CLINICAL THERAPEUTICS

Amiodarone for Atrial Fibrillation

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 73-year-old man with stable coronary artery disease, hypertension, and chronic renal insufficiency presents with recurrent atrial fibrillation at 80 to 90 beats per minute. His symptoms include shortness of breath and fatigue. He has had atrial fibrillation twice in the past year; with each episode, electrical cardioversion resulted in marked improvement in his symptoms. His echocardiogram shows symmetric left ventricular hypertrophy with evidence of diastolic dysfunction. His medications include warfarin and metoprolol (25 mg twice daily). He is referred to a cardiologist, who recommends rhythm control with oral amiodarone.

THE CLINICAL PROBLEM

Atrial fibrillation is the most common cardiac arrhythmia seen in clinical practice. It currently affects more than 2 million Americans, with a projected increase to 10 million by the year 2050.[1] Atrial fibrillation may occur in a paroxysmal, self-remitting pattern or may persist unless cardioversion is performed. It is rarely, if ever, a one-time event but can be expected to recur unpredictably. Symptoms, including palpitations, dyspnea, fatigue, and chest pain, are present in 85% of patients at the onset of the arrhythmia but often dissipate with rate- or rhythm-control therapy.[2] The morbidity and mortality associated with this disorder relate to these symptoms as well as to hemodynamic and thromboembolic complications. Strategies to maintain sinus rhythm have not been shown to reduce total mortality or the risk of stroke but have been shown to improve functional capacity and quality of life.[3-5] The failure to reduce the mortality associated with rhythm-control strategies is in part due to the toxicity of the therapies used to maintain sinus rhythm.[6]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The actual mechanism of atrial fibrillation is probably a focal source of automatic firing, a series of small reentrant circuits, or a combination of the two.[7] Atrial fibrillation is triggered by atrial premature depolarizations, which frequently arise from muscular tissue in the pulmonary veins or other structures in the left or, less commonly, right atrium.[8] Clinical factors such as hypertension, aging, and congestive heart failure, as well as recurrent atrial fibrillation itself, result in structural changes in the atria, including dilatation and fibrosis.[9] This type of mechanical remodeling promotes the development and perpetuation of atrial fibrillation. Continued rapid electrical firing in the atria also results in loss of the normal adaptive shortening of atrial and pulmonary-vein myocyte refractory periods in response to the rapid heart rate, a process called electrical remodeling.[10]

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The hemodynamic consequences of atrial fibrillation result primarily from the loss of atrioventricular synchrony but also from the rapid rate and irregularity of the ventricular response.[9] Patients with clinical syndromes that impair diastolic compliance (e.g., left ventricular hypertrophy) are most likely to have functional deterioration and symptoms, with loss of the atrial contribution to ventricular filling; such patients are also therefore most likely to benefit from restoration of sinus rhythm.

The precise mechanism through which antiarrhythmic drugs such as amiodarone suppress atrial fibrillation remains unknown.[11] Amiodarone (with its active metabolite, desethylamiodarone) blocks sodium, potassium, and calcium channels. It is also a relatively potent noncompetitive alpha-blocker and beta-blocker but has no clinically significant negative inotropic effect.[9,11] At rapid heart rates, sodium channel blockade is increased.[12]

The consequences of these channel-blocking effects can be demonstrated electrophysiologically. Most important, potassium-channel blockade slows repolarization, causing an increase in the duration of the action potential and in the refractoriness of cardiac tissue; this has the effect of prolonging the QT interval (Fig. 1). Amiodarone is also uniquely effective in preventing experimentally induced atrial electrical remodeling.[13]

CLINICAL EVIDENCE

Amiodarone has consistently been demonstrated to be superior to other antiarrhythmic medications for the maintenance of sinus rhythm.[14-16] The Canadian Trial of Atrial Fibrillation randomly assigned 403 patients with paroxysmal or persistent atrial fibrillation to treatment with amiodarone or with propafenone or sotalol.[14] During a mean follow-up period of 468±150 days, recurrence of atrial fibrillation was documented in 63% of patients taking propafenone or sotalol, as compared with 35% of those taking amiodarone. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial compared the efficacy of sotalol, amiodarone, and placebo in 665 patients with persistent atrial fibrillation.[15] Recurrence of atrial fibrillation after 1 year was documented in 35% of patients taking amiodarone, 60% of those taking sotalol, and 82% of those taking placebo.

