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Adverse Effects of Amiodarone

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JAFARI-FESHARAKI, M., ET AL.: Adverse Effects of Amiodarone. Amiodarone was introduced 30 years ago as an antianginal agent and subsequently has been used as an antiarrhythmic agent. This drug was initially used for patients with malignant ventricular arrhythmias; however, currently it is being used broadly for rate and rhythm control in patients with atrial fibrillation. At first, amiodarone was primarily used by cardiologists and today it is used throughout the medical profession. Amiodarone therapy can potentially result in a wide range of adverse effects. The majority of these adverse effects are dose related and reversible. The following is a review of the adverse effects and drug interactions of amiodarone along with recommendations for identification and management of these adverse effects. (*PACE* 1998; 21[Pt. I]:108-120)

amiodarone, digoxin, warfarin, antiarrhythmics, adverse effects, drug interactions

Amiodarone is an iodinated benzofuran derivative which is extremely effective in the treatment of life-threatening ventricular and refractory supraventricular arrhythmias.¹ Its use, especially at high doses exceeding 400 mg/day, has been associated with the development of numerous adverse reactions that require discontinuation of the drug in 2%–26% of patients.² The adverse effects are seen less in patients treated with 200 mg/day or less as used in patients with supraventricular tachycardia. Some of the most common adverse reactions include nausea, vomiting, constipation, anorexia, blue-gray skin discoloration, and corneal microdeposits. The most serious adverse reactions are, pulmonary toxicity, hepatotoxicity, and exacerbation of arrhythmias. These side effects are often reversible upon dose reduction or cessation of the drug. The mechanism of amiodarone induced toxicity is thought to be multifactorial with varying tissue effects. Reasons for the potential side effects include the wide distribution of amiodarone in all tissues containing adipose cells, accumulation in organs such as the lungs and liver, and the long elimination half-life

of 25–50 days (average of 26 days).^{3–5} Direct accumulation of amiodarone and iodine, phospholipidosis, free radical formation, immunologic injury, and altered cellular function all play a role in the mechanism of toxicity.^{2,3}

Gastrointestinal Effects

Up to 33% of patients receiving oral amiodarone experience gastrointestinal disturbances, which are most common during the loading period when high doses are prescribed. Gastrointestinal disturbances appear to be dose dependent and occur more frequently with doses exceeding 600 mg/day.^{4,5} The most common symptoms include but are not limited to: nausea, vomiting, constipation, and anorexia and have been reported in up to 80% of patients.^{6–11} Other rare gastrointestinal side effects include epigastric fullness or burning, abdominal pain, abnormal salivation, and abnormal taste. The mechanism of amiodarone induced gastrointestinal toxicity is unknown. Discontinuation of the drug is rarely required and the signs and symptoms of gastrointestinal side effects are usually alleviated by dose reduction, administration in divided doses with meals, and discontinuance of the drug.^{5,12,13}

Hepatic Effects

Amiodarone induced elevations in serum aspartate transaminase (AST, SGOT), alanine

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transaminase (ALT, SGPT), aminotransferase, and alkaline phosphatase concentrations are usually mild, transient, and not accompanied by clinical symptoms. These abnormalities are generally reversible with dose reduction or discontinuation of the drug.^{6,14}

Elevation of liver function tests have been reported in 5%–20% of patients receiving oral amiodarone, the incidence has been reported as high as 96% in some studies.¹⁴ Hepatic toxicity is generally dose dependent and reversible. Even though elevation of liver enzymes have been observed within 1 week of onset of therapy with doses as low as 200 mg/day, it usually takes several months for this adverse effect to become manifest. The incidence of severe symptomatic hepatic injury such as clinical hepatitis, cholestatic hepatitis, and cirrhosis is < 3% and, therefore, the need to discontinue the drug is unusual in the majority of patients experiencing hepatic side effects.^{14,15}

Signs and symptoms of amiodarone induced hepatotoxicity may include hepatomegaly, generalized muscular weakness, jaundice, fatigue, malaise, ascites, abdominal pain, nausea, vomiting, anorexia, and weight loss. Hyperbilirubinemia, leukocytosis, and increased prothrombin time have also been reported. Histologic abnormalities are very similar to those of alcoholic hepatitis or cirrhosis. Microscopic tissue changes may include Mallory bodies within hepatocytes, mild lymphocytic infiltrates, collagen deposits, fibrosis, steatosis, hepatocyte destruction, cholangitis, and portal inflammation.^{14,16} The results of electron microscopic studies demonstrate phospholipid laden lysosomal inclusions within hepatocytes, bile duct epithelium, Kupffer cells, and endothelial cells. The exact mechanism of hepatic injury has not been established, however, limited evidence suggests that amiodarone may form complexes with phospholipid and hepatic lysosomes resulting in phospholipidosis.¹⁶

