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# What internists should know about amiodarone

## ABSTRACT

Amiodarone is a potent and versatile anti-arrhythmic. Despite side effects involving the lungs, heart, thyroid, and other organs, it is effective in the treatment of refractory atrial and ventricular arrhythmias and it has unique safety in patients with coronary disease and left ventricular dysfunction. This review discusses the evolving indications for amiodarone and management of toxicities and drug interactions.

## KEY POINTS

Amiodarone therapy reduces the frequency of shocks from implantable defibrillators by improving control of atrial and ventricular arrhythmias.

Current data do not support routine use of amiodarone after myocardial infarction, even in high-risk patients. The population likely to benefit most from amiodarone has yet to be defined, but will probably include some patients who receive implantable cardioverter-defibrillators after myocardial infarction.

Pulmonary toxicity related to amiodarone is usually reversible by stopping the drug. High-dose corticosteroids may hasten resolution of lung injury.

Amiodarone increases the effect of warfarin and digoxin. Because of its beta-blocking activity, it potentiates the effect of other beta-blockers and may slow atrioventricular nodal conduction when used with some calcium-channel blockers.

AMIODARONE'S POPULARITY has waxed and waned since it was originally introduced in the 1960s as an anti-ischemic drug,[1] and approved by the FDA in 1985 as an antiarrhythmic. It is the most effective anti-arrhythmic drug available, and is now used almost exclusively for this purpose, even though it has gained some notoriety for toxicity.

We believe it will play an increasingly important role in the treatment of many arrhythmias, given its neutral effects on inotropy and low incidence of associated proarrhythmia.[2] Furthermore, it has unique safety in the setting of coronary disease and left ventricular dysfunction.

## INDICATIONS

Although the only approved indication for amiodarone is the treatment of life-threatening arrhythmias unresponsive to adequate doses of other available anti-arrhythmics, there is substantial data on its use in other populations. In this review, we propose a practical approach for follow-up of patients on long-term amiodarone therapy, and for use of amiodarone in four clinical categories:

- Atrial fibrillation.
- After myocardial infarction (MI).
- Primary prevention of sudden cardiac death.
- Secondary prevention of sudden cardiac death.

## ANTI-ARRHYTHMIC EFFECTS

Amiodarone suppresses and prevents cardiac arrhythmias by directly prolonging the duration of the action potential—the "electrocardiogram" of each cardiac cell—and the repo-

larization time, and it does this mainly by blocking cellular potassium channels. While its essential mode of action is uncertain, homogenous lengthening of repolarization likely contributes to its antiarrhythmic activity. Amiodarone also depresses sinus and atrioventricular node automaticity, ie, the ability to initiate electrical impulses without an external stimulus. In addition, amiodarone has some beta-adrenergic, alpha-adrenergic, calcium-channel blocking, and sodium-channel blocking activity.[3]

## PHARMACOKINETIC PROFILE

Amiodarone is an iodine-rich benzofuran derivative that is eliminated primarily by hepatic metabolism and biliary excretion. Because of first-pass metabolism in the liver and the intestinal mucosa and incomplete absorption, only 35% to 65% of an oral dose is bioavailable. Amiodarone has a high volume of distribution[4]: concentrations in the myocardium are 10 to 50 times those in plasma.[5] Because it has such an affinity for adipose tissue, an estimated 10 to 15 g of the drug are necessary to saturate these stores.[3] Once the steady state has been reached, the elimination half-life is long and variable, ranging from 16 to 180 days (mean, 52 days).[6]

**The dose for atrial fibrillation is lower than for ventricular arrhythmia**

In clinical practice, these characteristics mean that:

- Loading doses are necessary.
- The anti-arrhythmic effect is delayed.
- The elimination phase is protracted once the drug has been discontinued.
- There will usually be no serious consequences if the patient misses a dose or two by mistake.

Its major metabolite is desethylamiodarone, which is pharmacologically active. Interestingly, the iodide concentrated in the liver during amiodarone metabolism acts like radiographic contrast, increasing the radiographic density of the liver on computed tomography.

## AMIODARONE FOR ATRIAL FIBRILLATION

Amiodarone is effective in treating a wide range of atrial arrhythmias. However, radiofrequency ablation has superseded drug therapy for atrioventricular (AV) nodal and bypass tract tachyarrhythmias, such as Wolff-Parkinson-White syndrome. Amiodarone is of greatest clinical use in atrial fibrillation and atrial flutter. Moreover, amiodarone is clearly effective in patients with arrhythmias refractory to conventional agents.[7]

As part of medical therapy for atrial fibrillation, amiodarone may:

- Slow the ventricular response, due to its AV nodal blocking activity.
- Convert the rhythm to sinus rhythm.
- Maintain sinus rhythm after cardioversion.

