

# Monitoring Amiodarone Therapy In Cardiac Arrhythmias In The Intensive Care Unit Of A Teaching Hospital In Ghana

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## Abstract

Amiodarone hydrochloride, an iodinated benzofuran derivative, is recognized for its antiarrhythmic properties in treating both ventricular and supraventricular arrhythmias, and for converting atrial fibrillation to sinus rhythm and maintaining sinus rhythm. Amiodarone has unusual and complicated pharmacokinetics: it is incompletely absorbed from the gastrointestinal tract and bioavailability is very variable, around 20-80%. Its major metabolite is desethylamiodarone which is pharmacologically active. Amiodarone is one of the most widely used antiarrhythmic medications but in spite of its usefulness amiodarone may have numerous and sometimes lethal side effects and the patient should be counseled on both the minor and serious adverse effects that are possible when taking this antiarrhythmic drug. The properties of amiodarone differ in a significant manner electrophysiological, pharmacokinetically and structurally from those of conventional as well as other investigational antiarrhythmic agents. The unique mechanism of action and the pharmacokinetics of amiodarone and how these factors impact adverse reactions and adhering to the recommended monitoring procedures and thereby providing effective patients counseling form the objectives of this article.

## INTRODUCTION

Amiodarone is generally indicated for life-threatening recurrent ventricular arrhythmias such as recurrent ventricular fibrillation (VF) and ventricular tachycardia (VT). Amiodarone is chosen when other available antiarrhythmics or alternative agents are not tolerated or the patient does not respond to other treatments. Amiodarone is effective in over 60-70% of these patients, but it is unknown if the drug is superior to an automatic implantable cardioverter-defibrillator device (AICD) in patients with ventricular tachycardia or ventricular fibrillation(1).

Amiodarone is the antiarrhythmic of choice, along with beta-blockers, in patients with sustained ventricular tachyarrhythmias who also have structural heart disease.

Amiodarone has greater than 60% two-year efficacy in reducing arrhythmias in patients with sustained ventricular tachyarrhythmias (VF/VT). Additional benefits to this patient population include minimal negative inotropic effects and proven long-term safety in post-myocardial infarction patients(2).

Atrial fibrillation (AF) is the most common sustained arrhythmias in general population and because AF is the most common cardiac arrhythmia occurring after

cardiothoracic surgery, amiodarone is often given to prevent postoperative atrial fibrillation. In a study by Barnes et al., patients receiving amiodarone prophylaxis experienced less postoperative atrial fibrillation (31% in the control group vs. 22% in the amiodarone treated group,  $p=0.027$ ) or had a shorter duration of atrial fibrillation after surgery than those not receiving amiodarone prophylaxis (4.7 days in the control group vs. 2.7 days in the amiodarone treated group,  $p=0.025$ ). Amiodarone was also noted to be cost effective in patients at high risk of developing postoperative a atrial fibrillation(3).

Amiodarone may also be used for the pharmacologic cardioversion of atrial fibrillation to normal rhythm (NSR), as well as to prevent recurrence of symptomatic paroxysmal and persistent atrial fibrillation after either electrical or pharmacological cardioversion. Amiodarone has been shown to be effective than placebo in the maintenance of sinus rhythm when continued for eight weeks following successful cardioversion. Additionally, when amiodarone was used long-term compared to placebo, more patients remained in sinus rhythm after one year, but these patients also developed an increased number of adverse events, such as thyroid abnormalities, bradyarrhythmias, abnormal liver function tests and photosensitivity. Due to the proven

efficacy of amiodarone treatment for eight weeks following cardioversion or cardiovascular surgery, it is a widely used option, especially in high risk patients, such as those with increasing age, a history of atrial fibrillation or chronic obstructive pulmonary disease, patients undergoing heart valve surgery or in patients whose beta-blockers or angiotensin converting enzyme inhibitors are discontinued after surgery(3,4)

Because of its minimal negative inotropic effects, amiodarone is sometimes chosen for heart rate control in patients with both atrial fibrillation and heart failure (HF). During long term therapy with amiodarone, there is a significant improvement in left ventricular ejection fraction with no impairment of ventricular function(1).

Amiodarone is also often used to help control a rapid ventricular heart rate due to accessory pathway conduction in pre-excited atrial arrhythmias(5).

Finally, when patients have a hemodynamically stable ventricular tachycardia, polymorphic ventricular tachycardia with a normal QT interval, or wide-complex tachycardia of unknown origin, amiodarone can be used as a treatment option (5).