Hepatic dysfunction may not resolve upon withdrawal of the drug. The slow elimination of amiodarone (mean half-life of 26 days) accounts for the persistence of elevated levels of amiodarone and its metabolite desethylamiodarone in plasma and tissue for weeks to months following withdrawal of the drug.^{14,17} It is recommended that levels of serum hepatic enzymes be checked prior to initiating therapy and be monitored every 6

months thereafter. The dose of amiodarone should be reduced or discontinued in patients with persistent serum hepatic enzyme levels of three times the upper limit of normal values. If elevations persist or hepatomegaly develops, a liver biopsy should be performed in order to ascertain and characterize the type and degree of hepatic injury.¹⁸

Dermatological Effects

Dermatological side effects such as photosensitivity and blue-gray skin discoloration are commonly reported with amiodarone.² Dermatological adverse effects due to amiodarone occur universally in unprotected skin areas exposed to light. Amiodarone photosensitivity manifests as a sunburn with erythema and varying degrees of edema. Microscopic evaluation of the pigmented skin specimens of patients with amiodarone induced dermatological problems show that the concentration of amiodarone and its metabolite, desethylamiodarone, are 10 times higher in skin areas exposed to light compared to nonexposed areas. Because of these characteristics, amiodarone skin reactions are classified as phototoxic rather than photoallergic reactions. Zachary et al.,¹⁹ using monochromator light tests, reported that UV-A and UV-B radiation predisposed the skin to this phototoxic reaction. Although reducing the amiodarone dose appears to alleviate some of the symptoms, it is still unclear whether or not amiodarone induced photosensitivity is dose related.^{2,19,20} Photosensitivity to amiodarone is considered a mild adverse reaction that can be minimized by educating patients to use sunscreens that contain zinc or titanium oxide.

Amiodarone induced blue-gray pigmentation is commonly observed in unprotected light exposed skin.²¹ However, Raeder et al.¹² report that skin discoloration occurs in two of their patients in nonexposed areas. The incidence of amiodarone induced blue-gray skin discoloration ranges from 2%–57% and it appears to be dose related.² Histopathological studies by Zachary et al.¹⁹ confirm the presence of iodine bound to lipofuscin granules within the dermal macrophages of skin biopsies of patients who developed blue-gray skin discoloration with amiodarone therapy. These findings demonstrate that lipid-soluble amiodarone molecules are phagocytosized by the

macrophages of the dermis cells and appear as a blue-gray skin discoloration. Amiodarone induced blue-gray skin discoloration usually fades slowly after discontinuation of the drug.¹⁹

Hair loss, allergic-type reactions such as pruritic rash, and exacerbation of psoriasis have also been infrequently reported with amiodarone therapy. Raeder et al.¹² reported the occurrence of hair loss in nine of their patients (4%) after an average of 10 months of therapy. Of note, they reported that hair growth resumed when amiodarone was discontinued.¹² Hair loss may be secondary to severe hemodynamic compromise.

Even though the incidence of dermatological side effects with amiodarone therapy is high, amiodarone is rarely discontinued for this reason.

Ophthalmological Effects

Ocular adverse effects during amiodarone therapy are asymptomatic in the majority of cases but they are universal. The development of corneal microdeposits is the most common side effect observed with amiodarone therapy. In a small number of patients, corneal microdeposits lead to symptoms such as photophobia, blurred vision, and halos. Despite these symptoms, discontinuation of the drug is rarely required. Ingram retrospectively evaluated the ocular complications of amiodarone in 103 patients. He reported that microdeposits were observed in 98% of patients after a total dose of 9 g or less and about 1 month of therapy.²² Morphological studies of amiodarone induced keratopathy reveal that microdeposits have a whorl-like pattern, and are bilateral, often symmetrical, golden-brown, and located in the epithelium anterior to Bowman's membrane. The pattern of keratopathy evolves over the duration of therapy and it is believed to be dose related. Histological studies suggest that microdeposits are composed of intracytoplasmic lysosomal-like inclusions of drug or drug-lipid complexes.^{23,24} In addition, Ghosh and McCulloch²⁵ reported the presence of intracytoplasmic membrane bound lamellar bodies in all layers of cornea and conjunctival epithelium. The structure of these lamellar bodies were very similar to myelin. Ghosh and McCulloch supported the theory of drug induced lipidosis in the formation of amiodarone induced corneal microdeposits.²⁵

The progress of amiodarone induced keratopathy is related to the dose and duration of therapy.^{2,23,25-27} However, discontinuation of the drug is not necessary even in symptomatic patients, dose reduction may alleviate ocular symptoms. Discontinuation of amiodarone is recommended only in patients with severe retinal abnormalities.