CLINICAL USE

Amiodarone is approved by the Food and Drug Administration for the treatment of lethal ventricular arrhythmias but not for the management of atrial fibrillation. Nonetheless, it is widely prescribed for this indication.[17,18]

The safe and effective use of amiodarone requires a firm understanding of its unusual pharmacokinetics as well as the potential for drug interactions and adverse events. Amiodarone is a highly lipophilic compound with a large volume of distribution (66 liters per kilogram of body weight). This property results in a delayed onset of action (an interval of 2 to 3 days) and a long elimination half-life (up to 6 months).[19] As a result, there is a substantial lag between the initiation, modification, or discontinuation of treatment with amiodarone and a change in drug activity. Amiodarone is metabolized to desethylamiodarone in the liver, and its use should be avoided in patients with advanced hepatic disease. There is no clinically significant renal metabolism of amiodarone, and the dose is not affected by renal dysfunction or dialysis. Amiodarone crosses the placenta in pregnant women and is excreted in varying amounts in breast milk.[20] Its use should therefore be avoided in women who are pregnant or breast-feeding.

Amiodarone is an excellent choice for use in patients with structural heart disease or congestive heart failure.[9,21] It is generally reserved as an alternative to other agents for patients without underlying heart disease, given its multitude of side effects.[9] Many physicians hesitate to use amiodarone in young patients because of the concern about side effects related to long-term use.

Contraindications to the use of amiodarone include severe sinus-node dysfunction and advanced conduction disease (except in patients with a functioning artificial pacemaker). The drug should also be used cautiously in patients with severe lung disease (which may interfere with the detection of adverse effects).

Before choosing amiodarone for the treatment of atrial fibrillation, clinicians should consider other options. Rate control alone (i.e., the use of agents to maintain a slow ventricular response rate in atrial fibrillation) is often as effective as rhythm control in managing the symptoms of this arrhythmia, and it has been shown to be at

