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Comparative Review Between Ranolazine and Amiodarone as an Antidysrhythmic Drugs

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Abstract

Dysrhythmia can be life threatening and results in stroke or heart failure if untreated. Up to 65% of patients had sudden cardiac death as first manifestation of cardiac dysrhythmia. In the United States, more than 850,000 people are hospitalized for dysrhythmia each year. Cardiac dysrhythmias could occur in up to 25% of patients treated with digitalis, 50% of anaesthetized patients and over 80% of patients of myocardial infarction.

Cardiac ischemia increases the activity of late sodium entry (INa) that results in higher intracellular sodium with subsequent calcium overload through interference with sodium-calcium exchange. Increased intracellular calcium triggers cardiac dysrhythmia.

Amiodarone is a powerful antidysrhythmic medication for supra-ventricular and ventricular arrhythmias. A majority of patients treated with amiodarone suffer from mild adverse events, however, serious life-threatening adverse effects caused by amiodarone are also seen, for the serious complications caused by Amiodarone treatment, this review asses antidysrhythmic effects of Amiodarone compared to that exerted by Ranolazine.

Ranolazine is an anti-anginal drug that selectively inhibits late INa 10-fold more than peak INa. Blocking of late sodium channels during phase 3 of cardiac action potential leads to a decrease in late sodium entry with subsequent decrease in intracellular calcium, which will probably improve ischemia and may have antidysrhythmic potential

Keywords: Ranolazine, Amiodarone, Dysrhythmia

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Introduction

Cardiac dysrhythmia is any abnormality in rate, regularity, site of origin of the cardiac impulses or a disturbance in conduction that cause abnormal activation sequences of the myocardium.

Dysrhythmia can be life threatening and result in stroke or heart failure if untreated. Up to 65% of patients had sudden cardiac death as first manifestation of cardiac dysrhythmia. In the United States, more than 850,000 people are hospitalized for a dysrhythmia each year (John et al, 2010).

Cardiac dysrhythmias are commonly manifested with lightheadedness, dizziness, fluttering, pounding, quivering, shortness of breath, syncope, nausea, chest discomfort and forceful or painful extra beats (Al-Khatib et al, 2003).

Many types of heart diseases cause dysrhythmia. Coronary disease is often a trigger. It triggers dysrhythmia because coronary heart disease produces scar tissue in the heart. This scar tissue disrupts the transmission of signals, which control the heart rhythm, in addition there is an over activity of the late sodium entry (INaL) in phase 3 of action potential during ischemia (Fozzard, 2002) (Fig 1).

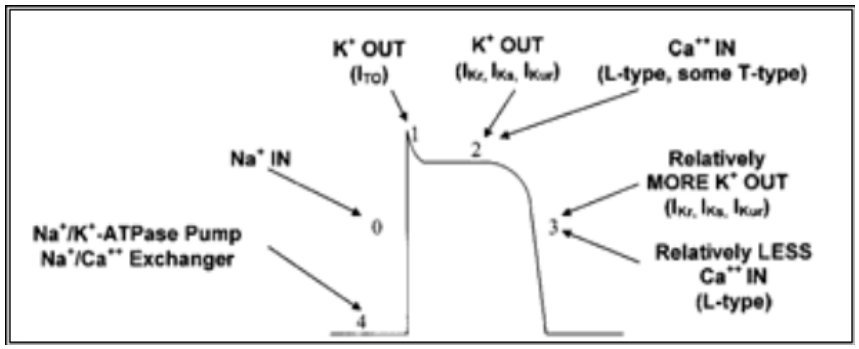

Fig1: Phases of cardiac action potential. (Fozzard, 2002)

Late sodium current in cardiac cells is very small compared with the fast component, but as it flows throughout the action potential, it may make a substantial contribution to sodium loading during each cardiac cycle. There are four types of late Na channel currents: (1) isolated brief openings, (2) scattered openings, (3) long openings and (4) bursts.

The occurrence frequencies of the four types are different. Bursts appeared about 1 in every 2,000 depolarization, with an open time constant longer than others **(Sheng et al 1997).**

Late sodium current may contribute to triggering dysrhythmia in two ways: by causing repolarisation failure (early afterdepolarisations) and by triggering late afterdepolarisations attributable to calcium oscillations in sodium–calcium overload conditions **(Fig 2)**.