Nervous System Effects

Neurological adverse effects occur in approximately 20% of patients receiving long-term amiodarone treatment.²⁸ The most common signs and symptoms include tremor, ataxia, and peripheral neuropathy and they all appear to be dose dependent occurring as early as 1 week after initiating therapy.²⁹⁻³¹ Although, in the majority of studies these adverse effects are rarely reported, some investigators have reported incidences as high as 74%.¹⁰ In a retrospective study on 408 patients examining the neurological problems with amiodarone, paresthesia (8.8%), gait ataxia (9%), vertigo (8.6%), and tremor (7%) were considered the most common adverse effects. Several studies indicate that the neurological effects with amiodarone were dose and duration related, other studies did not find any correlation based on serum concentration of amiodarone.²⁸

Amiodarone induced peripheral neuropathy is well documented, it affects all four limbs, and is generally symmetrical.³² Neuropathy usually manifests after several months of therapy.³³ Neuropathological and nerve conduction studies in animals receiving amiodarone have revealed pure demyelination and complete axonal degeneration resulting in reduced nerve conduction velocities.^{34,35}

Tremor is generally the earliest reported nervous system adverse effect and is classified as a mild adverse effect, which subsides with dose reduction and it rarely requires discontinuation of the drug.^{28,33}

Ataxia is another common side effect with amiodarone with gait ataxia being the most common form. Common complaints are reported as frequent falls and impaired ambulation, which could be dangerous in the elderly population, which compromises the majority of patients on long-term amiodarone therapy. Amiodarone in-

duced nervous system effects can be alleviated within a few days by dose reduction and rarely require discontinuation of the drug.

Pulmonary Effects

Pulmonary complications are the most serious side effects attributed to long-term amiodarone therapy.^{1-3,5,17,36-39} Amiodarone induced pulmonary toxicity has been observed in approximately 0.5%–10% of patients and in some instances has been associated with mortality.¹ It is not clearly established whether or not pulmonary toxicity is dose dependent but it appears to be rare in patients receiving < 400 mg of amiodarone per day. The total cumulative dose or duration of exposure may possibly be more important than the daily dose.^{2,40} Amiodarone induced pulmonary toxicity is rarely reported with doses below 400 mg/day when the drug is administered for < 2 months.^{5,36}

Amiodarone induced pulmonary toxicity has been described as pulmonary alveolitis, pulmonary infiltrates, pneumonia, and pulmonary fibrosis.³⁷⁻⁴⁰ Amiodarone induced pleural effusions are very unusual. Signs and symptoms are non-specific but the most common manifestations of amiodarone induced pulmonary toxicity include exertional dyspnea, malaise, decreased breath sounds, bilateral rales, pleural rub, pleuritic chest pain, weakness, myalgia, myopathy, and weight loss.^{2,10,27-29, P3}

Polkey et al.³⁷ have suggested two distinct patterns of amiodarone induced pulmonary toxicity. The more common symptoms in patients with amiodarone induced pulmonary toxicity include the onset of a new nonproductive cough, dyspnea, weight loss, occasional fever, and diffuse interstitial infiltrates. The less common symptoms include the acute onset of fever and peripheral alveolar infiltrates, which occur early during therapy and may represent an allergic or hypersensitivity reaction.^{2,37} However, clinicians should not attribute these symptoms to amiodarone without ruling out congestive heart failure or pulmonary embolism.⁴¹ The hypersensitivity reaction hypothesis is based on the findings of increased suppressor and cytotoxic T cells (CD8+, T8+) and neutrophils in bronchoalveolar lavage in most patients with amiodarone induced pulmonary toxicity.^{1-3,17,37}

It may be difficult to distinguish between amiodarone induced pulmonary toxicity and signs and symptoms of congestive heart failure in patients with underlying left ventricular dysfunction or pulmonary infection.² Right heart catheterization may be required to exclude the diagnosis of cardiac failure. Laboratory abnormalities are at best suggestive and include leukocytosis, hypoxemia, hypercarbia, and a slight increase in lactate dehydrogenase levels.^{2,42} Chest X ray findings are variable and may consist of peripheral, apical, bilateral diffuse interstitial infiltrates, or patchy alveolar infiltrates.^{2,17,37,43} Pulmonary function tests reveal a decrease in diffusion capacity, which is the most consistent abnormality. A decrease in diffusion capacity is not useful in predicting amiodarone induced pulmonary toxicity in asymptomatic patients. It should be noted that usual symptoms, abnormal chest X rays, abnormal pulmonary function tests, decreased lung compliance, and a positive gallium scan do not provide specific diagnostic criteria for a diagnosis of amiodarone induced pulmonary toxicity.^{1,2,5,17,42,44}

Bronchoalveolar lavage reveals "foamy" cytoplasmic inclusions, which may represent drug impregnation rather than a manifestation of toxicity since they can be seen in up to 50% of patients without toxicity.^{1,2,17,38,42} Figures 1 and 2 show sections of transbroncheolar biopsies of a patient with amiodarone induced pulmonary toxicity. Figure 1 shows alveolar spaces filled with large foamy macrophages. These macrophages contain multiple laminated bodies. Figure 2 shows late patchy architectural distortion with "honey combed" air spaces and fibrosis in their walls.

