Use of amiodarone in emergency

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Abstract. – Amiodarone is one of the most common anti-arrhythmic drugs used in the Emergency Department. Recent guidelines on cardiac arrest with shockable rhythm [refractory ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT)] recommend amiodarone as anti-arrhythmic of first choice. Amiodarone is also first choice drug in the treatment of various ventricular and supraventricular tachyarrhythmias.

This paper deals with the main therapeutic indications of amiodarone in emergency medicine: dosage, side effects, contraindications and pharmacological interactions are reviewed. Amiodarone is effective for control of hemodynamically stable VT, polymorphic VT and wide-complex tachycardia of uncertain origin. It is also helpful for ventricular rate control of rapid atrial arrhythmias in patients with severely impaired left ventricular (LV) function, when digitalis has been ineffective, and is an adjunct to electrical cardioversion. The major side effects of amiodarone are hypotension, bradycardia and peripheral phlebitis. Major contraindications to the intravenous (iv) injection of amiodarone are bradycardia, senoatrial block, severe disturbances of conduction, second or third degree atrio-ventricular blocks. Other contraindications are hypotension, severe respiratory failure, hepatocellular failure and hyperthyroidism. Pharmacological interactions are reported with HMG-CoA reductase inhibitors, class I antiarrhythmic agents and other drugs which contribute to prolong QT interval, digoxin, oral anticoagulants and general anaesthesia.

Key Words: Amiodarone, Emergency, Arrhythmias, Tachycardias, Cardiac arrest, Ventricular tachycardia, Atrial fibrillation.

Introduction

Amiodarone, a derivative of benzofuran, is one of the most common anti-arrhythmic drugs, frequently used in the Emergency Department. In the last decade many trials and meta-analysis described amiodarone as anti-arrhythmic agent of first choice in the treatment of hemodynamically unstable ventricular tachycardia (VT), of hemodynamically stable wide-complex tachycardias1, and of many supraventricular tachyarrhythmias1,2.

The European Resuscitation Council recommends its use in shockable cardiac arrest [ventricular fibrillation (VF) and pulseless VT]3. Finally, its use has been suggested in post-infarction patients, either presenting frequent or repetitive extra systolic beats and/or VT4 or presenting low left ventricular ejection fraction (below 40%)5.

Up to 2% of the patients admitted to the Emergency Department present tachyarrhythmias. In more than 90% these are narrow QRS arrhythmias, such as atrial fibrillation (AF) (45%), paroxysmal supraventricular tachycardia (35%) and atrial flutter (8%). Around 50% of large QRS tachyarrhythmias are supraventricular tachycardias. VT are in most cases hemodynamically stable, while only a small part of large QRS tachyarrhythmia are hemodynamically unstable VT or shockable cardiac arrest (VF/pulseless VT)6.

Often tachyarrhythmia end spontaneously or resolve after appropriate treatment in the Emergency Department, and around half of the patients can be discharged after a short period of observation.

Pharmacodynamic Properties

Electrophysiologic Effects

Amiodarone exerts a non-competitive block of alpha and beta-adrenergic receptors
antagonizing tachycardia, hypertension and oxygen consumption of the myocardium induced by circulating catecholamines. These effects contribute to the anti-arrhythmic and anti-anginal properties of amiodarone. After amiodarone administration there is no significant decrease of the myocardial contractility.

The most relevant effects of amiodarone on cardiac cells are the reduction of the depolarization (phase 4), the late repolarization, caused by a prolongation of the action potential (phase 3) and the prolongation of the effective refractory period. Therefore amiodarone is included among class III anti-arrhythmic drugs. It is known that torsades de pointes are the classic form of proarrhythmia observed during therapy with any drug that prolongs repolarization. Among the class III drugs the proarrhythmic risk appears to be lowest for amiodarone, probably due to its complex electrophysiologic profile that may create significant myocardial electrical homogeneity.