The dose generally required for controlling atrial fibrillation is lower than that required for controlling ventricular arrhythmias, with less consequent toxicity.[8] Recently, amiodarone has shown some promise in the prevention of atrial fibrillation following cardiac surgery.[9]

## AMIODARONE AFTER MYOCARDIAL INFARCTION

It became clear by the mid-1970s that frequent ventricular ectopic beats and depressed left ventricular function after MI predicted increased mortality.[10] An intensive search began for an antiarrhythmic to suppress ventricular ectopic beats and thereby improve prognosis. Data from the Cardiac Arrhythmia Suppression Trial (CAST) indicated that flecainide, encainide, and moricizine were proarrhythmic and actually increased sudden death after MI, thus precluding their use in coronary disease.[11,12]

Early reports, such as the Basel Antiarrhythmic Study of Infarct Size (BASIS),[13] suggested that amiodarone could significantly reduce arrhythmic events and total mortality after MI. In this study of 312 post-MI patients, mortality was reduced by 61% ($P < .05$) in patients receiving amiodarone, compared with those receiving placebo.

In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT),[14] survivors of MI with repetitive ventricular premature depolarizations were treated with either amiodarone or placebo. In the European Myocardial Infarct Amiodarone

Trial (EMIAT),[15] survivors of MI with depressed left ventricular function received amiodarone or placebo. In EMIAT, the rate of mortality from all causes did not differ between the two groups, but there were 35% fewer ($P$ = .05) deaths due to arrhythmia in the treated group. In CAMIAT, deaths due to arrhythmia were reduced by 48.5% ($P$ = .016), with a trend towards a reduction in all-cause mortality.

### Conclusions about optimal use of amiodarone after MI

While the CAMIAT and EMIAT results are less striking than the earlier BASIS results, they confirm that amiodarone has a low incidence of proarrhythmia and is safe to use in patients with left ventricular dysfunction. However, the results do not support the routine use of amiodarone after MI, even in high-risk patients. The population likely to benefit most has yet to be defined, but it will likely include some patients who receive implantable cardioverter-defibrillators.

## PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

Amiodarone has been studied in a number of large trials in the primary prevention of sudden cardiac death.

The markers of increased risk of sudden cardiac death include:

- Left ventricular dysfunction.
- Frequent or complex ventricular ectopic beats.
- Nonsustained ventricular tachycardia.

The *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina* (GESICA) trial,[16] which randomized 516 heart failure patients to amiodarone or standard treatment, was stopped early because of a 27% ($P$ = .16) risk reduction in sudden death in the amiodarone group, which generated considerable excitement at the time. However, this early optimism was offset by the results of the more recent Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF STAT),[17] which studied a similar patient population and found no survival benefit in the amiodarone group. These disparate results can perhaps be explained by the larger number of patients in the GESICA trial with nonischemic dilated cardiomyopathy, a subgroup in which amiodarone may be more effective in preventing sudden cardiac death.[18]

These results leave us ambiguous about amiodarone's role as monotherapy in the primary prevention of sudden cardiac death. The Multicenter Automatic Defibrillator Implantation Trial (MADIT)[19] attempted to resolve this ambiguity by randomizing patients to undergo conventional therapy—usually amiodarone—or implantation of a cardioverter-defibrillator. To be included in this trial, patients had to have coronary disease, nonsustained ventricular tachycardia, an ejection fraction of 35% or less, and ventricular tachycardia induced at electrophysiology study. The all-cause survival rate at 5 years was 61% in patients receiving medical therapy, vs 84% in patients with an implantable cardioverter-defibrillator ($P$ = .009).

Other trials of implantable cardioverter-defibrillators as primary prevention are underway. Combination therapy with an implantable cardioverter-defibrillator plus amiodarone is now commonplace; the rationale is to limit shocks due to fast atrial fibrillation and frequently recurring ventricular arrhythmias.

In short, the patient at high risk of sudden cardiac death (eg, the MADIT population) is best served by an implantable cardioverter-defibrillator. Although in the future a survival benefit may be demonstrated in certain patient subgroups, such as those with non-ischemic dilated cardiomyopathy, amiodarone's greatest use is currently in the control of symptoms related to ventricular arrhythmias.

