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Amiodarone: Updated Review of its Current Usefulness

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Abstract

Amiodarone has been used for more than half a century, and has multiple electrophysiological and hemodynamic effects. It is one of the most effective antiarrhythmics but it has potential adverse effects (some of them serious). It is useful in the treatment of supraventricular and ventricular arrhythmias, and in preventing them. Its mechanisms of action, the general - pharmacology, the current indications and the main clinical trials are reviewed.

***Key words:** Amiodarone; atrial fibrillation; Heart failure*

1. Introduction

The treatment of cardiac arrhythmias is complex and carries potential adverse effects, so in all cases risk-benefit situations arise. One of the most widely used drugs is amiodarone. Cardiology has introduced major changes in recent years, successfully reducing mortality and morbidity of major diseases. The pharmacology of amiodarone and its role in cardiovascular therapeutics is presented in this non-systematic review.

2. Pharmacodynamics

2.1 Electrophysiological effects

It is a group III antiarrhythmic drug of the Vaughan Williams classification. Although it was developed primarily as a coronary vasodilator, Rosenbaum et al. in Argentina described its electrophysiological properties in the 1970s. Group III drugs from the Vaughan Williams classification prolong the effective refractory period (PRE) by blocking potassium channels (Ikr, Ikur, Iks) responsible for repolarization in phase 3 of the action potential. The main arrhythmogenic mechanism that modifies is reentry. The common adverse effect of blocking potassium channels is QT interval prolongation with risk of arrhythmias early postdespolarizaciones as polymorphic torsades de pointes or torsades de pointes, which is an

arrhythmia with a high fatality rate. Its appearance is enhanced by certain conditions such as hypokalemia, hypomagnesemia, other drugs that prolong the QT interval, as well as in patients with congenital long QT syndromes.

Amiodarone, has many mechanisms of action, effects in acute and chronic, has utility for multiple arrhythmias, but unfortunately, a wide variety of adverse effects. All this makes necessary its continuous monitoring. It blocks Na^+, Ca^{++}, K^+ channels and also blocks alpha and beta adrenergic receptors (for beta receptors, its competition is intracellularly and not on membrane). Another mechanism that would explain some electrophysiological effects is the inhibition of 5'-deiodinase, blocking the passage from T4 to T3.

The blockade of sodium channels prolongs the conduction time at the His-Purkinje level, widening the QRS, mainly at high rates. It has a fast recovery time, exerting similar effects to group Ib antiarrhythmics, for this reason it is useful intravenously for serious ventricular arrhythmias. The blockade of calcium channels and beta receptors would explain sinus bradycardia and atrioventricular conduction block (AV) with prolongation of the PR interval in the electrocardiogram.

Amiodarone blocks virtually all potassium currents in all cardiac cells, having shown blockage of I_{TO} currents (transient outward in phase 1), as well as those in phase 2-3 of repolarization (I_{kr}, I_{kur}, and I_{ks}). It provokes a prolongation of the absolute refractory period (PRA), of the effective refractory period and of the duration of the action potential (APD). This mechanism is useful to interrupt reentry, being effective in the reversal of supraventricular arrhythmias such as flutter and atrial fibrillation (AF). Desetilamiodarone, its active metabolite, has similar effects, with greater activity on fast channels. By blocking all potassium currents, the QT interval is prolonged, but repolarization is homogenized between the different types of cardiac cells [1].

2.2 Hemodynamic effects

Due to the direct blockade of vascular alpha-1 adrenergic receptors, it is a coronary and systemic vasodilator, reducing afterload. In intravenous bolus it has a significant negative inotropic effect, capable of decompensating the patient with heart failure, however this effect is not observed with i.v. slow maintenance dose or chronic oral use, as this effect is adjudicated to the i.v. excipients.

3. Pharmacokinetics

It is an iodinated benzofuran highly liposoluble. It has poor oral absorption with a bioavailability of 30% to 65%, and can be administered orally or intravenously. It accumulates in adipose tissue, liver, skin, lung, myocardium, and other tissues, with a volume of distribution of 60 l / kg. It has high plasma protein binding (96%), and easily crosses barriers. Its half-life varies between 25 and 110 days, requiring approximately 265 days to reach the state of equilibrium, so it is necessary to use loading doses to reduce this interval. It is metabolized in the liver, via CYP3A4 (it's an inhibitor), to desethylamidodarone, an active metabolite with similar electrophysiological properties, and then it is eliminated via the bile duct, with enterohepatic recirculation. According to several authors, it would also have a metabolism at cytochrome CYP2C9 being able to inhibit it. It is described an excretion by cutaneous route and by tear secretion.

