widening is a regular feature of class IC antiarrhythmic agents. This need not be cause for alarm as long as the increase in QRS duration does not exceed 50 percent of its baseline value. Flecainide and encainide are probably best avoided in patients with preexisting bundle branch block.

Amiodarone

The last antiarrhythmic agent to be discussed, amiodarone, is a unique drug in many ways. It is the first class III agent approved for oral antiarrhythmic therapy. Drugs in this class prolong the action potential duration of myocardial cells. In addition, amiodarone exerts a noncompetitive alpha and beta adrenergic blocking action and causes systemic and coronary vasodilatation.

The half-life of amiodarone is unusually long and has been reported to range from 20 to 100 days.[19] This has the advantage of eliminating fluctuating peaks and troughs of the drug while allowing once-daily doses and affording antiarrhythmic protection even if one or more doses are missed. The extended half-life of the drug may act as a double-edged sword, however, because onset of therapeutic effects and achievement of steady-state plasma concentrations can be delayed for 2 to 21 days.[19] Moreover, if toxic effects of the drug develop, they may persist for weeks after discontinuation.

Amiodarone is an exceedingly potent antiarrhythmic agent that is effective in up to 50 percent of patients with recurrent life-threatening ventricular arrhythmias, which are refractory to other treatment.[19-22] Extensive experience with the drug has been accumulated abroad both for this indication and for treatment of supraventricular tachyarrhythmias, especially in patients with Wolff-Parkinson-White syndrome. Unfortunately, adverse reactions are numerous.[19,23] The drug may cause gastrointestinal distress, neurologic side effects (ataxia, tremor, dizziness), photosensitivity, a bluish-gray discoloration of the skin, corneal microdeposits, hyperthyroidism, hypothyroidism, liver function abnormalities, bradyarrhythmias, a proarrhythmic effect, and pulmonary fibrosis. In addition, there are multiple drug interactions including warfarin, phenytoin, digoxin, beta-blockers, quinidine, procainamide, and diltiazem. At the present time, the Food and Drug Administration has restricted use of the oral preparation of amiodarone for the last-resort treatment of life-threatening ventricular arrhythmias that are refractory to other drugs. The parenteral formulation remains investigational. We believe that the seemingly endless side-effect profile of this drug and the need for meticulous and long-term patient monitoring make it unlikely that this agent will ever be used by the nonspecialist.

Additional Means of Treating Lethal Arrhythmias

Programmed Electrophysiologic Stimulation (PES) Studies

PES studies have been used to monitor the effectiveness of antiarrhythmic therapy in patients with lethal ventricular arrhythmias.[24-28] An intravenous electrode catheter is fluoroscopically guided into the right ventricle, and one or more ventricular extrastimuli are introduced at various points in the cardiac cycle in an attempt to induce ventricular tachycardia. Ability to induce this arrhythmia in the laboratory appears to

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be an excellent indicator of which patients are at greatest risk of its spontaneous occurrence. Unfortunately, PES studies are invasive, time-consuming, expensive, and not generally available. In addition, PES studies are successful in finding an effective drug in only about one-third of cases.[29,30] However, for those patients in whom induction of sustained ventricular tachycardia is no longer possible following administration of an antiarrhythmic agent, recurrence of the arrhythmia becomes much less likely when the drug is continued on a long-term basis.[27,28,30,31] In other persons, a beneficial response to PES testing may be achieved despite continued inducibility of ventricular tachycardia. Waller, et al. have shown that sudden death mortality may be substantially reduced in such patients if ventricular tachycardia becomes inducible at a slower rate that no longer produces severe hemodynamic symptoms.[32] In the event that no drug regimen is able to suppress inducibility of ventricular tachycardia completely, achievement of a beneficial response may prove to be an acceptable clinical alternative.[32]

A number of investigators have compared the effectiveness of PES studies and Holter monitoring in the management of patients with lethal ventricular arrhythmias. Holter monitoring is unsuitable for evaluation of at least 10 percent of patients with recurrent ventricular tachycardia because of the lack of frequent or complex ventricular ectopy on baseline recording. Among the others, a poor outcome is likely if malignant ventricular arrhythmias are not suppressible by Holter criteria. The problem is that up to 50 percent of patients whose frequent and complex ventricular ectopy is effectively treated by Holter criteria remain inducible if also tested by PES studies.[30] Prognosis is uncertain in these persons because arrhythmia control by Holter criteria does not guarantee a favorable outcome.