## **MECHANISM OF ACTION**

Amiodarone is able to be used in such numerous medical scenarios including both ventricular and supraventricular arrhythmias because of its unique mechanism of action. It is considered to be a Vaugh Williams Class III antiarrhythmic agent, but it exhibits activities related to Class I, II and IV as well. Oral amiodarone therapy ultimately prolongs the duration of the action potential and the refractory period of all cardiac fibers by blocking sodium, calcium, and potassium channels. Its also noncompetitively inhibits alpha and beta-adrenergic receptors and displays vasodilatory and anti-ischemic effects. Amiodarone has the potential to decrease the sinus rate by 15-20%. It also increases PR and QT intervals by 10%. Along with leading to changes in T-wave contour, amiodarone can also cause U-wave development when looking at an electrocardiogram(EKG/ECG)(6)

## **PHARMACOKINETICS**

Absorption of Amiodarone is slow and variable after oral administration. Bioavailability is approximately 30-50%, but may vary by patient. The maximum concentration (C<sub>max</sub>) is attained 3-7 hours after a single dose. The onset of action is

seen anywhere between 2-3 days and 1-3 weeks after oral administration. However, the onset of action is noticed within hours of intravenous administration. The use of higher loading doses reduces this time interval.

Distribution is also variable, but is approximated to be around 60L/kg. Amiodarone is highly lipophilic and protein bound. Therefore, there is extensive accumulation in adipose tissue, liver, lungs, skin, and spleen. Many of these organs are affected by amiodarone and must be monitored appropriately. The ventricular myocardium develops a concentration 10-50 times that found in plasma. Plasma concentrations in patients successfully treated with amiodarone are usually in the range of 1.5-2.5mcg/mL.

Amiodarone is extensively metabolized to desethylamiodarone by CYP450 3A4 and 2C8 in the liver and the intestines. This metabolite is electro-pharmacologically active with a pattern similar to that of amiodarone.

Excretion of amiodarone is primarily via hepatic metabolism and biliary excretion. There is a negligible excretion of amiodarone and desethylamiodarone in the urine, and neither of these compounds is dialyzable. Doses of amiodarone do not have to be reduced in patients with renal impairment. The mean plasma terminal elimination half-life is 53 days for amiodarone and 36 days for desethylamiodarone. Therefore, without a loading dose, steady-state plasma concentration of oral amiodarone is reached between 120 and 535 days, with an average steady-state occurring in 265 days, or about nine months after starting the medication. When discontinuing amiodarone, levels of both the parent compound and the metabolite can be detected for up to nine months following cessation of therapy(1).

## **MONITORING**

Amiodarone interacts with a number of other cardiovascular medications that are also metabolized through CYP 450 3A4 and 2C8 in the liver. Included in these interacting drugs are digoxin, warfarin, quinine, procainamide, N-acetylprocainamide, flecainide, propafenone and phenytoin. Especially notable in this list are digoxin and warfarin. If digoxin is administered concurrently with amiodarone, plasma levels of digoxin double and when warfarin is given along with amiodarone, the INR may triple. Pharmacist must be diligent in finding and monitoring for these potentially fatal drug interactions(1)

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Patients often experience adverse side effects if amiodarone. In fact, adverse drug reactions are seen in as many as 15% of patients during the first year of amiodarone use, while 50% of patients will experience some type of unwanted side effect during long term use. However, many of these adverse drug reactions are manageable, and the need to actually discontinue amiodarone completely due to serious reactions occurs in less than 20% of patients. Because steady state is not achieved for greater than six months or longer, and because long term use produces greater numbers of side effects, physicians and pharmacists should ask about frequencies and changes in the following patient history accounts at each visit.

**Figure 1**

Patient History Questions	Purpose
Fatigue	<ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• AV block</li> <li>• Hypothyroidism</li> </ul>
Dyspnea/cough	<ul style="list-style-type: none"> <li>• Pulmonary toxicity</li> </ul>
Palpitations	<ul style="list-style-type: none"> <li>• Hyperthyroidism</li> <li>• Arrhythmias</li> </ul>
Syncope	<ul style="list-style-type: none"> <li>• Arrhythmias</li> </ul>
Visual changes (including loss of vision)	<ul style="list-style-type: none"> <li>• Optic neuropathy</li> <li>• Cornea microdeposits</li> </ul>
Skin changes	<ul style="list-style-type: none"> <li>• Photosensitivity</li> <li>• Slate blue skin discoloration</li> </ul>
Weight change	<ul style="list-style-type: none"> <li>• Hypothyroidism</li> <li>• Hyperthyroidism</li> </ul>
Weakness or paresthesias	<ul style="list-style-type: none"> <li>• Peripheral neuropathy</li> </ul>
Changes in medication therapy—especially additional antiarrhythmic medications, warfarin, beta-blockers, and digoxin.	<ul style="list-style-type: none"> <li>• Drug interactions/dosage adjustments</li> </ul>
Implanted devices (pacemakers, cardioverter-defibrillators)	<ul style="list-style-type: none"> <li>• Resolution of bradycardia</li> <li>• Possible ICD retesting due to increased defibrillation threshold</li> </ul>