The loading doses are from 1200 to 1600 mg / day orally for 7 to 14 days, usually up to 10 g, and then a gradual reduction to a maintenance dose that is variable, from 200 to 400 mg / day or even less. Intravenously, it starts with a rapid load of 5 mg / kg in 10 to 20 min, and then 500 to 1000 mg in 24 hrs, and then it is passed to the oral route. The use of intravenous amiodarone to terminate ventricular arrhythmias or AF deserves special consideration: The acute effects of amiodarone are due to the blockage of sodium channels and stabilization of the membrane of myocardiocytes, for which a large amount of amiodarone reaches the biophase in a short time, but the fear of adverse effects often causes the intervening physician not to administer the loading dose at the appropriate time, rendering its application useless. On the other hand, administration of the drug in the form of direct intravenous bolus without dilution is also discouraged, since in this case the negative inotropism is such that the situation of electrical instability caused by the arrhythmia is transformed into a great hemodynamic instability, independently of the resolution or not of the arrhythmia.

3.1 Adverse effects

Adverse effects of amiodarone are observed in 75% of patients, of which 18% to 37% should suspend.

- Pulmonary fibrosis is the most feared reaction with a mortality of 10%. Pneumonitis, a previous phase, is observed in 10% to 17% of patients. It manifests as dyspnea, dry cough, crackles, fever, hypoxia, and is detected by a reduced diffusion in the lung diffusion of carbon monoxide test (DLCO). High doses, advanced age and previous lung disease are risk factors. It is a phenomenon of dose-dependent appearance: With doses lower than 300 mg / day, pulmonary toxicity is infrequent. Chest x-rays and DLCO are recommended every three months the first year and then every 6 months. The appearance of radiological alterations usually expresses advanced disease. Corticoids can be administered empirically, but with variable responses. There are cases described in the literature, however, of pulmonary fibrosis reactions in patients who had started treatment with amiodarone recently, and it cannot be ruled out that there are idiosyncratic phenomena beyond the classic cases related to the accumulation of the drug. A derivative of amiodarone called dronedarone would have a lower rate of lung adverse effects.
- In the liver, it can produce an asymptomatic increase in transaminases, without the need for discontinuation unless they increase three times their value. Hepatic fibrosis is uncommon, and is characterized by being histologically indistinguishable from alcoholic cirrhosis.
- Amiodarone has iodine and a structure similar to thyroxine (approximately one third of its molecular weight is attributed to iodine). Inhibits the peripheral conversion of T4 to T3, usually observing an increase of TSH, T4 and T3r, and slight decrease of T3. Hypothyroidism is more frequent (2% to 4%) than hyperthyroidism (1%), although some series describe a higher prevalence (even up to 20% of hypothyroidism). Hyperthyroidism by amiodarone manifests increased levels of T3. Baseline TSH, and Bi-annual thyroid function checks are recommended. In current therapy, it is not uncommon to find patients treated for atrial fibrillation with amiodarone, who present new episodes of high-response AF, and in these cases a drug-induced hyperthyroidism should always be suspected.
- Adverse cardiac effects are of low incidence, and include symptomatic bradycardia, hypotension, with decompensation of heart failure (especially after parenteral administration) and ventricular arrhythmias, with the occurrence of torsade de pointes being rare (unless there are predisposing factors such as other drugs that prolong the QT interval, hypokalemia, or hypomagnesemia). The bradycardia events may be due to slowing of the discharge

rate of the sinus node, with sinus bradycardia, or slowing down of the atrioventricular conduction with the appearance of AV blocks of different degree.

- Corneal microdeposits are observed in 100% of patients and are pathognomonic of amiodarone and asymptomatic, but more serious effects such as optic neuritis can appear.
- On the central nervous system produces proximal muscle weakness, peripheral neuropathy, headaches, ataxia, tremors, memory disorders, insomnia and nightmares.
- In 10% of patients produce skin photosensitivity phenomena, having to avoid sun exposure and use screens. The bluish-gray coloration of the skin occurs in patients impregnated with amiodarone, and is due to the fact that one of the routes of elimination of the drug is cutaneous.
- Gastrointestinal disorders (rare, mainly nausea after administration of high doses orally).
- Testicular dysfunction with increased gonadotropins.

3.2 Interactions

As an inhibitor of CYP3A4 and CYP2C9, it may increase the concentrations of warfarin oral anticoagulants, quinidine, procainamide, or digoxin, and it is necessary to reduce their doses by approximately half. Phenytoin and other microsomal inducers increase the metabolism of amiodarone.

