AMIODARONE
(Cordarone®, Pacerone®)

Amiodarone is an anti-arrhythmic medication initially developed and approved to treat angina in Europe in the 1960's by Labaz laboratories in Belgium. The additional benefit of arrhythmia suppression was quickly recognized and thus electrophysiologists in the United States began obtaining samples for their patients. By the early 1980’s tons of thousands of patients were using amiodarone and the U.S. Fodd and Drug Administration (FDA) approved amiodarone for treatment of life-threatening ventricular arrhythmies in 1985. The wide range of its therapeutic and toxic effects has come to light since its approval. Amiodarone is currently used for both acute and chronic suppression of supraventricular arrhythmias such as atrial fibrillation and flutter, and ventricular tachyarrhythmias.

PHARMACOLOGY

Amiodarone is an iodinated benzofuran derivative. It is similar in structure to thyroxine, with iodine accounting for 37% of its molecular weight, which is the likely source of some of the drug’s side effects. It has a complex mechanism of action and its true method of arrhythmia suppression is not entirely understood. However, as a Vaughn-Williams class III drug, amiodarone prolongs repolarization in the myocardium through the blockade of the delayed rectifier potassium currents involved in phase three of the action potential. Subsequently, the effective refractory period is increased, disrupting re-entrant phenomena, and reducing automaticity of the entire myocardium. Amiodarone also has mild effects in blocking fast-acting sodium channels in early depolarization, as well as blocking beta-agonist receptors and calcium channels, thus giving it properties of all four Vaughn-Williams anti-arrhythmic classes. Additionally, it has been shown to prolong the QT interval. With intravenous bolus doses, amiodarone causes vasodilation and suppression of myocardial contractility which may result in hypotension; oral dosing has no such effects.

Amiodarone’s pharmacokinetics are highly variable between patients, especially in the oral form. Bioavailability ranges from 22-86% and peak serum levels usually occur four to six hours after ingestion of a single dose, although the highest levels may not occur for up to twelve hours. However, serum levels of amiodarone do not correlate with anti-arrhythmic efficacy. The effect of a 200 mg daily dose on any given patient’s arrhythmia may not be appreciated until weeks to months after the initiation of oral therapy. Therefore, loading regimens are used followed by a reduced maintenance dose so that the interval of the onset of effects is shortened to within one week. Amiodarone is 98-99% percent protein bound and, due to its highly lipophilic nature, has a huge volume of distribution (60 L/kg) that concentrates in lung, adipose and, to a lesser extent, myocardial tissue. For these reasons it is very poorly dialyzable and has an extremely long and variable elimination half-life, depending upon the duration of its use. Single ingestion elimination ranges from ten to eighty hours, while chronic therapy exhibits biphasic elimination with peaks at two and a half to ten days and twenty-six to 107 days.

Metabolism of amiodarone to N-desethylamiodarone is through the cytochrome P450 3A4 system in the liver and intestines. Serum levels of the metabolite seem to correlate more closely with anti-arrhythmic action and, therefore, presumably indicate active effects from drug treatment. Induction of the P450 enzymes occurs with amiodarone use, and reductions in dosages of up to 50% are often necessary, particularly in
patients on digoxin, warfarin, cyclosporine and any other anti-
arhythmic.\textsuperscript{3} Clearance is through biliary excretion with
presumed enterohepatic circulation.\textsuperscript{11} No dose adjustment is
necessary in kidney, liver or cardiac failure. Amiodarone
crosses the placenta and has been shown to result in transient
hypothyroidism and goiter in 8-17% of neonates; it is a
pregnancy category D substance.\textsuperscript{3}

The usual daily dose of oral amiodarone is 100-200 mg daily
after a loading regimen of 800-1600 mg/day for two to four
weeks. Intravenous bolus doses are 150 mg for stable
ventricular tachycardia and 300 mg for ventricular fibrillation or
unstable ventricular tachycardia. This bolus may be followed
by continuous infusion at 1 mg/min drip for eight hours, with a
subsequent 0.5 mg/min as a loading regimen equivalent until
the patient may be transitioned to oral dosing.\textsuperscript{2,3,7} In pediatric
cases, a dose of 5 mg/kg rapid IV or intraosseous push is
recommended in the PALS algorithms for VF/VT arrest;
antiarrhythmic dosing should be made in consultation with a
pediatric cardiologist.

