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LONG TERM DRUG THERAPY OF AMIODARONE ON BIOLOGICAL SYSTEMS

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ABSTRACT

Amiodarone is an antiarrhythmic drug that is commonly used for the treatment of ventricular and supraventricular arrhythmias. Amiodarone as an iodinated benzofuran derivative is a potent antiarrhythmic drug that is being used for the treatment of a wide variety of cardiac arrhythmias. Thyroid, lung, liver, ophthalmologic and neurologic systems can be affected by Amiodarone. Most of the adverse effects of the drug are related to its dosage and duration of administration. Therefore the effectiveness of Amiodarone in long-term treatment of patients with heart arrhythmia is limited because of the development of its adverse side effects. Acute adverse effects of amiodarone include hypotension, bradycardia, chemical peripheral phlebitis and nausea.[15] 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. Lung-toxicity determines cough, dyspnoea, fever, loss of weight, chest pain, and rarely haemoptysis

KEYWORDS: Amiodarone, arrhythmia, biological system, overdose.

INTRODUCTION

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 antiarrhythmic of first choice. Amiodarone is also first choice drug in the treatment of various ventricular and supra-ventricular tachyarrhythmias.[1] 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 im- paired left ventricular (LV) function, when digitalis has been

ineffective, and is an adjunct to electrical cardioversion.[2] The major side effects of amiodarone are hypotension, bradycardia and peripheral phlebitis. Major contraindications to the intravenous (iv) injection of amiodarone are bradycardia, Sino atrial block, severe disturbs 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. Amiodarone, a derivative of benzofuran, is one of the most common anti-arrhythmic drugs, frequently used in the Emergency Department. Amiodarone is used 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 tachyarrhythmias.[3]

ELECTROPHYSIOLOGICAL 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.[4] The most relevant effects of amiodarone on cardiac cells are the reduction of the depolarization (phase 4)[5], the late repolarization, caused by a prolongation of the action potential (phase 3) and the prolongation of the effective refractory period.[6]

MECHANISMS OF ACTION

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 trans- membrane carrier of T3 at cardiac level.[7,8] 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 trans membrane currents.[9,10]

THERAPEUTIC INDICATIONS IN EMERGENCY

Cardiac Arrest with Shockable Rhythm (Refractory FV/Pulseless VT) Hemodynamically Unstable VT and Hemodynamically Stable Wide-Complex Tachycardia Narrow-Complex Tachycardia (Supraventricular Arrhythmias).

SIDE EFFECTS, CONTRAINDICATIONS AND PHARMACOLOGICAL INTERACTIONS

Side Effects

Adverse reactions have been very common in virtually all series of patients treated with amiodarone for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7 to 18%. Hypotension was the most common adverse event report- ed with amiodarone iv. The hypotension was not dose-dependent, but related to the rate of infusion.

Acute adverse effects of amiodarone include hypotension, bradycardia, chemical peripheral phlebitis and nausea.[15] 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. Lung-toxicity determines cough, dyspnoea, fever, loss of weight, chest pain, and rarely haemoptysis.[17] 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 inhibition 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 contemporary reduction of fT3. Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported.[22]

CONTRAINDICATIONS

Main contraindications to the iv administration of amiodarone are sinus bradycardia, sino atrial block and severe conduction disturbances like second or third degree atrio- ventricular block.[23] 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.

PHARMACOLOGICAL INTERACTIONS

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 is enzyme is present in both the liver and intestines. Amiodarone is an inhibitor of CYP3A4 and p-glycoprotein. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 and substrates of p-glycoprotein.[24,25]

DOSAGE AND ADMINISTRATION

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting.

Overdose

Over dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances amiodarone should be temporarily withdrawn and if necessary beta adrenostimulants or glucagon given. In the event of ingestion of a toxic dose, gastric lavage should be employed to reduce absorption and in addition general supportive measures should be applied.

CONCLUSION

Amiodarone is one of the most common anti-arrhythmic drugs used in the Emergency Department. Side effects occur more frequently with long-term administration of the drug, e.g. more than 6 months and is related to total dose of the drug administered; therefore the effectiveness of Amiodarone in long-term treatment of patients with heart arrhythmia is limited because of the development of its adverse side effects.

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