Beta-blockers and calcium blockers should be administered with caution due to their nodal inhibitory effect. The association with lidocaine for the treatment of episodes of recurrent ventricular tachycardia in the context of myocardial infarction must be carried out with caution since the combined effect of both drugs can cause infrahisian AV blocks.

Due to its microsomal inhibitory effect, it is usual in therapeutics that when patients with AF are being anticoagulated with warfarin, at the time of initiating amiodarone, the anticoagulant scheme should be reduced at approximately half the dose.
With respect to the therapy of AF, in recent years new anticoagulant drugs (apixaban, dabigatran, edoxaban, and rivaroxaban) have been developed, and an interaction mainly between dabigatran and amiodarone has been found at the level of the P-glycoprotein, with a slight increase observed in the doses of dabigatran.

3.3 Indications

The antiarrhythmic efficacy of amiodarone exceeds most of the time to that of other antiarrhythmics, being currently one of the most used in its group for acute and chronic tachyarrhythmias, both supraventricular and ventricular, in primary or secondary prevention.

- Treatment of supraventricular arrhythmias such as supraventricular paroxysmal tachycardia due to typical and atypical intranodal reentry, when conventional treatments fail.
- Cardioversion, control of heart rate and frequency in patients with atrial flutter.
- In the case of AF, amiodarone fulfills different roles at each time of the therapy. On one hand it can be used for pharmacological cardioversion in acute atrial fibrillation, mainly by intravenous administration in loading and maintenance. It can also be used as a "facilitator", when administered orally the days before electrical cardioversion, increasing the chances of successful cardioversion. Amiodarone is one of the only antiarrhythmics available orally

for chronic use as a "rhythm control" strategy, avoiding the recurrence of AF episodes (more so, in patients with ventricular dysfunction, coronary heart diseases, or left ventricular hypertrophy, it is the only drug available in most countries at present for this strategy). Finally, a controversial indication of this drug is its use as a strategy of "rate control" in patients with permanent AF, mainly in individuals with contraindications to other drugs or in whom the heart rate can not be reduced with conventional strategies (beta blockers, calcium channel blockers, or digoxin).

- Certain arrhythmias in Wolff Parkinson White syndrome.
- It may be useful to improve survival in patients with hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy, and ventricular tachycardia after resuscitation.
- Its systematic use before and after cardiac surgery reduces the incidence of postoperative atrial fibrillation (although beta blockers would have similar benefit and lower risk of adverse effects). It is also used for the treatment of acute AF after surgery.
- Randomized studies have shown a decrease in overall mortality in patients with heart failure with low ejection fractions, and a decrease in mortality due to sudden death in patients after a myocardial infarction. However, these studies were conducted in the pre-beta-blocker and pre-ICD era (see clinical trials).

As contraindications, sinus bradycardia, high-grade AV block, multinodular goiter, and difficult-to-manage thyroid disease are described.

4. Main Clinical Trials with Amiodarone

- Treatment of atrial fibrillation: In several clinical trials with less than 100 patients in the 70s and 80s, amiodarone had been shown to be superior to other antiarrhythmics and to placebo in the conversion to sinus rhythm, as well as in the preservation of rhythm. Globally clinical trials about the treatment of AF show neutral results in terms of the benefit of the rhythm control strategy compared to the control of heart rate, however, when comparing specifically the drugs for rhythm control, a subanalysis of the AFFIRM study [2] showed that amiodarone is superior to sotalol and that the group 1 drugs evaluated (quinidine, disopyramide, procainamide, moricizine, flecainide, propafenone), are more likely to preserve sinus rhythm and lower rate of adverse effects than others antiarrhythmics. The SAFE-T study [3] demonstrated in patients with persistent AF similar rate of reversion to sinus rhythm than sotalol, but more chances of preserving sinus rhythm during follow-up. On the other hand, a study conducted in Argentina (GEFACA) [4] with 100 patients found that amiodarone compared to placebo reversed AF more times, increased the rate of successful electrical defibrillation, decreased the rate of recurrences and delayed them. More recently, amiodarone was compared head-to-head with dronedarone (DIONYSOS) [5], showing lower efficacy but less adverse effects with dronedarone (later said drug fell into disuse due to the risk of worsening heart failure). Finally, other drugs were currently developed for the reversal of acute AF, one of them (vernakalant) showed a higher rate of reversion than amiodarone (AVRO study) [6].
- Treatment of ventricular arrhythmia: The ARREST study [7] randomized 500 patients with out-of-hospital cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia to receive amiodarone (300 mg) or placebo in addition to conventional treatment, and proved to increase the survival rate until the hospitalization by 60% (OR 1.60 [1.08-2.37], $p < 0.05$). On the other hand, the ALIVE study published later [8], compared head-to-head amiodarone with lidocaine, proving that amiodarone achieves twice as many chances of reaching the hospital alive (OR 2.17, [1.21-2.82] $p < 0.05$).