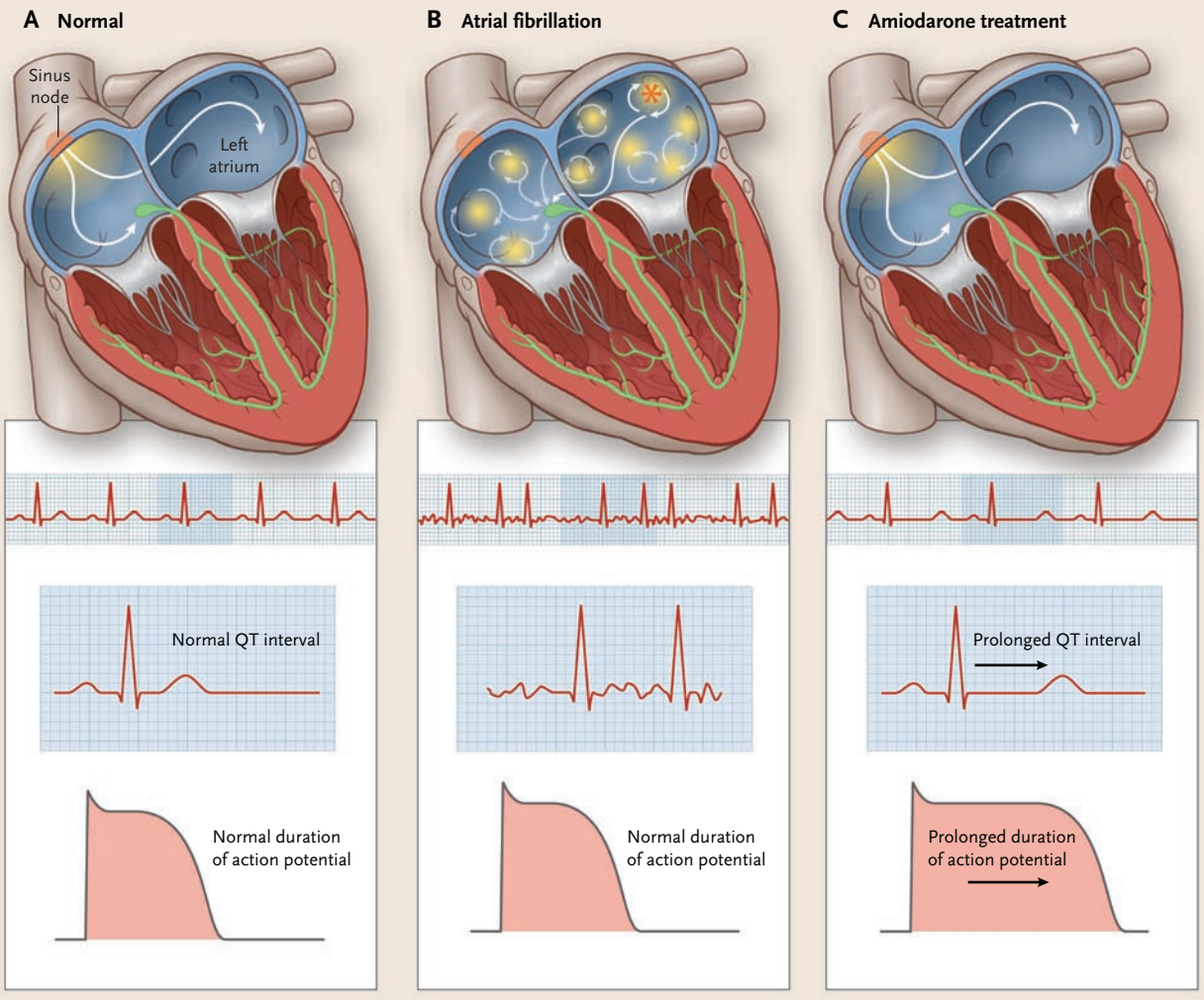

Figure 1. Electrophysiological Action of Amiodarone.

During normal sinus rhythm (Panel A), myocardial activation is initiated in the sinus node, with a resulting coordinated wavefront of depolarization that spreads across both atria (arrows) to the atrioventricular node and specialized conduction system (green). Atrial fibrillation (Panel B) is triggered by atrial premature depolarizations arising in the region of the pulmonary veins (red asterisk) and propagates in an irregular and unsynchronized pattern (arrows). The resulting pattern of ventricular activation is irregular (as shown on the electrocardiographic recording). Amiodarone (Panel C) has several electrophysiological effects. Chief among these in the control of atrial fibrillation is the effect on the potassium channel blockade, which slows repolarization, thus prolonging the action potential and the refractoriness of the myocardium. Waves of depolarization are more likely to encounter areas of myocardium that are unresponsive; thus, propagation is prevented. Although the prolongation of the action potential is most apparent on the electrocardiogram as an effect on the ventricular myocardium (prolonged QT interval), a similar effect occurs in the atria.

least as effective as rhythm control with respect to the long-term outcome.[3] Therefore, a trial of rate control should always be considered. Other antiarrhythmic drugs, such as sotalol and propafenone, should also be considered, with the recognition that the balance of risks and benefits for these agents as compared with amiodarone depends on the clinical setting.[9] Finally, invasive procedures, such as pulmonary-vein isolation, have an increasing role in the management of this disorder,[22] although in most cases, these approaches have been used only after the failure of other therapies.

Before initiating treatment with amiodarone,

it is critical to establish therapeutic anticoagulation, because the potential exists for conversion to sinus rhythm (with a consequent risk of thromboembolism) at any point during the drug-loading phase. The recommended criterion for anticoagulation is an international normalized ratio (INR) of 2.0 to 3.0 for 3 consecutive weeks or a transesophageal echocardiogram demonstrating the absence of left atrial thrombus.

Amiodarone therapy is initiated with a loading dose of approximately 10 g in the first 1 to 2 weeks. This loading dose can be given in divided doses — for example, 400 mg given orally twice a day for 2 weeks followed by 400 mg given orally each day for the next 2 weeks. Reducing the individual dose and administering it three times daily may reduce the gastrointestinal intolerance sometimes associated with amiodarone loading. A more protracted loading period with a lower daily dose may be used when sinus- or atrioventricular-node dysfunction is a concern.

It is relatively safe to initiate treatment with amiodarone in the ambulatory setting.[23] Electrocardiographic monitoring (with 12-lead electrocardiography or an event recorder) should be performed at least once during the loading period to evaluate the patient for excessive prolongation of the QT interval (>550 msec) or bradycardia. Prolongation of the QT interval is common and generally responds to dose reduction.[15]

Given the delay in the onset of antiarrhythmic action with amiodarone, it is common for atrial fibrillation to persist or recur during the loading phase of drug administration; however, this does not predict rates of sinus rhythm at 1 month.[24] Approximately 30% of patients have a reversion to sinus rhythm during this loading phase, and the remainder can undergo electrical cardioversion, which has a high rate of success.[15,23]

Once the loading phase is completed, the maintenance dose of amiodarone for atrial fibrillation is 200 mg a day. Monitoring of levels of amiodarone or desethylamiodarone is not recommended, given the lack of correlation between drug levels and efficacy or adverse events.[12] However, monitoring with the use of various laboratory tests for evidence of adverse effects is recommended.