The exact mechanism of amiodarone induced pulmonary toxicity is unknown. However, an accumulation of phospholipids within the lung tissues, free radical formation, increased iodine content, and altered cellular function secondary to the amphiphilic nature of amiodarone have been suggested as causative factors. Phospholipid accumulation is thought to be caused by amiodarone inhibiting phospholipase A. Since the lung is the main organ of phospholipid metabolism, it is very susceptible to amiodarone's toxic effects.^{1,3} Phospholipidosis results in an accumulation of lamellar bodies, membrane stiffness, and cell damage. Damage of immunological cells such as macrophages is of particular concern

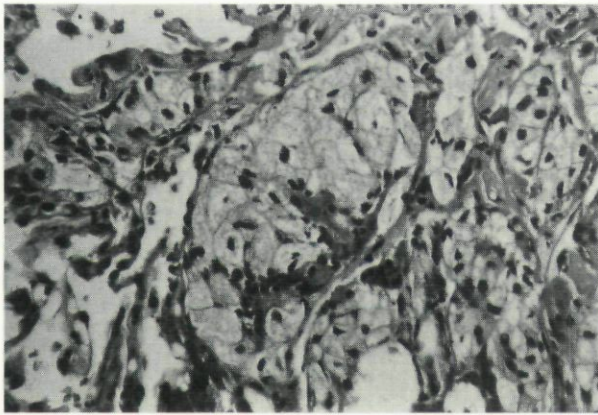


Figure 1. Section of transbronchiolar biopsy of a patient with amiodarone induced pulmonary toxicity. Some alveolar spaces filled with large foamy macrophages which contain multiple laminated bodies (magnification $\times 275$).

since they are able to release immunological or toxic mediators inducing inflammation. No definite mechanism of amiodarone induced hypersensitivity has been established.

It is not clear whether patients with preexisting lung diseases have a higher risk of developing amiodarone induced pulmonary toxicity. It is likely that such patients have the same risk but are more symptomatic with the development of amiodarone induced pulmonary toxicity.

Symptoms of amiodarone induced pulmonary toxicity usually diminish with dose reduction, discontinuation of the drug, or administration of steroids.¹⁷

Thyroid Effects

Amiodarone contains two atoms of iodine, which represent approximately 37% of the molecular weight of the compound. There are 75 mg of organic iodine in a 200-mg amiodarone tablet. The average daily intake of iodine is 0.5–1 mg. Therefore, 75 mg of iodine is far in excess of the normal daily iodine intake. In addition, there are structural similarities between amiodarone and thyroid hormones. Because of these features, the effects of amiodarone on thyroid function are of particular importance to clinicians. A number of studies have reported the effects of amiodarone on thyroid hormones. Although long-term administration of amiodarone increases significantly thyroxine (T4)

and reverse T3 (rT3), and increases moderately thyroid stimulating hormone (TSH), and decreases triiodothyronine (T3), yet the overt clinical effects of amiodarone on thyroid function remain complex.⁴⁵ Amiodarone decreases the peripheral conversion of T4 to T3, inhibits T3 binding to thyroid receptors, and inhibits entry of thyroxine and T3 into peripheral tissues. As a result of various metabolic effects of amiodarone on thyroid function, both hypo- and hyperthyroidism may develop with amiodarone.⁴⁶ The overall incidence of thyroid dysfunction with amiodarone is 2%–24%. Thyrotoxicosis is more common in areas with low iodine intake and hypothyroidism is more common in areas with high iodine intake.^{47,48}

Thyrotoxicosis

Thyrotoxicosis occurs in about 1%–23% of patients and this incidence may be as high as 10% during long-term amiodarone therapy.³⁰ Although the exact mechanism of amiodarone induced thyrotoxicosis is not well defined, it is postulated that the high iodine content of amiodarone increases thyroid hormone synthesis. Classic symptoms of amiodarone induced thyrotoxicosis are unexplained weight loss, goiter, tremor, muscle weakness, recent occurrence of sinus tachycardia, a significant increase in T4 and T3 levels, and marked decreases of 96% in TSH levels. Treatment of amiodarone induced thyrotoxicosis is dif-