It should be noted that each piece of information is used to rule out and gain insight into several potential adverse reactions of amiodarone.

Along with interviewing the patient, laboratory work and diagnostic testing should be performed at regular intervals and should be compared to baseline values obtained before the start of amiodarone. Only with baseline lab values available is it possible for the prescriber and pharmacist to determine if abnormal values are due to amiodarone therapy

or to other causes. There have been no universally accepted guidelines published for the proper frequency of laboratory monitoring in amiodarone patients, but The North American Society of Pacing and Electrophysiology has made their recommendation as follows:

**Figure 2**

Laboratory Test	Frequency
Liver function Tests	Baseline and every 6 months
Thyroid Function Tests (T4 and TSH)	Baseline and every 6 months
Serum creatine and electrolytes	Baseline and every 6 months
Chest X-ray	Baseline then yearly
Ophthalmologic evaluation	At baseline and if visual impairment or for symptoms
Pulmonary Function Tests (including DLCO)	Baseline and for expected dyspnea, especially in patients with underlying lung disease, and if there are suggestive x-ray abnormalities
ECG	Baseline then yearly

The reason why it is necessary to ask these various questions and obtain so many types of laboratory/diagnostic data is the fact that amiodarone is capable of inducing adverse reactions in numerous parts of the body. Amiodarone may cause hepatitis, thyroid abnormalities, pulmonary toxicity, ophthalmologic effects, worsening arrhythmias, neurological changes, photosensitivity and gastrointestinal tract disturbances (to list but a few). One must be cautious when gathering information to be sure to look at the entire patient profile. Amiodarone can cause all of the previous disorders, but there are also numerous other drugs and conditions that can lead to the same signs and symptoms that are unrelated to amiodarone. The clinical pharmacist must be able to monitor for adverse effects, interpret laboratory/diagnostic data and patient symptoms and answer patient questions regarding these possible adverse events.

### ELECTROLYTE DISTURBANCES

Although unlikely, amiodarone has the potential to be proarrhythmic or ineffective, especially in hypokalaemic patients. However, it is important to note that despite all of amiodarone's possible side effects it will not cause electrolyte disturbances. Both potassium and magnesium deficiencies should be corrected before the start of amiodarone therapy and should be monitored periodically. Caution should be noted when amiodarone is given concurrently with medications known to induce

hypokalaemia (diuretics, laxatives, theophylline, verapamil, high-dose penicillin, and ampicillin) or hypomanganesemia (aminoglycosides, amphotericin B, cyclosporine, diuretics, digitalis and cisplatin) (2).

### **ADVERSE CARDIAC REACTIONS**

Although only occurring in 2%-5% of patients, there are various types of arrhythmias that may occur with amiodarone therapy. The most common include new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and torsades de pointes associated with QT prolongation. Torsades de pointes is a life-threatening ventricular tachyarrhythmia characterized by QRS complexes continuously changing in morphology around an imaginary isoelectric line. This condition is triggered by extra ventricular beats which can be induced by early depolarization in cells with long repolarization phases such as cardiac fibers affected by amiodarone. Amiodarone almost always causes an increase in the QT interval, but torsades de pointes is rather rare. A meta-analysis covering more than 2,800 patients taking amiodarone reported torsades de pointes in only 0.7% of these patients(7). Case reports show that an elevated QT interval leading to torsades de pointes has occurred when amiodarone is administered at high loading doses to control atrial fibrillation in patients already receiving a beta-blocker and digitalis. After treatment for torsades de pointes and discontinuation of amiodarone, case studies show that patients did not experience ventricular arrhythmias. Therefore, although torsades de pointes is rare with amiodarone use, patients may be at higher risk of this arrhythmia when also taking rate control medications (8). An abnormally long QT interval may also occur when amiodarone is administered along with other drugs known to prolong the QT interval such as fluoroquinolones or known to inhibit the metabolism of amiodarone such as macrolides especially erythromycin, azole antifungals, and high dose of certain statins (especially simvastatin).