Amiodarone interferes with the hepatic metabolism of many medications, the most common of which are digoxin and warfarin. Generally, digoxin should be discontinued if possible, or the dose at least reduced by 50%. The INR must be monitored closely during amiodarone loading and maintenance therapy. It is usually necessary to reduce the warfarin dose by 25 to 50% when the drug is coadministered with amiodarone.

The cost of amiodarone is typically about $1.25 per tablet in the United States. In addition, the initial screening tests performed before treatment begins (chest radiography and tests of pulmonary, thyroid, and liver function) cost approximately $250, with a similar expense annually to screen for adverse effects.

ADVERSE EFFECTS

Amiodarone is associated with both cardiovascular and noncardiovascular adverse events (Table 1). Side effects resulting in discontinuation of therapy occur in 13 to 18% of patients after 1 year.[12,15] The most frequent cardiovascular side effect is bradycardia, which is often dose-related, occurs more frequently in elderly patients than in younger patients, and can often be mitigated by dose reduction.[24,25] Prolongation of the QT interval is seen in most patients but is associated with a very low incidence of torsades de pointes (<0.5%) as compared with other drugs that prolong the QT interval (e.g., sotalol and dofetilide).[17]

Clinical evidence of hypothyroidism occurs in up to 20% of patients taking amiodarone. It develops most often in patients with preexisting autoimmune thyroid disease and those living in areas replete with iodine (that is, they are not iodine-deficient).[26] Hypothyroidism is easily managed with levothyroxine and generally is not cause for discontinuing amiodarone.[12,26] Hyperthyroidism occurs in 3% of patients in areas where dietary iodine is sufficient but in 20% of patients in iodine-deficient areas. It can be difficult to recognize clinically because many of the typical adrenergically mediated signs are blocked by amiodarone. The recurrence of atrial fibrillation during maintenance amiodarone therapy should prompt an evaluation for amiodarone-induced hyperthyroidism. Management requires the assistance of an experienced endocrinologist and may require discontinuation of amiodarone therapy. Thyrotropin levels should be checked in all patients before amiodarone therapy is initiated and at least every 6 months thereafter.[12]

Pulmonary toxicity is one of the most serious

Table 1. Adverse Effects of Oral Amiodarone.

Adverse Effect	Incidence	Recommended Monitoring	Special Considerations
Cardiac		Baseline electrocardiogram at least once during loading period, especially if conduction disease is present; yearly thereafter	Consider reduction of loading dose in elderly patients and those with underlying sinoatrial or atrioventricular conduction disease; reduce dose or discontinue if QT interval exceeds 550 msec
Bradycardia	5%		
Prolonged QT interval	In most patients		
Torsades de pointes	<1%		
Hepatic	15%	Aspartate and alanine aminotransferase measurements at baseline and every 6 months thereafter	Avoid in patients with severe liver disease
Thyroid		Thyroid-function tests at baseline and two or three times a year thereafter	Avoid in presence of preexisting, nonfunctioning thyroid nodule; higher incidence of thyroid effects in patients with autoimmune thyroid disease
Hyperthyroidism	3%		
Hypothyroidism	20%		
Pulmonary	<3%	Pulmonary-function tests at baseline and if symptoms develop; chest radiograph at baseline and yearly thereafter	Discontinue amiodarone immediately if pulmonary effects suspected
Dermatologic	25–75%	Routine	Recommend use of sunscreen with a high sun protection factor
Neurologic	3–30%	Routine	Consider dose reduction
Ophthalmologic		Examination at baseline if there is underlying abnormality; examinations as needed thereafter	Avoid in presence of preexisting optic neuritis
Corneal deposits	100%		
Optic neuritis	<1%		

complications of amiodarone use. It occurs in less than 3% of patients and is thought to be related to the total cumulative dosage.[12] In the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, there was a slightly increased incidence of pulmonary toxicity in patients with preexisting pulmonary disease, but mortality from pulmonary causes and overall mortality were not higher among these patients than among those without preexisting pulmonary disease.[27] The management of acute pulmonary toxicity involves discontinuation of therapy, supportive management, and, in extreme cases, corticosteroid administration.[12] Screening pulmonary-function tests and chest radiography should be performed at baseline, and chest radiography should be performed yearly thereafter.[9,12] Pulmonary-function tests should be repeated if symptoms develop.