**TOXICOLOGY**
The long-term toxicity of amiodarone is well established, but
there is very limited data on acute overdoses, consisting
mainly of case reports. Many of the toxic side effects are
related to the patient’s cumulative dosage and improve with a
reduction in dose or withdrawal.\textsuperscript{4} Reports of deaths from
chronic amiodarone use exist, but no deaths have been
reported from acute ingestion.

Chronic side effects of amiodarone involve the lungs, liver,
thyroid, eyes and skin. Pulmonary toxicity occurs via multiple
mechanisms in 4-17% of patients, and can be fatal in up to
10% of those affected. Acutely, patients may have either a
hypersensitivity or interstitial pneumonitis develop within days
of initiating therapy. Pulmonary fibrosis has a much more
insidious onset and is monitored with chest x-rays every three
to six months. Symptoms of both lung processes include
dyspnea, cough and hemoptysis.\textsuperscript{2,3} Hepatic enzyme elevation
occurs in up to 30% of patients who are chronically exposed,
but rarely progresses to fulminant hepatic failure. Due to its
iodine content and similar structure to thyroxine, amiodarone
can disrupt thyroid function, although the exact mechanism is
not known. Hyperthyroidism is more common in iodine-
deficient areas while hypothyroidism is more common in
iodine-replete areas.\textsuperscript{12} Most cases respond to appropriate
medical therapy, but severe thyrotoxicosis requiring urgent
thyroidectomy has been reported.\textsuperscript{13} Ocular manifestations of
amiodarone include corneal deposits in almost 100% of
patients; these lesions are usually asymptomatic but may
cause visual field deficits. Optic neuropathy or neuritis is much
less common, occurring in less than 1% of patients, and
causes visual changes in the affected eye. A bluish-gray skin
discoloration can develop, otherwise known as the “smurf
syndrome,” which may not resolve even after withdrawal of
therapy. Photosensitivity is also common.\textsuperscript{2,3}

There have been fewer than ten case reports of acute
amiodarone overdose over the past twenty years.\textsuperscript{14,15} Based
upon these reports and the drug’s known pharmacologic and
anti-arrhythmic mechanisms of action, the methods for optimal
management are not clearly defined. Amiodarone is regarded
as relatively safe even in acute ingestions up to 15 g, as no
deaths or long-term sequelae have been reported. In rat
studies the LD\textsubscript{50} (dose that is lethal in 50% of exposures) of
amiodarone was shown to be more than 3 g/kg, while dogs
receiving 3 g/kg oral doses all survived.\textsuperscript{7} Delayed onset of
effects may be expected based upon amiodarone’s
pharmacokinetics, but there have been no reports of
development of chronic toxicities after large acute ingestions.
The most worrisome toxicity is due to its multiple effects on the
myocardium. Potential sinus bradycardia and a block in AV
conduction may cause hypotension and symptoms of
hypoperfusion, which may not respond to atropine.\textsuperscript{6}
Amiodarone’s pro-arrhythmic effects may result in ventricular
tachyarrhythmias, particularly torsades de pointes even in the
absence of a prolonged QT interval. One case report of
torsades de pointes was successfully treated with isoproterenol
and overdrive pacing.\textsuperscript{4}

**MANAGEMENT**
Initial management of an acute amiodarone ingestion should
focus on evaluation and support of the patient’s respiratory and
circulatory status. Atropine should be administered to patients
with symptomatic bradycardia but they will likely also require
transcutaneous or transvenous pacing. Tachyarrhythmias are
treated by current ACLS protocols. Patients with torsades de
pointes should receive intravenous magnesium, isoproterenol
or overdrive pacing as necessary to convert to sinus rhythm.\textsuperscript{16}
Gastrointestinal decontamination with activated charcoal is
recommended as it has been shown to reduce the bicaavailability of a single dose by 98%; the initial dose is 1g/kg. Multiple dose charcoal with 25 g every four hours for twelve hours may be effective due to amiodarone’s presumed enterhepatic circulation, although it has not been studied. Cholestyramine was used in the past because it binds amiodarone in the gut, reducing its elimination half-life. However, it is not currently widely recommended due to the effectiveness and widespread availability of activated charcoal. There is no role for hemodialysis or other methods of enhanced elimination. Patients will likely require admission to the intensive care unit after an acute amiodarone ingestion for forty-eight hours to monitor for arrhythmias. The absolute duration of cardiac monitoring is not precisely defined but there have been no reported cases of unstable cardiac rhythms after forty-eight hours of observation.

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REFERENCES