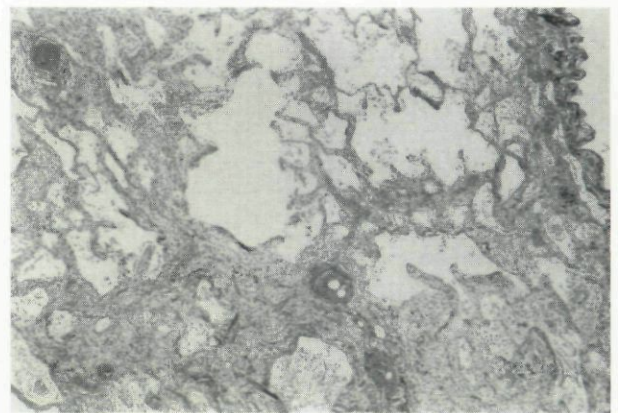


Figure 2. Section of transbronchiolar biopsy of a patient with amiodarone induced pulmonary toxicity. Late patchy architectural distortion with enlarged "honey combed" air spaces with fibrosis in their walls (magnification $\times 85$).

difficult because of the long half-life of amiodarone and more importantly in situations when the drug may not be discontinued in cases of refractory ventricular arrhythmia. Thionamides, methimazole, and propylthiouracil have been tried as medical therapy with as an effective first line treatment. Medical regimes can take many weeks and often requires discontinuation of the amiodarone. In patients with severe refractory ventricular arrhythmia thyroidectomy is considered a safer and more effective approach. Thyroidectomy controls thyrotoxicosis without risking discontinuing amiodarone therapy.⁴⁷ Thyrotoxicosis occurs mostly after 3–5 years of treatment with amiodarone.⁴⁸

Hypothyroidism

Hypothyroidism occurs in 1%–32% of patients receiving amiodarone and it usually occurs early in the therapy (< 12 months). The mechanism of this side effect is even less well understood and it is thought to be multifactorial. Some investigators believe that this could be mediated by the iodine content of amiodarone. Amiodarone metabolism releases iodine, which inhibits thyroid hormone biosynthesis and release. Thyroid hormone biosynthesis resumes with further exposure to iodine. However, in patients who remain in a hypothyroid state, inhibiting effects of iodine persists. Some suggest that this is secondary to a defect in thyroid hormonogenesis. On the other hand, some investigators suggest that underlying autoimmune thyroiditis increases the risk of amiodarone induced hypothyroidism. Preexisting thyroid antibodies in women increases the risk of amiodarone induced hypothyroidism by 13.5-fold.⁴⁷

Amiodarone induced hypothyroidism can be transient or persistent. In general, persistent hypothyroidism develops in patients with underlying thyroid abnormalities, such as nodular goiter or autoimmune thyroid disorders.⁴⁹ Classic signs and symptoms of amiodarone induced hypothyroidism include fatigue, intolerance of cold, dry skin, and a low level of T₃, elevated levels of thyrotropin, and low or normal levels of T₄.^{3,47}

Treatment of amiodarone induced hypothyroidism seldom requires amiodarone discontinuation and dosage reduction. Supplementation with

thyroid replacement therapy usually suffices. Thyroid replacement agents must be administered with extreme caution in patients with angina pectoris or other cardiovascular diseases because such drugs can aggravate these conditions. It is advised to test thyroid function at the baseline, 3 months after initiation amiodarone therapy, and every few months thereafter.

Cardiovascular Effects

Cardiovascular complications secondary to amiodarone are rare and mostly result from the potentiation of the pharmacological properties of the drug. Among cardiovascular adverse effects of amiodarone, exacerbation of congestive heart failure, sinus bradycardia, and arrhythmia such as torsades de pointes (TdP) have been mentioned in the literature.⁵⁰ The incidence of amiodarone induced TdP is reported to be < 2% with the highest prevalence when amiodarone was used concomitantly with other antiarrhythmic agents, such as Class I agents (quinidine and procainamide).⁵¹ Although amiodarone prolongs QT intervals, it rarely induces TdP.^{50–54} The low incidence of amiodarone induced TdP could be due to the fact that amiodarone decreases QT dispersion as well as lengthening the repolarization. This electrophysiological property of amiodarone is very significant and makes the drug very safe in patients with a history of quinidine or procainamide induced TdP.⁵¹ Amiodarone is commonly used in patients with refractory congestive heart failure due to its vasodilatory and anti-ischemic effects. Preliminary results from CHF-STAT trial, reported that amiodarone can actually increase the ejection fraction in patients with cardiac failure.⁵⁰ Middlekauff et al. studied 205 patients to assess amiodarone safety in patients with congestive heart failure who have had prior episodes of antiarrhythmic drug induced TdP. They concluded that prior history of drug induced TdP could be a risk factor for the development of TdP during amiodarone therapy only in patients with advanced heart failure.^{2,55}

Sinus bradycardia occurs in approximately 2% of patients on amiodarone. This adverse effect is usually not profound enough to require amiodarone discontinuation or pacemaker therapy. Bradycardia often resolves with dose reduction.⁵⁶

Although cardiovascular side effects are of concern in some patients, they occur very rarely and it is usually difficult to differentiate them from the pharmacological properties of the drug.