**Mechanisms of Action**

Some chemical peculiarities of the drug (high iodine’s content and structural analogies with thyroid hormones) suggested possible influences of amiodarone on the thyroid function. Furthermore, it is known that some of the cardio-electrophysiologic effects of the chronic administration of amiodarone are very similar to those of hypothyroidism. Actually, it has been shown a competition or an interaction between amiodarone and the thyroid hormones at many levels (i.e. deiodases, trans-membrane ionic channels). Two main mechanisms concerning the antiarrhythmic activity of amiodarone have been suggested:

- The “T3-mediated” hypothesis: amiodarone antagonizes the thyroid hormones on the nuclear receptor and/or on transmembrane carrier of T3 at cardiac level. This T3-mediated mechanism could explain the non-competitive adrenergic block of amiodarone.
- The “Membrane-active” hypothesis: amiodarone impairs the lipid environment of the cell membranes where the main ionic channels are located, directly modulating the ionic myocardial transmembran currents.

**Pharmacokynetic Properties**

Amiodarone’s chemical structure can be summarised in three points: (1) presence of aromatic rings; (2) a relatively high iodine content; (3) presence of an aliphatic chain with low polarity.

This chemical structure highlights some specific pharmacological characteristics like the high lipophylia, the low oral absorption rate, the extended tissue distribution, the slow elimination rate and finally the late therapeutic response during oral treatment.

After intravenous (iv) administration plasma peak concentration is reached in 6-8 hours. Drug tissue distribution occurs differently after acute administration (lungs, liver, heart and kidney) and after the achievement of dynamic equilibrium (mainly in the liver, fat tissue and in the lungs).

Drug clearance occurs mainly through the liver and only 1% is excreted through the kidneys. Amiodarone cannot be dialysed and crosses easily the placenta (10-50%). N-desethyl-amiodarone (DEA) is its main active metabolite. After a single oral dose, amiodarone’s half life is calculated to be around 24 h, during long-term therapy it increases reaching 28 days; while DEA’s half life is around 60 days.

**Therapeutic Indications in Emergency**

**Cardiac Arrest With Shockable Rhythm (Refractory VF/Pulseless VT)**

The Resuscitation 2000 Guidelines recommend amiodarone as the antiarrhythmic drug of choice in treatment of resistant VF or pulseless VT. Even if the administration of amiodarone may cause a slight delay during the resuscitation procedure, evidence supports its use after epinephrine administration in the treatment of shock-refractory cardiac arrest due to VF or pulseless VT (Class of evidence IIb). Some studies demonstrate that amiodarone, like any other antiarrhythmic agent, must be given before the fourth shock in order to be effective.

In patients with out-of-hospital cardiac arrest, due to refractory ventricular arrhythmias, treatment with amiodarone resulted in
a higher rate of survival to hospital admis-
sion. Whether this benefit extends to survival
to discharge from the hospital merits further
investigation26.

In the CASCADE trial, carried out in sur-
vivors of cardiac arrest, the administration of
amiodarone in patients with an implanted au-
tomatic defibrillator significantly reduced the
number of defibrillation shocks27.

Amiodarone 300 mg (made up to 20 ml
with dextrose) should be administered into a
peripheral vein. A further dose of 150 mg
may be given for recurrent or refractory
VT/VF, followed by an infusion of 1 mg min⁻¹
for 6 hours and then 0.5 mg min⁻¹, to a max-
imum daily dose of 2 g. This maximum dose
is less than the current European
datasheet recommendation of 1.2 g. Pre-
loaded syringes are not available because
amiodarone adheres to the plastic surface of
preloaded syringes28.

Hemodynamically Unstable VT and
Hemodynamically Stable Wide-Complex
Tachycardias

VT is considered “hemodynamically sta-
ble” if there are no symptoms or clinical evi-
dence of tissue hypoperfusion or shock. On
the contrary “hemodynamically unstable” VT
requires immediate resolution through syn-
chronized cardioversion.