On the other hand, use of sufficiently sensitive PES testing (i.e., employing protocols that introduce as many as three extrastimuli) successfully induces ventricular tachycardia in up to 95 percent of patients with documented recurrence of this arrhythmia. Nevertheless, there are limitations to this procedure. In addition to invasiveness, lack of availability, cost, and modest effectiveness, one should be aware of the lack of standardization in PES testing protocols and the less than perfect reproducibility of results when similar patients are tested on different days. The efficacy of some of the newer antiarrhythmic agents (such as amiodarone) is difficult to evaluate by PES testing because prognosis may be improved despite persistent inducibility of ventricular tachycardia in the laboratory.[33] Finally, evaluation by PES studies may lack sensitivity in determining clinical efficacy because of a failure to assess the prevalence of the potential *trigger* for the arrhythmia. Ventricular tachycardia due to reentry may require the existence of both a *substrate* (the reentry circuit) and a triggering event (ectopic activity). Antiarrhythmic agents that dramatically reduce the frequency of ventricular ectopy therefore may improve the prognosis of certain patients even if they fail to alter the physiology of the reentry circuit.

In summary, many drawbacks are inherent in the use of both Holter monitoring and PES studies. Failure to suppress lethal ventricular arrhythmias by Holter criteria is often associated with poor outcome. Unfortunately, even successful control of lethal arrhythmias by Holter criteria does not guarantee a favorable outcome. Preventing inducibility of ventricular tachycardia by PES testing, if achievable, is usually associated with improved prognosis. Obtaining a beneficial response to PES testing (slowing the rate of ventricular tachycardia and decreasing hemodynamic symptoms) may be an acceptable clinical alternative in the event that noninducibility cannot be achieved. Holter monitoring facilitates outpatient follow-up after evaluation by PES testing, and use of both the Holter and PES testing may be superior to either technique used alone.[34]

Surgical Means of Treating Lethal Ventricular Arrhythmias

Occasionally, ventricular arrhythmias are refractory to all forms of medical management. In such cases, surgery or implantation of an automatic defibrillator may prove to be a viable alternative. If significant coronary artery disease is present and ischemia is the substrate for malignant ventricular arrhythmias, coronary artery bypass grafting may control arrhythmias by treating the underlying process. This is especially true for patients with exertion-induced ventricular tachycardia or ventricular fibrillation with severe proximal coronary artery stenoses and preserved left ventricular function.[3]

Another surgical option to consider is cardiac transplantation. Although viewed as an experimental procedure as recently as a few years ago,

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significant advances in immunosuppression, patient selection, management of complications, and myocardial preservation have led to a marked resurgence of interest in the technique.[35] As a result, more than 1,000 cardiac transplants were performed in 1985, and patients had a greater than 80 percent 1-year survival.[35] Cardiac transplantation may prove to be a viable option for a small number of selected patients with end-stage cardiomyopathy and life-threatening ventricular arrhythmias.

Segmental wall motion abnormalities (ventricular aneurysms) are common in patients with recurrent or sustained ventricular arrhythmias. Arrhythmias in these persons are rarely controlled by myocardial revascularization alone.[3] However, use of a technique known as endocardial mapping may allow localization of an arrhythmogenic focus responsible for the arrhythmia. Ideally, the area may then be surgically excised at the same time the aneurysm is resected.[28] In other instances, endocardial scarring will be the anatomic substrate for recurrent ventricular tachycardia. With intraoperative electrophysiologic mapping, precise localization of the arrhythmogenic focus may often be accomplished. Surgical ablation by endocardial resection or by cryothermia will result in control of the arrhythmia in up to 85 percent of patients, frequently without the need for subsequent antiarrhythmic therapy.[36-38]

The Automatic Implantable Cardioverter-Defibrillator

The final modality to consider for treatment of lethal ventricular arrhythmias is the automatic implantable defibrillator (AID). Since the first human implantation in 1980, the AID has undergone significant evolution and improvement in design. The device consists of a pulse generator that weighs approximately 300 grams and is implanted in the abdomen. Two defibrillating electrodes that also serve as sensors are positioned on the heart. Newer models include a bipolar right ventricular electrode that allows R-wave synchronization and cardioversion (i.e., automatic implantable cardioverter-defibrillator or AICD). The AICD is able to detect tachyarrhythmias and cardiovert or defibrillate depending on the rhythm sensed.

Survival rates of patients who have received implantable defibrillators have been truly remarkable. One-year mortality from sudden death is reduced to well below 10 percent compared with a 30–50 percent expected 1-year mortality rate for patients with lethal ventricular arrhythmias who are left untreated.[39-41] Currently, the device has been implanted in more than 400 patients in more than 40 centers across the country. Because of its phenomenal success, it holds promise of becoming even more widespread in its use within the very near future. However, implantation of an AICD is expensive and does require a thoractomy.