**The patient at high risk of sudden cardiac death is best served by an implantable defibrillator**

## SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH

Amiodarone is effective in preventing and terminating refractory ventricular arrhythmias.[20] Before the advent of the implantable cardioverter-defibrillator, amiodarone was the only treatment for arrhythmias refractory to conventional therapy. The Cardiac Arrest in Seattle: Conventional Versus Amiodarone

TABLE 1

**Incidence of amiodarone-induced side effects**

| SYSTEM AND SIDE EFFECTS | INCIDENCE |
|---|---|
| **Cardiac** | |
| Sinus bradycardia* | 0% to 10% |
| Torsades de pointes | <1% |
| **Pulmonary** | |
| Pneumonitis† | 5% to 7% |
| Asthma exacerbation | Not available |
| Cough | Not available |
| **Thyroid** | |
| Hypothyroidism | <3% |
| Hyperthyroidism | <2% |
| **Gastrointestinal** | |
| Nausea/vomiting* | Common |
| Constipation* | Common |
| Mild transaminase elevation | 15% to 20% |
| Alkaline phosphatase elevation | Uncommon |
| Hepatitis | Rare |
| **Neurologic** | |
| Fatigue | 1% to 16% |
| Ataxia | 4% to 24% |
| Headaches* | |
| Neuropathy | 6% to 10% |
| Sleep disturbance | Not available |
| Myositis | Rare |
| **Ocular** | |
| Corneal microdeposits | Common |
| Macular degeneration | Rare |
| Optic neuritis | Rare |
| **Renal** | |
| Elevated creatinine | Rare |
| **Dermatologic** | |
| Photosensitivity† | Common |
| Blue-grey skin discoloration | 1% to 7% |
| Pruritic rash | Infrequent |
| **Miscellaneous** | |
| Hyperglycemia | Rare |
| Mild elevation of lipids | Common |
| Anemia | Rare |
| Thrombocytopenia | Rare |
| Epididymitis | Rare |

*Dose-related
†Partially dose-related

**Amiodarone's elimination half-life is long and variable**

Drug Evaluation (CASCADE) study,[21] which randomized cardiac arrest survivors to empiric amiodarone vs conventional therapy, demonstrated favorable results for amiodarone: survival at 6 years was 58% in the amiodarone group and 37% in the group treated conventionally. The recently reported Anti-arrhythmics Versus Implantable Defibrillator (AVID) trial[22] randomized 509 patients with symptomatic ventricular arrhythmias to antiarrhythmic drug therapy, primarily amiodarone, and 507 patients to implantation of a cardioverter-defibrillator. Survival at 3 years was 75% in the group that received an implantable cardioverter-defibrillator and 64% in the drug therapy group. Interestingly, after 24 months, about 20% of patients had either crossed over to or added the alternative treatment, suggesting the complimentary nature of both therapies.

Still ongoing are the Canadian Implantable Defibrillator Study (CIDS) and Cardiac Arrest Study Hamburg (CASH), which will further elucidate the roles of amiodarone and the implantable cardioverter-defibrillator in treating and preventing the recurrence of life-threatening arrhythmias.

Currently, in patients at risk for a second sudden cardiac death event or serious destabilizing ventricular arrhythmias (hypotension, syncope), therapy with an implantable cardioverter-defibrillator is preferred. Amiodarone monotherapy is acceptable if a device is contraindicated, for whatever reason.

## TOXICITY

Although amiodarone has serious toxicities which involve, primarily, the lung, heart, liver, or thyroid gland, and which raise the threshold for its use, these toxicities can be managed effectively to take advantage of its unique antiarrhythmic properties (TABLE 1). (Notably, in the AVID trial,[22] 85% of the amiodarone-treated patients continued to take the drug 2 years after the trial began.) Side effects can be minimized by using lower doses or, sometimes, by reducing the daily dosage if symptoms occur. Regular monitoring of a variety of body systems is useful in preventing and managing amiodarone-induced side effects (TABLE 2).

## Pulmonary effects

Amiodarone-induced pulmonary toxicity is a much-feared complication of amiodarone therapy. Chest x-ray is the primary surveillance test, and radiographic changes are typically bilateral and diffuse with a combination of interstitial infiltrates (FIGURE 1). A reasonable estimate of the incidence is 5% to 7% of patients receiving amiodarone, 5% to 10% of whom may die.[23] Amiodarone-induced pulmonary toxicity seems more common in patients receiving a higher maintenance dose, in patients of advanced age, and in those with a lower pretreatment hemoglobin-corrected diffusing capacity (DLCO).[24]

Nonspecific symptoms of dyspnea, cough, and chest pain are typical, and the patient may be febrile, with rales or a pleural rub. Exacerbation of asthma occurs only rarely.