In all patients with unstable hemodynam-
ics, immediate direct current (DC)-cardiover-
sion is indicated. In particular, hemodynami-
cally unstable large QRS complex tachycar-
dia should be treated with a series of three
synchronized shocks29. Pharmacological treat-
ment with amiodarone is indicated only after
failure of electrical cardioversion. Many stud-
ies evaluated amiodarone for the treatment of
hemodynamically unstable VT. Patients
with clinical congestive heart failure or de-
pressed left ventricular (LV) function should
be treated cautiously with antiarrhythmic
therapy. In these patients, many antiarrhyth-
mic agents depress LV function precipitating
or worsening congestive heart failure. Amio-
darone and lidocaine cause the least addition-
al impairment of LV function30. Because of its
broad antiarrhythmic spectrum and lesser
negative inotropic effect, amiodarone is com-
monly used in these cases.

Empirical pharmacological therapy may be
necessary for a hemodynamically stable wide-

complex tachycardia of unknown origin. Pro-
cainamid, amiodarone, and sotalol are effec-
tive in the treatment of VT and supraventric-
ular tachycardias with an accessory pathway
conduction. On the other hand, depressants
of the AV node conduction (such as adeno-
sine, beta-adrenergic receptor blockers, and
calcium channel blockers) are hazardous in
patients with preexcited atrial arrhythmias.
Therefore, the therapeutic options are re-
duced to DC cardioversion, or procainamide
or amiodarone. At presentation in the Emer-
gency Department, most of the patients with
VT are hemodynamically stable, thus allow-
ing first-line antiarrhythmic drug administra-
tion. However, in the course of the disease,
half of the patients need electrical therapy for
definitive termination of the tachycardia31. There-
fore, DC-cardioversion must be avail-
able in the Emergency Department.

When electrical cardioversion is not ap-
propriated, possible therapeutic options are:
procainamide (Class of evidence IIa), sotalol
(Class of evidence IIa), amiodarone (Class of
evidence IIb), or disopyramide (Class of evi-
dence IIb)32.

In stable and unstable large QRS tachycar-
dias, amiodarone should be administered at a
loading dose of 150 mg diluted with 5% dex-
trose for slow bolus injection (10 min) in pe-
ripheral or central vein, followed if necessary
by a second dose of 150 mg. In order to avoid
acute side effects, the second bolus should be
given after a period of 15 minutes. The therape-
utic effects should become evident already
in the first few minutes, and decrease pro-
gressively until the next administration29,28.

The maintenance dose ranges between 10
and 20 mg/kg over 24 hours (usually 600-900
mg/24 hours and up to 1200 mg/24 hours) di-
luted in 500 ml of dextrose 5%28.

Narrow-Complex Tachycardias

(Supraventricular Arrhythmias)

Supraventricular arrhythmias include
supraventricular tachycardia, atrial extrasys-
tole, atrial flutter, AF, supraventricular
paroxysmal reciprocant tachycardias as the
Wolff-Parkinson-White syndrome.

In the supraventricular paroxysmal tachy-
cardia, amiodarone is effective because it de-
presses the conduction through the accessory
pathway (Class of evidence IIa). Amio-
darone becomes the antiarrhythmic agent of
choice (after failure of adenosine) if cardiac function is impaired and the ejection fraction is < 40% or there are signs of congestive heart failure33.

Therapeutic goals for AF include ventricular rate control, stroke prevention, conversion to normal sinus rhythm, and maintenance of normal sinus rhythm. In the treatment of AF, amiodarone is commonly used34-36.

Recently, a meta-analysis suggests that amiodarone is an effective and relatively rapid acting drug for the conversion of AF to normal sinus rhythm and recommends amiodarone as a first-line drug37. AF in young patients, with a duration of symptoms of less than 48 h and without heart failure can be managed in the Emergency Department with amiodarone in order to avoid a longer hospitalization38. Since amiodarone shows only slight inotropic, dromotropic and chronotropic negative effects, it can be safely administered in patients with organic cardiomyopathy or heart failure in an Emergency Unit34-36.