Bradycardia is another expected effect of amiodarone and permanent pacing is sometimes required. An electrocardiogram should be monitored frequently in patients taking amiodarone therapy to determine if there are possible arrhythmias that could be prevented.

### **ELECTROCARDIOGRAM (ECG)**

Because amiodarone is known to cause QT prolongation, an ECG should be monitored at baseline and at least yearly

thereafter. The risk of torsades de pointes is not related linearly to the degree of QT prolongation, but any drug that prolongs the QT interval beyond 500 msec is thought to confer an elevated risk. At this point, it is important to note that one should address the QTc rather than the QT because QT may be affected by heart rate (i.e. the faster the heart rate, the shorter the QT interval. When reading an ECG, the dose of amiodarone should be decreased or the drug should be discontinued if the length of the QTc closely approaches or exceeds 500 msec(9).

### **THYROID ABNORMALITIES**

Amiodarone has the potential to cause either hypothyroidism or hyperthyroidism. Hypothyroidism is the more common side effect, occurring in 2%-10% of patients. Hypothyroidism is due to the inhibition of the peripheral conversion of thyroxine (T4) to triiodothyronine (T3). Also, the amiodarone molecule is rich in iodine and a 100mg tablet contains 250mg the recommended daily iodine requirement. The Wolf-Chaikoff effect states that an increased ingestion of inorganic iodine may lead to hypothyroidism.

Amiodarone-induced hypothyroidism is identified by clinical symptoms and by monitoring the thyroid stimulating hormone (TSH) level. It can be managed by amiodarone dose adjustment and/or the administration of thyroid replacement therapy such as levothyroxine.

Hyperthyroidism occurs in only two percent of patients taking amiodarone. Amiodarone-induced hyperthyroidism is more dangerous than hypothyroidism because of the possibility of thyrotoxicosis or arrhythmia recurrence, both of which could be fatal. Because of the severity of hyperthyroidism in patients with an already established arrhythmia, aggressive medical treatment, along with dose reduction or withdrawal of amiodarone is usually necessary.

Treatment options may include antithyroid medications, beta-blockers, corticosteroids or even thyroidectomy. Radioactive iodine therapy is contraindicated due to the low radioactive uptake associated with amiodarone-induced hyperthyroidism.

### **PULMONARY TOXICITY**

Amiodarone is also known to cause pulmonary injury which can be acute or chronic, and may progress to respiratory failure or death. Many times amiodarone-induced pulmonary toxicity mimics congestive heart failure, which a cough and progressively worsening dyspnea. Many amiodarone patients

might have already been diagnosed with congestive heart failure, so care must be taken to evaluate these patients for pulmonary toxicity related to amiodarone instead of just assuming they are experiencing a heart failure exacerbation. Because pulmonary toxicity is a relatively rare adverse effect of amiodarone, it can be easily missed by physicians and pharmacists when patients complain of nonspecific pulmonary complaints during amiodarone treatment. Amiodarone often must be discontinued if pulmonary toxicity occurs, so other causes of respiratory impairment should be ruled out before the drug is immediately stopped. Along with congestive heart failure, the patients with life threatening arrhythmias should be evaluated for infection, pulmonary embolism, and malignancy before discontinuing amiodarone(15).

There are two main types of amiodarone-induced pulmonary toxicity. Hypersensitivity pneumonitis usually occurs early in the course of amiodarone therapy. A rechallenge with amiodarone will likely result in a more rapid recurrence with greater severity. A bronchiolar lavage can confirm the diagnosis of hypersensitivity pneumonitis, as it will show CD8 positive lymphocytosis. In cases of hypersensitivity pneumonitis, amiodarone should be permanently discontinued, and the patient should begin treatment with steroids.

Interstitial/alveolar pneumonitis, leading to pulmonary fibrosis is a chronic condition that often occurs after prolonged amiodarone use, but may result after short term use in high risk patients (advanced age and/or pre-existing pulmonary abnormalities). Pulmonary fibrosis results from oxygen radicals and/or phospholipids, which have direct cytotoxic effects on the alveolar-capillary membrane in the lungs. Clinical signs of pulmonary fibrosis include diffuse alveolar damage, interstitial pneumonitis and fibrosis upon lung biopsy. Pulmonary function tests will reveal a restrictive pattern and a reduction in diffusing capacity of carbon monoxide (DLco). Arterial blood gases will show hypoxemia exaggerated with exercise. Patients diagnosed with pulmonary fibrosis have a 50%-70% chance of mortality in five years, so if pulmonary fibrosis is expected, amiodarone should be discontinued if other causes are first ruled out. There is no known effective treatment for pulmonary fibrosis, but the standard of care remains corticosteroids such as prednisolone 0.5-1mg/kg/day by mouth once daily for three months, tapered to 0.25mg/kg/day over the next three to six months. Although

not proven effective, cyclosporine or azathioprine is often given for treatment as well(6).