Toxicity has been defined as two of the following:

- New or worsening symptoms.
- A new lung abnormality or worsening of infiltrates on chest roentgenogram.
- A decline of at least 15% in either the total lung capacity or the DLCO.

Gallium scanning of the lungs may help distinguish amiodarone-induced pneumonitis from congestive heart failure or pulmonary embolism. Baseline pulmonary function tests with DLCO and chest roentgenography are recommended, with periodic retesting based on symptoms. A chest roentgenogram should be obtained every 4 to 6 months. Withdrawal of the drug must be balanced against the risk of arrhythmia recurrence. There is no single laboratory test or clinical parameter that unequivocally establishes the diagnosis of amiodarone-related pulmonary toxicity. Diagnosis requires the exclusion of occult heart failure, infection, and other possibilities, such as pulmonary embolism, together with a reasonable collection of symptoms or findings. Occasionally, when amiodarone is the best or the only therapy available, one can consider reinstituting therapy at a lower dose.

## Cardiac effects

Amiodarone prolongs the action potential duration and the refractory period of myocardial cells and therefore prolongs the QT interval. Nevertheless, the incidence of amio-

**TABLE 2**

### Recommended monitoring during amiodarone therapy

| TEST | INTERVAL |
|---|---|
| **Laboratory tests** | Baseline, as symptoms occur, and every 4 to 6 months |
| Renal function | |
| Complete blood count | |
| Liver function | |
| Thyroid function | |
| **Electrocardiogram** | Baseline, as symptoms occur, and every 4 to 6 months |
| **Chest x-ray** | Baseline, as symptoms occur, and every 4 to 6 months |
| **Eye examination** | Baseline and as symptoms occur; regular examinations optional |
| **Pulmonary function tests** | Baseline and as symptoms occur |

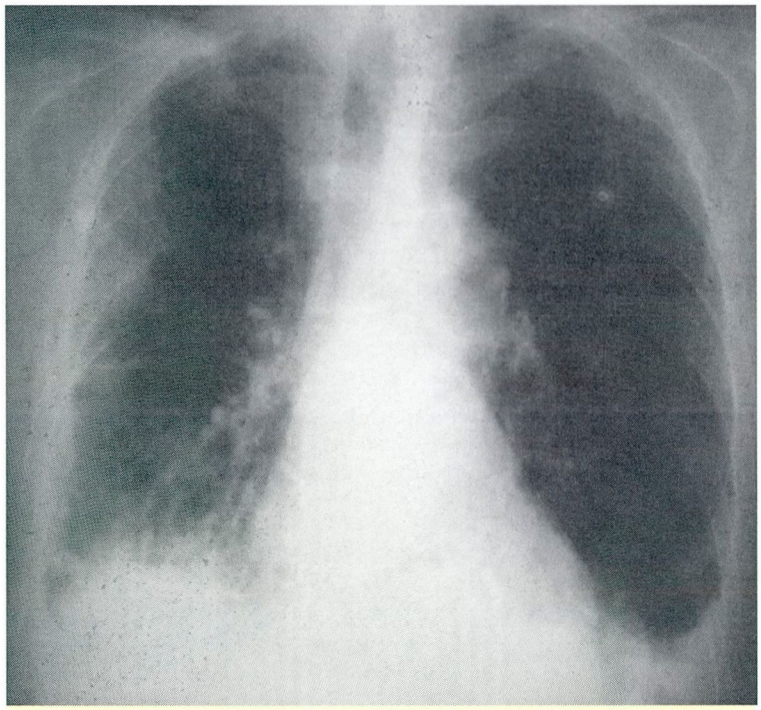

**FIGURE 1.** Chest x-ray showing asymmetric interstitial and alveolar changes with a right basal predominance consistent with amiodarone toxicity.