Pre-treatment with amiodarone the month before a planned electric cardioversion in patients with AF lasting more than 48 h increases the percentage of conversion and reduces the number of early recurrence of AF35. Moreover, amiodarone is more effective than propafenone and sotalol in the prevention of AF recidives, in patients suffering from paroxysmal and persistent AF39.

In the Wolff-Parkinson-White syndrome, AF and atrial flutter are usually precipitated by an episode of atrioventricular re-entrant tachycardia. In patients with short accessory-pathway refractory periods and rapid ventricular rates during AF, class I antiarrhythmic drugs that lengthen the refractory period of the accessory pathway and reduce ventricular rates are first choice treatment. Class I drugs may be used alone or in combination with an atrioventricular nodal depressant agent. Sotalol and amiodarone have been used in high-risk symptomatic patients. However, the risk of ventricular arrhythmias and the occurrence of side effects limit their usefulness40. Radiofrequency ablation should be the treatment of choice in Wolff-Parkinson-White syndrome and symptomatic atrioventricular re-entrant tachycardia.

As for large QRS tachycardias, amiodarone’s loading is 150 mg diluted with 5% dextrose in slow bolus injection (10 min), followed if necessary by a second dose of 150 mg. The maintenance dose ranges between 10 and 20 mg/kg over 24 hours38. Table I summarizes the main therapeutic indication of amiodarone in emergency.

### Side Effects, Contraindications and Pharmacological Interactions

#### Side Effects

Acute adverse effects of amiodarone include hypotension, bradycardia, chemical peripheral phlebitis and nausea41. Hypotension was the most common adverse event reported with amiodarone iv. The hypotension was not dose-dependent, but related to the rate of infusion. Therefore amiodarone should be administered over 10 minutes42. Long-term treatment can produce adverse effects presenting several degrees of severity, frequency and time of beginning, especially on the lung, the thyroid, the liver or the cornea (Table II).

Lung-toxicity determines cough, dyspnoea, fever, loss of weight, chest pain, and rarely haemoptysis43. These symptoms often emerge few days after treatment beginning, but sometimes they become evident after a few years.

Amiodarone causes large modifications of the peripheral metabolism of thyroid hormones. The most important effect is the inhi-

Table I. The main therapeutic indications of amiodarone in emergency.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Class of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular Fibrillation/pulseless Ventricular Tachycardia refractory to defibrillation</td>
<td>IIb</td>
</tr>
<tr>
<td>Wide-Complex Tachycardia haemodynamically unstable and stable, including the polymorphic VT as well as wide-complex tachycardia of uncertain origin</td>
<td>IIb</td>
</tr>
<tr>
<td>Narrow-Complex Tachycardias hemodynamically stable or instable but resistant to electric cardioversion: TPSV (Class of evidence IIa), atrial fibrillation (Class of evidence IIa), atrial tachycardia (Class of evidence IIb), atrial tachycardia due to pre-excitation (Class of evidence IIb)</td>
<td>IIb</td>
</tr>
</tbody>
</table>
bition of the enzyme 5'-monodeiodinase type I that removes the iodine from the fenolic T4 ring, forming T3, and resulting in a relevant increase of the serum concentration of fT4 and the contemporaneous reduction of fT3. Other effects are an alteration of the “reverse T3” due to a decreased clearance and a change of serum levels of pituitary-thyroid axis hormones with a TSH increase. Moreover, since amiodarone contains iodine its administration may cause a modification of the thyroid function, either hypothyroidism or thyrotoxicosis, especially at the beginning of the treatment and on pre-existing thyroid disease (autoimmune thyroiditis or nodular goiter).15

Regarding liver dysfunction, some cases of chronic hepatitis, with histopathological features similar to alcoholic hepatitis, have been observed. In patients with clear signs of liver failure amiodarone is best avoided.