Intravenous Amiodarone

Hypotension, bradycardia, and worsening of CHF are reported with intravenous amiodarone.⁵⁷⁻⁶² The safety of intravenous amiodarone has been evaluated in controlled and open labeled trials. Overall, intravenous amiodarone was well-tolerated and the drug was only discontinued in < 5% of patients due to life-threatening adverse events such as asystole, hypotension, and cardiogenic shock.^{63,64}

Intravenous amiodarone is administered as a loading infusion (15 mg/min over 10 min and 1 mg/min over the next 6 hours) followed by a maintenance infusion (0.5 mg/min). Hypotension and bradycardia, the most commonly adverse events reported with intravenous amiodarone, usually occurs during the loading infusion.

Although vasodilatory and negative inotropic effects of amiodarone may contribute to hypotension, it is postulated that benzyl alcohol and polysorbate 80 diluent, which possessed vasodilatory properties, rather than amiodarone itself cause hypotension. In a dose ranging study, Scheinman et al. reported that intravenous amiodarone induced hypotension and bradycardia were infusion rate related and not dose related.⁶³ Although the need for vasopressor therapy was reported as high as 14% in a multicenter study conducted by Levine et al.,^{65,66} in the majority of cases, these adverse events were self-limiting and vasopressor therapy or the placement of a pacemaker were rarely used to treat these adverse events.^{63,67}

The use of intravenous amiodarone is usually warranted for critically ill patients with refractory ventricular arrhythmias and who often have pre-existing heart failure.^{65,67} On the other hand, the worsening of congestive heart failure has been reported with intravenous amiodarone. As it was previously mentioned under the cardiovascular effects of amiodarone, the extent to which amiodarone contributed to CHF is not well-established. Because of amiodarone's negative inotropic activity, a temporary depression in left ventricular

function develops after initiating intravenous amiodarone. This effect in general is only clinically significant in patients with severe heart failure.⁶⁸ Therefore, close hemodynamic monitoring is highly recommended during intravenous amiodarone therapy.

Typical adverse effects seen with chronic use of oral amiodarone were not observed with intravenous amiodarone, hepatic toxicity was seen in 9%–17% of patients. Among the liver function tests abnormalities, elevated alanine aminotransferase (AST), γ -glutamyl transferase, and bilirubin were most common. Of note, hepatic dysfunction was not considered to be dose related and changes in liver function tests returned to normal within a few days of therapy with or without withdrawal of the drug.^{70,71} Clinicians should be cautious in interpreting elevated AST since the value may be elevated in patients with severe congestive heart failure and not reflecting an adverse effect caused by amiodarone.¹⁸

The underlying mechanism for acute hepatotoxicity associated with intravenous amiodarone is unknown. However, Rhodes et al. suggested that polysorbate 80 contributes to intravenous amiodarone induced hepatotoxicity.⁷⁰ Similar adverse reactions have been observed with polysorbate 80 in association with the "E-ferol" syndrome in infants.⁷⁰

The occurrence of hepatitis due to intravenous amiodarone does not necessarily require withdrawal of the drug nor preclude its oral administration.⁷² However, close monitoring and conservative does adjustments of intravenous amiodarone allow a more favorable outcome.⁷³ Table I summarizes the most common adverse events reported with intravenous amiodarone in large scale clinical trial.^{65,74,75}

Other Rare Adverse Effects

Amiodarone has been associated with a few rare, but nonetheless significant side effects. Epididymitis has been reported in a few cases and may be related to high semen concentration of desethylamiodarone, which in one case was reported as five times higher than in the serum.⁵ It has been speculated that high concentrations of desethylamiodarone in the epididymis causes epididymal pain and swelling in some male patients.