Evaluation of the Efficacy of Antiarrhythmic Therapy

Efficacy of the treatment plan chosen should be frequently assessed (Table 2). The first question to consider is how to classify the arrhythmia. Is it benign, potentially lethal, or lethal? Implicit within this classification is a clear understanding of whether the patient should be treated and, if so, why. The *only* reason to treat patients with benign ventricular arrhythmias is for symptom relief. Treatment of *asymptomatic* persons with benign or potentially lethal ventricular arrhythmias has never been shown to reduce the risk of sudden cardiac death and is therefore of unproved benefit. Exacerbation of the arrhythmia or development of adverse effects from the drug should prompt the clinician to reevaluate whether treatment should be continued.

Before initiating antiarrhythmic therapy, consideration should always be given to determine whether extracardiac or exacerbating factors are operative, because identification and elimination of such factors may occasionally obviate the need for antiarrhythmic medication. Once antiarrhythmic therapy is begun, it is essential to evaluate the effect of the drug on the patient. Is the medication being taken? (A randomly drawn blood level should answer this question.) If so, is the medication well tolerated? Or has treatment become worse than the disease? If symptoms were present from the arrhythmia, are they fewer with the drug? Finally, is the risk of sudden cardiac death less? (Although the clinician may not be able to answer this last question, it should still be asked!)

What is the end point of therapy for each patient? Control of symptoms? Total elimination of PVCs? Or partial suppression of PVCs with elimination of the most worrisome forms? This latter goal is often a much more realistic one than trying to abolish all PVCs. When combined with maintenance of therapeutic antiarrhythmic blood levels,

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Table 2. *Evaluation of the Efficacy of Antiarrhythmic Therapy.*

1. How should the arrhythmia be classified?
   - Benign?
   - Potentially lethal?
   - Lethal?
2. Why am I treating the patient?
   - To decrease symptoms?
   - To reduce the risk of sudden cardiac death?
3. Are there any extracardiac or exacerbating factors that can be eliminated?
   - Stimulants, stress, insufficent sleep?
   - Electrolyte disturbance?
   - Angina pectoris, coronary artery spasm, silent ischemia?
   - Congestive heart failure?
4. What effect is the antiarrhythmic medication having on the patient?
   - Is the patient taking the medication?
   - Is the patient tolerating the medication?
   - Are symptoms fewer?
   - Are arrhythmias better or worse on the drug?
   - Is the risk of sudden cardiac death less?
5. What is my end point of therapy?
   - Control of symptoms?
   - Total elimination of PVCs or partial suppression?
   - Maintenance of therapeutic antiarrhythmic drug levels?
   - Prevention of induction of ventricular tachycardia?
   - Insertion of implantable cardioverter-defibrillator?
6. How aggressively need I monitor the patient to acheive this end point?
   - Patient history?
   - Electrocardiographic monitoring?
   - SDC monitoring?
   - Referral to center for invasive testing?
7. How long should antiarrhythmic therapy be continued?
   - Months? Years? Indefinitely?
   - Until underlying (or exacerbating) condition is controlled?

partial suppression of ventricular ectopy may indeed be the most practical end point for management of benign and potentially lethal ventricular arrhythmias. For patients with lethal arrhythmias, preventing inducibility of ventricular tachycardia by means of PES studies or implantation of an automatic cardioverter-defibrillator will probably be needed for optimal results.

Once the end point of therapy has been decided, one should determine how aggressively to pursue this goal. Will subjective improvement of the patient suffice? Or must documentation of a statistically significant reduction in PVC frequency or complexity be shown? Need serum drug levels be therapeutic? Is referral to a center for PES studies in order?

The final question to address is the optimal duration of antiarrhythmic therapy. Is a potentially treatable underlying condition present? Or should antiarrhythmic therapy be continued indefinitely? All too often in the past, the answer to this latter question was yes. A study by Pratt, et al. suggested that indefinite treatment with antiarrhythmic agents is not always needed. This is because significant spontaneous variability in arrhythmia frequency may occur with time.[42] In more than a third of the patients in this study, dramatic improvement in arrhythmia frequency and severity was seen when follow-up Holter monitoring was performed during a drug-free period 1 to 2 years later. It may therefore be reasonable to reassess periodically the need for antiarrhythmic therapy in patients without life-threatening ventricular arrhythmias. This can be done by stopping drug therapy and repeating a Holter monitor every 6–12 months to see if the need for treatment still exists.

Conclusion

Evaluation and management of patients with ventricular arrhythmias are complex tasks demanding an individualized approach. Numerous pitfalls may surprise the unwary. We hope attention to the points reviewed in this article will provide the family physician with the information needed to address the problem successfully.

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