After prolonged treatment it is possible to observe corneal microstores, normally asymptomatic which don’t contraindicate the continuation of the therapy. These microstores, formed by complex lipids, are irreversible, even after treatment discontinuation.43

**Contraindications**

Main contraindications to the iv administration of amiodarone are synus bradycardia, senoatrial block and severe conduction disturbances like second or third degree atrioventricular block. Other contraindications are hypotension, severe respiratory failure, thyroid disease, liver failure, cardiomyopathy and cardiac failure. Amiodarone is best avoided during pregnancy since it may induce fetal thyroid diseases, and during breast-feeding since significant amounts of amiodarone are eliminated through the breast milk during the treatment (Table III).

**Pharmacological Interactions**

Administration of amiodarone in patients taking HMG inhibitors-CoA reductase inhibitors, in particular simvastatin, may in-
crease the risk of myopathy. The daily intake of simvastatin should not exceed in these cases 20 mg/day.

Potassium wasting diuretics and some class I anti-arrhythmic agents may contribute to prolong the QT interval and should therefore be administrated cautiously in patients taking amiodarone.

Amiodarone may increase the plasma level of some anti-arrhythmic agents as chinidin, procainamide, disopyramide and flecainide. The interaction of amiodarone with non anti-arrhythmic agents as vincamine, sulpotride, erythromycin iv and pentamidine iv, can raise the risk of potentially lethal torsades de pointes.

Hypokaliemia may enhance the potential pro-arrhythmic action of anti-arrhythmic agents. Therefore, hypokaliemia should always be corrected before any amiodarone-based treatment is started.

Cardiopathic patients are often treated with digoxin (whose clearance decreases when associated with amiodarone) and with oral anticoagulants (whose anticoagulant effect increases after amiodarone administration). Dose adjustment and frequent prothrombin and electrocardiogram monitoring is mandatory in these patients. Careful clinical monitoring and prompt dose adjustment, if needed, are indicated in these patients.

Severe adverse reactions are reported in patients on amiodarone treatment undergoing general anaesthesia: severe bradycardia (not responsive to atropine), hypotension, conduction disturbances and decrease of the cardiac output. Some cases of severe respiratory failure were also reported, generally occurring after surgery (Table IV).

In conclusion, amiodarone is a highly effective antiarrhythmic agent for many cardiac arrhythmias, ranging from AF to malignant ventricular tachyarrhythmias. It is considered the antiarrhythmic drug of choice in treatment of resistant VF or pulseless VT. It can be safely administered in patients with organic cardiomyopathy or heart failure because it shows only slight negative inotropic, dromotropic and chronotropic effects. Further-

### Table III. Most important contraindications to acute amiodarone administration.

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
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</thead>
<tbody>
<tr>
<td>Bradycardia of the synus</td>
</tr>
<tr>
<td>Sinoatrial block</td>
</tr>
<tr>
<td>Severe second or third degree atrio-ventricular blocks (unless paced)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Breast-feeding</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Cardiomyopathy or cardiac failure</td>
</tr>
<tr>
<td>Severe respiratory failure</td>
</tr>
<tr>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Hepatocellular failure</td>
</tr>
<tr>
<td>Possible drug interaction causing the risk of torsades de pointes</td>
</tr>
</tbody>
</table>

### Table IV. Most important pharmacological interactions of amiodarone.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Result of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Elevated digoxin plasma concentration</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Elevated prothrombin time</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Increased incidence of myopathy if simvastatin dosage is &gt; 20 mg per day</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Increased sildenafil plasma concentration</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Increased cyclosporine plasma concentration</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>Additive effects: possible elevated plasma concentrations of quinidine, disopyramide, flecainide, propafenone and dofetilide</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Additive QT effect: possible increased risk of proarrhythmia</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Increased plasma concentration of hepatically metabolized drugs: possible increased risk of proarrhythmia</td>
</tr>
<tr>
<td>Potassium-wasting drugs</td>
<td>Additive QT effect: possible increased risk of proarrhythmia</td>
</tr>
</tbody>
</table>
more, amiodarone prevents the recurrence of life-threatening ventricular arrhythmias and produces a modest reduction of sudden deaths in high-risk patients.

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