- Prevention of recurrence of ventricular arrhythmias: In the three clinical trials that evaluated the utility of implanted cardioverter-defibrillators in survivors of ventricular arrhythmias (secondary prevention, AVID, CIDS, and CASH), the benefit of the device was compared with amiodarone (and in some cases with other antiarrhythmics), demonstrating greater survival with the ICD [9-11].
- Prevention of post-myocardial infarction arrhythmias: The first clinical trials were developed in the pre-reperfusion era and pre-defibrillators, among them the BASIS [12] of 1990, where amiodarone demonstrated superiority when compared to placebo or other antiarrhythmics in patients with a history of infarction and presence of complex ventricular extrasystole. A clinical trial conducted in Argentina, GEMICA, used high doses intravenously from the first day of the infarction in the mid-1990s, and although it reduced arrhythmias, there was a trend increase in mortality [13]. This study did not have a comparison group, but the Spanish SSSD study carried out by Bayés de Luna and colleagues [14] demonstrated a benefit in reduction of ventricular arrhythmias after infarction with amiodarone compared to beta-blockers (metoprolol). Two large clinical trials with more than 1000 patients carried out simultaneously in Canada (CAMIAT) and in Europe (EMIAT), used oral intermediate doses of amiodarone in patients who had recently had a heart attack, achieving a frank reduction of extrasystole , arrhythmic death, but not total mortality [15,16]. Subsequent analyzes showed that the effect of amiodarone was independent and additive to that of beta-blockers.
- Primary prevention of arrhythmias and major events in patients with heart failure: One of the pioneering studies on ventricular arrhythmias and death in patients with heart failure was the Argentine study GESICA, published in 1994 in The Lancet by Hernán Doval, Daniel Nul, Hugo Grancelli, and collaborators [17]. 500 patients were randomized to receive the conventional treatment to date or the addition of amiodarone, demonstrating reduction in death and hospitalizations with the drug, regardless of the presence or absence of ventricular arrhythmias. A later substudy showed that the patients who benefit the most from the treatment are those who are most tachycardic. Another small-scale clinical trial showed similar results (EPAMSA) [18]. On the other hand, researchers from the CHF-STAT [19] clinical trial demonstrated comparable benefits, mainly in patients with non-ischemic heart disease, and they were able to verify the efficacy of amiodarone both to reverse atrial fibrillation and to prevent its occurrence in patients with heart failure. A meta-analysis of more than 6000 patients in patients receiving amiodarone for heart failure or myocardial infarction [20], demonstrated a reduction in total mortality of 13% (HR 0.87 [0.78-0.99], p = 0.030), mainly due to the reduction in arrhythmic death by 29% (HR 0.71 [0.59-0.85], p = 0.0003).
- Comparison with the defibrillator: Several studies were conducted to analyze the benefit of defibrillators in patients with left ventricular dysfunction (the majority with an ejection fraction cutoff <30% or <35%), and in several of them the point for comparison was amiodarone. The AMIOVIRT study (21) in 100 patients with myocardiopathies of non-ischemic etiology presented similar results between amiodarone and defibrillators, so it had to be interrupted, although there was a tendency toward a lower rate of ventricular arrhythmias. More recently, the superiority of the defibrillator over amiodarone was demonstrated in terms of reduction of mortality in patients with ischemic (MADIT, MADIT II, MUSTT) and nonischemic cardiomyopathy (SCD-HeFT) [22-24].
- Prevention of cardio-defibrillator shocks: Patients who receive an ICD benefit because the device treats and reverses most of the ventricular arrhythmias detected, however, the defibrillator does not prevent the appearance of arrhythmias, so a clinical trial (CASCADE) used concomitant amiodarone, demonstrating a significant reduction in the rate of shocks, but with an increase in the adverse effects of the drug, so its concomitant use should be analyzed

individually (probably the most symptomatic individuals are the most benefited with the use of amiodarone). The OPTIC study also showed a benefit with the concomitant use of amiodarone and blockers to reduce the shock rate (63% reduction compared to beta-blockers alone, HR = 0.27 [0.14-0.52], p <0.001) [25,26].

5. Conclusions

It was demonstrated in this review that amiodarone has unique pharmacological properties, and that it still has an important role in the treatment of several cardiovascular diseases.

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