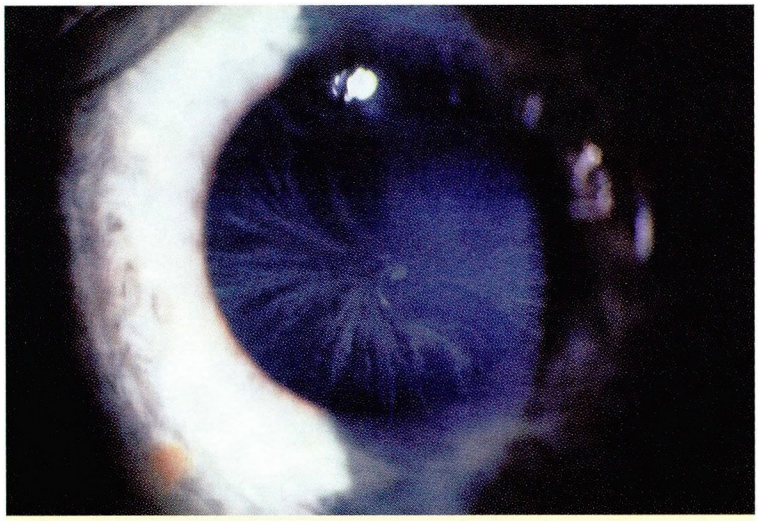

**FIGURE 2.** Typical whorled pattern (light gray streaks) of corneal micro-deposits in a patient taking amiodarone.

darone-induced arrhythmia is low, and the incidence of torsades de pointes is less than 1% when the drug is used as monotherapy.[2]

Bradycardia from sinus and AV nodal depression is common, sometimes necessitating permanent pacemaker implantation, but it generally reflects a loading dose that is too high and being given too quickly. Intravenous amiodarone may cause hypotension that responds to slowing of the infusion. Outpatient initiation of amiodarone therapy is possible; usually, patients are hospitalized more for arrhythmia management than for observation for amiodarone toxicity.

**Perform liver function testing at baseline and frequently thereafter**

### Hepatic and gastrointestinal effects

An increase in hepatic transaminase of up to 2 to 4 times baseline levels is seen in 15% to 20% of patients during long-term amiodarone therapy.[2,5] The elevation usually takes several months to develop and is generally not dose-dependent. A moderate and persistent increase in alkaline phosphatase has been reported, but changes in bilirubin are unusual. Overt hepatitis is rare (6 of 2210 patients in a large series).[5] Liver function testing is recommended at baseline and every 4 to 6 months thereafter. The drug should be discontinued for severe transaminase elevation and for evidence of cholestasis or hepatomegaly. Other side effects include nausea and constipation, which are usually dose-related.

### Thyroid effects

Amiodarone, which is about 30% iodine by weight, delivers a large iodine load to the body, and this may produce hypothyroidism and hyperthyroidism. In fact, the iodine load is such that tissue stores of iodine may still be elevated 6 to 9 months after discontinuation of amiodarone treatment.

Because amiodarone blocks the peripheral conversion of thyroxine ($T_4$) to triiodothyronine ($T_3$), it often causes elevated levels of serum $T_4$ and low levels of $T_3$. Because $T_3$ exerts a greater negative feedback effect on thyroid-stimulating hormone (TSH), TSH tends to rise, often returning to normal after a number of months; therefore, this mild elevation of TSH should not be equated with clinical hypothyroidism.

The incidence of clinical hypothyroidism associated with amiodarone is less than 3%, and the incidence of clinical hyperthyroidism is less than 2%.[2,5] Still, more than 50% of patients who receive long-term amiodarone treatment have abnormal thyroid function test results despite absence of clinical symptoms. Amiodarone-induced hypothyroidism—rare after the first 18 months of therapy—responds to thyroid hormone replacement therapy and to lowering the dose of amiodarone. Hyperthyroidism can occur at any time during amiodarone therapy, and clinicians should be aware that it sometimes manifests as a worsening of arrhythmia under treatment. For example, a sinus tachycardia or fast atrial fibrillation may develop, or typically, ventricular tachycardia may become more frequent or sustained due to the hyperthyroidism.

Thyroid function testing is advised at the start of amiodarone treatment, whenever symptoms occur, and at 4- to 6-month intervals thereafter.

The treatment of hyperthyroidism is difficult: radioactive iodine is ineffective, and long-term treatment with antithyroid agents such as methimazole and propylthiouracil has proved disappointing due to high intrathyroidal iodine stores. Addition of perchlorate produces a discharge of intrathyroidal iodine,

but aplastic anemia and nephrotic syndrome are associated side effects. Corticosteroids are somewhat effective, but the benefit is not sustained and the need for high doses is prohibitive. Thyroidectomy or discontinuation of amiodarone therapy may be necessary.[26]

### Other side effects

**Ophthalmic effects.** Corneal microdeposits (FIGURE 2) are universal during amiodarone therapy and do not in themselves warrant drug discontinuation or routine slit lamp examination. Symptoms of corneal deposits include photophobia, blurred vision, and blue-green halos around objects. Corneal breakdown with cyst formation has occurred from very dense deposits, but this is rare.[25] Because of recent reports of optic neuritis associated with amiodarone, the manufacturer now recommends regular ophthalmic examination, including fundoscopy and slit lamp examination, for the duration of amiodarone treatment.