Hepatic toxicity is a rare complication of amiodarone therapy when the drug is used in low doses. Amiodarone can cause nonalcoholic steatohepatitis, which is manifested as an asymptomatic increase in hepatic aminotransferase levels (more than two times the upper limit of the normal range). This condition can generally be reversed by discontinuing the drug but can result in cirrhosis if unheeded. Liver-function tests should be measured at baseline and every 6 months thereafter.[9,12,28]

Corneal microdeposits are seen in virtually all patients receiving long-term amiodarone therapy and are rarely of clinical significance.[12] Optic neuropathy has been reported in less than 1% of patients, but it may be a result of associated medical conditions rather than an effect of amiodarone. Nonetheless, the potential severity of optic neuropathy warrants discontinuation of amiodarone therapy if the condition is suspected. Ophthalmologic examinations are recommended at baseline only for patients with preexisting abnormalities.

Dermatologic side effects of amiodarone use include photosensitivity, with susceptibility to sunburn, particularly in patients with a fair complexion. Avoidance of direct exposure to the sun and use of sunscreen can diminish this reaction. A gray-bluish skin discoloration may be seen in patients who take large doses of amiodarone for long periods.[29] Alopecia is also an infrequent side effect of amiodarone.

Neurologic side effects, which occur in up to

30% of patients, include ataxia, tremor, peripheral polyneuropathy, insomnia, and impaired memory. These effects are often dose-related and occur more often in elderly patients than in younger patients.

AREAS OF UNCERTAINTY

The side effects of low-dose amiodarone therapy (200 mg daily) in patients taking the drug for more than 5 years — the duration of clinical studies that have been conducted — are unknown. Some patients, particularly those who are elderly and those with relatively little body fat, can be treated with a very low dose (100 mg per day). There are no available data from clinical trials that support this reduced-dose strategy, but it is common practice.

Amiodarone is frequently used for the prevention and treatment of atrial fibrillation associated with cardiac surgery, including the maze procedure for cure of atrial fibrillation.[9] Atrial fibrillation associated with cardiac surgery occurs most frequently in the first few days after surgery but can also occur weeks after surgery. For patients undergoing cardiac surgery, amiodarone is given at a dose of 600 mg a day for 1 to 2 weeks before surgery and is continued for 4 to 6 weeks after surgery. Although this approach is supported by data from clinical trials, beta-blockers have also been reported to reduce rates of postoperative atrial fibrillation,[30] and none of the major studies of amiodarone compared it with the use of a beta-blocker alone.

The use of amiodarone in combination with other antiarrhythmic drugs has not been thoroughly studied. One intriguing combination is that of angiotensin-receptor blockers with amiodarone. Emerging data suggest that the combination of these two agents is more effective than either is alone.[31]

GUIDELINES

Recently published guidelines of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology recommend reserving amiodarone as an alternative agent for most patients with atrial fibrillation, the exceptions being those who have clinical heart failure or hypertension with substantial left ventricular hypertrophy.[9] For patients at very high risk for recurrence of atrial fibrillation (e.g., those with severe mitral regurgitation), amiodarone may be the best choice of a first-line agent, given the low likelihood that treatment with other antiarrhythmic agents will be successful.

RECOMMENDATIONS

For the patient described in the vignette, it is reasonable to attempt to maintain sinus rhythm because of the presence of symptoms in spite of a well-controlled ventricular response. His symptoms are probably due to diastolic dysfunction. The presence of coronary artery disease limits the choice of antiarrhythmic drug to amiodarone, sotalol, and dofetilide. The patient's renal insufficiency makes sotalol and dofetilide unattractive options. The preferred agent to maintain sinus rhythm in this patient is therefore amiodarone. Baseline screening studies should include tests of liver, thyroid, and pulmonary function as well as chest radiography. The warfarin dose should be decreased by at least 25% when the loading dose of amiodarone is administered. It is reasonable to initiate amiodarone therapy in the outpatient setting. A slightly reduced loading dose (e.g., 600 mg per day in one dose or divided doses for 3 to 4 weeks) is reasonable, given that the patient's baseline heart rate is already well controlled on a low dose of a beta-blocker (which may suggest underlying atrioventricular-node conduction disease). The patient should undergo electrocardiography weekly or should be discharged with a loop recorder to monitor heart rhythm, heart rate, and duration of the QT interval. If conversion has not occurred by the end of the loading period, electrical cardioversion should be performed, followed by a reduction in the dose of amiodarone to 200 mg daily. The warfarin dose may need to be increased as the amiodarone dose is reduced.

No potential conflict of interest relevant to this article was reported.

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