Both a chest X-ray and pulmonary function tests should be obtained at baseline and monitored at frequent intervals throughout therapy with amiodarone to evaluate for the possibility of amiodarone-induced pulmonary toxicity. If patients have symptoms of pulmonary toxicity (i.e. cough, dyspnea, fever, bodyweight loss, respiration-related chest pain etc) these tests should also be performed and compared to baseline tests. If diagnosed early enough in the disease progression, pulmonary toxicity may be reversed if amiodarone is discontinued, but it might also be fatal.

### **CHEST X-RAY**

Pulmonary fibrosis should be suspected if a chest X-ray shows diffuse reticular opacities in the lower and peripheral lung zones. Small cystic lesions and dilated airways due to traction bronchiectasis also may be seen. If pulmonary function tests show a decrease in the diffusing capacity of carbon monoxide (DLco), the diagnosis of pulmonary toxicity is supported(2).

### **OPHTHALMOLOGIC EFFECTS**

The majority of patients taking long-term amiodarone therapy will develop corneal microdeposits, which are a reflection of the drug's absorption and are completely normal. These microdeposits can only be seen by a slit-lamp examination performed by an optometrist or an ophthalmologist, and do not cause any changes in vision. Therefore, if an optometrist notices these corneal microdeposits but the patient has no visual symptoms, the dose of amiodarone should not be changed or discontinued. However, about 10% of amiodarone patients will complain of visual halos and /or blurred vision. If these symptoms occur, a reduction of the dose of amiodarone or discontinuation of the drug will reverse the problem. The most serious ophthalmologic effect of amiodarone therapy is optic neuropathy or optic neuritis, which can lead to visual impairment and ultimate blindness. Optic neuropathy can occur at any time during amiodarone therapy, so if symptoms such as changes in visual acuity and decreases in peripheral vision are noted, prompt ophthalmic examination is needed, with possible discontinuation of amiodarone(2)

A baseline examination should be obtained in any patient who has significant visual abnormalities. Regular ophthalmic examination, including funduscopy and slit-lamp examination, is recommended during administration of

amiodarone(6).

## **NEUROLOGICAL CHANGES**

Chronic amiodarone administration orally may induce peripheral neuropathy that may resolve with the discontinuation of amiodarone therapy. Other neurologic effects that amiodarone can cause include cerebellar ataxia, sleep disturbances, and impaired memory. Both physician and pharmacists should periodically monitor patients taking amiodarone for any of these adverse drug effects.

Discontinuation of amiodarone should be considered if any of these effects become severe(2).

## **CONCLUSION**

Amiodarone is a unique medication with several mechanisms of action that makes it efficacious in multiple arrhythmias. Although used both acutely and chronically, cardiologists and clinical pharmacists can play a large role in helping to monitor long-term oral amiodarone therapy. Knowledge of a particular patient's serum level aids in maintaining the patients on the lowest possible dose of amiodarone. This is a sensible strategy since treatment is usually long term and the occurrences of side effects appears at least in some cases to be related to total dose consumed. The high incidence of amiodarone side effects makes it highly desirable to minimize the exposure of an individual patient to the drug whilst maintaining effectiveness of therapy. Fortunately, most of these side effects are relatively well tolerated and only in a small minority of patients are these effects serious enough to necessitate withdrawal of therapy. With close monitoring, serious side effects can be kept at a low and acceptable level by taking the appropriate action whenever the serum level rises above the minimum value associated with rhythm control in a particular patient and an elevated metabolite level is treated as an early warning system. Due to the chemical properties and structure of amiodarone, it has the capabilities of causing

adverse reactions in multiple organs including the liver, thyroid, skin, lungs, eyes and gastrointestinal system. By working together, cardiologists and clinical pharmacists can be sure that each patient taking amiodarone is monitored for adverse reactions appropriately. The clinical pharmacist can also help reassure and educate patients when questions and concerns evolve throughout the course of therapy. Although amiodarone can be a dangerous medication, when monitored appropriately, it can increase the quality of life and the time in normal sinus rhythm.

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