**Dermatologic effects.** Skin photosensitivity is almost universal in patients taking amiodarone. The main treatment is sun-avoidance. Prescribed sunscreens need to filter both ultraviolet A and ultraviolet B radiation. Dose reduction may alleviate symptoms of phototoxicity. Another dermatologic side effect is a blue-gray skin discoloration, seen in 1% to 7% of patients; in this instance, drug discontinuation would be for cosmetic reasons only.[25]

**Neurologic side effects** usually consist of tremor, ataxia, and peripheral neuropathy. The treatment is either dose reduction or drug discontinuation.[25]

**Plasma cholesterol levels** increase with amiodarone use—a noteworthy effect in the current climate of aggressive lipid lowering for prevention of coronary disease. This increase is independent of the drug's effect on thyroid function. In one study, serum cholesterol levels increased from 197±8 at baseline to 266±31 mg/dL during long-term amiodarone therapy.[27]

## INTERACTIONS WITH OTHER DRUGS

The clinician should anticipate certain drug interactions in patients taking amiodarone (TABLE 3). For example, amiodarone has beta-blocking activity, so combinations of beta-blockers and amiodarone can cause sinus bradycardia or AV nodal blockade. Similarly, some calcium-channel blockers such as verapamil and diltiazem and possibly the newer agent mibefradil may potentiate AV node blockade when used with amiodarone.[28] Amiodarone also potentiates the effects of digoxin and warfarin. When initiating amiodarone therapy, the need for concomitant digoxin or warfarin must be reevaluated. If the decision is made to continue both, then the dose of digoxin should be reduced by half and the dose of warfarin by one third to one half.

In addition, amiodarone may act to increase levels of cyclosporine, phenytoin, and methotrexate. Also of note, amiodarone has been used in combination with other antiarrhythmic agents such as mexilitine and flecainide to suppress refractory arrhythmias. Combination therapy such as this may increase the likelihood of torsades de pointes.

**TABLE 3**

**Selected concomitant drug effects and dose adjustments**

| CONCOMITANT DRUG | EFFECT | DOSE ADJUSTMENT |
|---|---|---|
| **Warfarin** | Prothrombin time increased | Decrease by 1/3 to 1/2 |
| **Digoxin** | Levels increased | Decrease by 1/2 |
| **Procainamide** | Levels increased | Decrease by 1/2 or stop |
| **Quinidine** | Levels increased | Decrease by 1/3 to 1/2 or stop |

**Skin photosensitivity is almost universal in patients taking amiodarone**

## COST AND DOSAGE

The approach to amiodarone dosage is empirical; the guiding principle is to control arrhythmia with the lowest possible level of toxicity.[29] Since serum amiodarone levels correlate poorly with antiarrhythmic efficacy and toxicity, they are useful only as an investigational tool or to monitor compliance and absorption.

**Intravenous amiodarone** is about 30 times more expensive than the oral prepara-

tion. The average wholesale price is $75.65 for a 150-mg vial and $3.26 for a 200-mg pill. For the urgent termination of refractory arrhythmias, intravenous amiodarone is given as a 150-mg bolus over 10 minutes, followed by an infusion of 1 mg/minute for 6 hours, and a maintenance infusion of 0.5 mg/minute. The other main indication for intravenous amiodarone therapy is in patients unable to tolerate oral amiodarone due to gastrointestinal upset.

**Oral amiodarone.** Relatively rapid suppression of arrhythmias has been reported with high loading doses of oral amiodarone.[30]

A recommended oral dosing schedule for refractory ventricular arrhythmias is divided doses of 1200 to 1800 mg/day for 1 to 2 weeks, then 800 mg/day for 2 to 4 weeks, then 600 mg/day for 1 month, and 200 to 400 mg/day thereafter.

For atrial arrhythmias, the loading dose is 600 to 800 mg/day for 4 weeks, then 400 mg/day for 2 to 4 weeks, and 200 mg/day thereafter.[3]

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