Table I.Adverse Effects Associated with IV Amiodarone⁶³⁻⁷⁴

Adverse Effect	Incidence
Hypotension	26-40%
Bradycardia	14-17%
EMD/Asystole	12%
Congestive heart failure	10%
Nausea	6-11%
Abnormal LFTs	9-17%
Fever	7-14%

Other side effects include hair loss,^{2,12} hyperglycemia,^{3,42} hypertriglyceridemia,^{2,5} thrombocytopenia, vasculitis, polyserositis,² and elevated serum creatinine.⁵

Drug Interactions with Amiodarone

The bioavailability of amiodarone is about 40% following oral administration and the drug undergoes extensive enterohepatic recirculation. The drug is highly protein bound (> 94%) and lipophilic, and it distributes throughout all adipose tissues. Amiodarone is primarily metabolized by hepatic cytochrome P450 (CYP3A4) to the active metabolite desethylamiodarone (DEA). Biliary excretion is the major route of elimination of amiodarone (renal excretion < 1%). The terminal elimination half-life is highly variable, ranging from 8-107 days.^{7,75}

Due to its unique pharmacokinetic properties, amiodarone may alter the pharmacokinetic and/or the pharmacodynamic activity of several commonly used drugs.^{76,77} The major mechanism of its drug interactions is the inhibition of hepatic metabolism, however, it can also affect the bioavailability, protein binding, and renal excretion of other drugs. Amiodarone significantly increases the plasma concentrations of digoxin, warfarin, several Class I antiarrhythmic drugs, and phenytoin, sometimes resulting in overt signs of clinical toxicity. Additive pharmacological interactions between amiodarone and β -blockers or calcium channel blockers have been associated with electrophysiological and hemodynamic toxicity, including sinus bradycardia and sinus arrest. Due to the long and variable half-life of amio-

darone, the potential for drug interactions exists not only with concomitant use of other medications, but also for drugs administered after recent discontinuation of amiodarone.

Digoxin

Amiodarone has been shown to significantly increase plasma concentrations of digoxin by 60%-70% within 24 hours of coadministration.^{76,77} This effect may progress for up to 2 weeks after amiodarone withdrawal. The mechanism of the amiodarone-digoxin interaction is multifactorial. There are several theories suggesting that amiodarone prolongs intestinal transit of digoxin, decreases its renal and nonrenal clearance by reducing the renal tubular secretion of digoxin, inhibits the metabolism of digoxin in the liver, and displaces digoxin from tissue binding sites.^{2,7} In addition, hypothyroidism is one of the amiodarone adverse reactions and may result in clinically significant changes in the pharmacokinetic and pharmacodynamic properties of digoxin. This interaction may also increase plasma digoxin concentrations and sensitivity to its therapeutic and toxic effects.⁷⁶

The interaction between amiodarone and digoxin is clinically significant and results in clear signs and symptoms of digitalis toxicity (sinoatrial node depression, atrioventricular node depression, gastrointestinal and/or central nervous system adverse effects). Therefore, it is recommended to reduce the digoxin dose by approximately 50% at the initiation of amiodarone with regular monitoring of serum digoxin concentrations, thyroid function tests, and signs and symptoms of digoxin toxicity (Table II).⁴²

Warfarin

Amiodarone may also affect the prothrombin time in patients taking warfarin.⁷⁸ The potentiation of the anticoagulant effects of warfarin may occur as early as 3 days after starting amiodarone. The persistence of amiodarone-warfarin interaction have been observed for up to 4 months after discontinuing amiodarone. According to *in vivo* studies, amiodarone inhibits the oxidation of both enantiomers (R and S) of warfarin; however, the effect of amiodarone on the metabolism of S-warfarin (via CYP2C9) is the primary cause of the en-

Table II.
Summary of the Commonly Reported Amiodarone-Induced Adverse Effects

Adverse Effects	Incidence	Recommendations
Gastrointestinal (Nausea, vomiting, anorexia, and constipation)	33%	reduce dose, take the drug with food, divided dosing
Hepatic (Elevation of LFTs)	5–20%	reduce dose, discontinue if abnormal LFTs persists check baseline LFTs and monitor LFTs every 6 months
Dermatological		
Photosensitivity	2–57%	use sunscreen with total sun blocking activity (i.e. Zinc)
Blue-gray skin	1–7%	
Ophthalmological (corneal microdeposits)	98%	ophthalmological exam if patient becomes symptomatic
Nervous System (tremor, ataxia, and peripheral neuropathy)	20%	reduce the dose
Pulmonary (Pulmonary alveolitis, pulmonary infiltrates)	0.5–10%	reduce dose, discontinue drug
Thyroid		
Hypothyroidism	1–32%	thyroid supplements
Hyperthyroidism	1–23%	methimazole or potassium perchlorate, thyroidectomy, or discontinue drug
Cardiovascular (Torsades de pointes, bradycardia, CHF)	< 2%	reduce dose, discontinue drug

hanced anticoagulant effect observed with this drug interaction. Other possible mechanisms include the direct displacement of warfarin from protein binding sites by amiodarone, or an indirect effect of amiodarone on the absorption or metabolism of vitamin K and clotting factors.^{76,77}

Bleeding has been frequently reported in patients taking both warfarin and amiodarone, therefore the dose of warfarin should be empirically decreased by one-third to one-half at the initiation of amiodarone to minimize bleeding events.^{76,77} Frequent determinations of prothrombin times and close observation of patients for signs and symptoms of bleeding are highly recommended when amiodarone and warfarin are used concomitantly (Table III).

Antiarrhythmics

Interactions between amiodarone and antiarrhythmic agents such as quinidine, procainamide, flecainide, disopyramide, and propafenone are among the most serious adverse effects.⁷⁶ Drug induced TdP with marked prolonged QT interval

has been reported in patients receiving amiodarone and quinidine, disopyramide, propafenone, or mexiletine. Amiodarone-antiarrhythmic interactions may be due to alterations in pharmacokinetic and pharmacodynamic properties of these drugs (Tables III and IV).⁷⁸

β -Adrenergic Blockers and Calcium Channel Antagonists

Amiodarone exhibits both mild β -adrenergic and calcium channel blocking activities. Sinus node depression, atrioventricular nodal block, and hypotension have been reported with concomitant use of amiodarone, β -blockers, and calcium channel antagonists. These effects are partly due to the potentiation of the cardiovascular pharmacological properties of these agents when used together.^{2,7,76}

Other Rare Drug Interactions

There are isolated reports of possible drug interactions between amiodarone and other drugs in the medical literature.^{79–82} The clinical signifi-

ADVERSE EFFECTS OF AMIODARONE

Table III.

Most Common Drug-Drug Interactions with Amiodarone^{50,76-78}

Drug	Interaction		
	Onset (days)	Magnitude	Recommendation
Digoxin	1	Increases digoxin serum concentrations by 60 to 70%	Decrease digoxin dose by $\frac{1}{2}$
Warfarin	3-4	Increases prothrombin time by 100%	Decrease warfarin dose by $\frac{1}{3}$ to $\frac{1}{2}$
Quinidine	1-5	Increases quinidine serum concentrations by 33%	Avoid combination, or decrease quinidine dose by $\frac{1}{3}$
Procainamide	< 7	Increases procainamide serum concentrations by 55%, and NAPA concentrations by 33%	Avoid combination, or decrease procainamide dose by $\frac{1}{3}$

cance of these reactions has yet to be determined (Table IV).

Conclusion

The use of amiodarone has increased significantly over the past decade, primarily due to an increased understanding of its therapeutic indications and toxicities. Prolonged use of amiodarone may result in a variety of adverse effects involving all organ systems. Although, the majority of these side effects are mild and do not occur at doses < 400 mg/day, some are potentially fatal. The patho-

physiology of these adverse reactions is not well-established, which makes early clinical diagnosis more difficult. Patients taking amiodarone on a regular basis should be carefully monitored for the development of any toxicity associated with amiodarone. Careful follow-up of these patients is essential in order to diagnose early and reversible side effects prior to irreversible damage (Table II). It is recommended to obtain liver function tests, chest X rays, and thyroid function tests at the initiation of therapy. These tests should be obtained no less than every 6 months to monitor for potential adverse effects.

Table IV.

Rare Drug-Drug Interactions with Amiodarone^{80,80-82}

Drug	Interaction	Case Reports
β -blockers	Symptomatic bradycardia, sinus arrest	3
Calcium channel blockers	Sinus arrest, AV block	1
Clonazepam	Decreased clearance of clonazepam, increased sensitivity to clonazepam effects, likely due to amiodarone-induced hypothyroidism	1
Cyclosporine	Increased cyclosporine serum concentrations resulting in increased serum creatinine	3
Disopyramide	Prolongation of QT interval, Torsade de pointes	2
Fentanyl	Profound bradycardia, sinus arrest, hypotension	3
Flecainide	Increased flecainide serum concentration, increased toxicity	2
Lidocaine	Oral amiodarone-seizure; IV amiodarone-sinoatrial arrest	1
Methotrexate	Increased methotrexate serum concentration, increased toxicity	1
Phenytoin	Increased phenytoin serum concentrations	6

Because of the presence of an extensive adverse drug reaction profile associated with amiodarone, the benefit of therapy should be weighed against the risks of toxicity prior to initiating therapy.

Although few drugs appear to influence the pharmacokinetics of amiodarone, amiodarone has significant effect on the pharmacokinetics and

pharmacodynamics of several commonly used drugs, particularly drugs used for cardiovascular diseases. The interactions between amiodarone and digoxin, warfarin, and several different antiarrhythmics have led to documented adverse effects. Clinicians should be aware of these drug interactions in order to prevent toxic effects of drugs administered concomitantly with amiodarone.

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