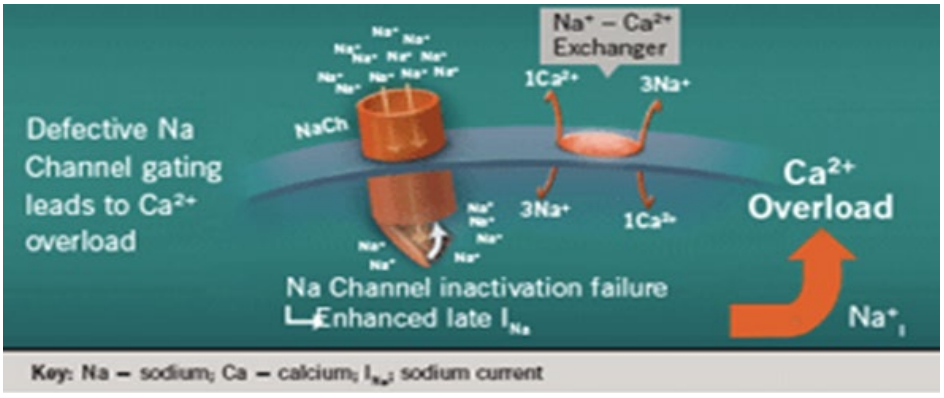

Fig2: Diagram of the sodium channel **(Maltsev et al, (2008)**

Reduction of late sodium current would therefore be expected to have therapeutic benefits, particularly in disease states such as ischemia and dysrhythmia in which sodium–calcium overload is a major feature **(Noble et al (2006).**

Ranolazine "Ranexa"

Ranolazine (Ranexa) is a new antianginal drug innovated by CV Therapeutics. FDA approved it for clinical use in the United States in January 2006 and by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in 24 April 2008.

Anti-ischemic effect of Ranolazine specifically inhibits late sodium entry in phase 3 action potential leading to decrease intracellular sodium which subsequently will lead to decrease intracellular calcium through preserving Na+/Ca+2 exchanger that will probably improve ischemia and dysrhythmia (Belardinelli et al 2006).

Chemical structures and doses

Ranolazine is a racemic mixture and chemically described as 1-piperazineacetamide, N-(2, 6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]. It has an empirical formula of $C_{24}H_{33}N_3O_4$, a molecular weight of 427.54 g/mole. **(Andreson, 2006).**

Ranolazine is a white to off-white powder. It is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Ranexa is available for oral administration as film-coated, extended-release tablets containing 500 mg or 1000 mg of Ranolazine.

Pharmacokinetics

Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable. For example, at a dose of 1000 mg twice daily, the mean steady-state Cmax was 2600 ng/mL with 95% confidence limits of 400 and 6100 ng/mL. The apparent terminal half-life of ranolazine is 7 hours. Steady state is generally achieved within 3 days of twice-daily dosing with Ranexa. At steady state over the dose range of 500 to 1000 mg twice daily, Cmax and AUC0-τ increased slightly more than proportionally to dose, 2.2- and 2.4-fold,

respectively. With twice-daily dosing, the trough:peak ratio of the ranolazine plasma concentration is 0.3 to 0.6. The pharmacokinetics of ranolazine is unaffected by age, gender, or food **(Jerling, 2006).**

After oral administration of ranolazine, peak plasma concentrations are reached between 2 and 5 hours. After oral administration of 14C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from Ranexa oral tablets relative to that from a solution of ranolazine is 76%.

Because ranolazine is a substrate of P-glycoprotein (P-gp), inhibitors, P-gp may increase the absorption of ranolazine. Food, high-fat breakfast, has no important effect on the Cmax and AUC of ranolazine. Therefore, ranolazine may be taken without regard to meals. Over the concentration range of 0.25 to 10 µg/mL, ranolazine is approximately 62% bound to human plasma proteins **(Donck et al, 1993).**

Following a single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and 25% in feces. Ranolazine is metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces.

The pharmacologic activity of the metabolites has not been well characterized. After dosing to steady state with 500 mg to 1500 mg b.i.d., the four most abundant metabolites in plasma have AUC values ranging from about 5 to 33% that of ranolazine, and display apparent half-lives ranging from 6 to 22 hours. Ranolazine is metabolized mainly by CYP3A and to a lesser extent by CYP2D6 **(Donck et al, 1993).**

Mechanism of action

Ranolazine is believed to have its effects via inhibition of the late sodium current. This decrease in the intracellular sodium level by ranolazine affects the sodium-dependent calcium channels during myocardial ischemia **(Hale and Kloner, 2006).** Thus, ranolazine indirectly prevents the calcium overload by preserving Na/Ca exchanger **(Belardinelli et al 2006).**

It was developed as an antianginal medication. Clinically, ranolazine has been shown to be distinct from other conventional antianginal agents such as beta blockers, calcium channel blockers, and nitrates in that it did not have a clinically significant effect on heart rate or blood pressure **(Jain et al, 2006).**

Changes in ion homeostasis in acute ischemia are immediate, and the mechanisms are complex. Intracellular sodium and intracellular calcium rise in parallel along with internal protons and extracellular potassium **(Schram et al, 2004).** In the laboratory setting, cardiac INaL has been shown to be acutely increased in ischemia **(Ju et al, 1996)** increased concentrations of ischemic metabolites such as lysophosphatidylcholine and cardiac dysrhythmia **(Undrovinas et al, 1992 and Shander et al, 1996).**

The increase in calcium may be caused by sodium induced calcium overload through a decreased activity or actual reversal of the sodium–calcium exchanger **(Imahashi et al, 2005).** In any event, the rise in intracellular calcium in myocardial cells increases diastolic wall tension and increases end-diastolic pressure, which increases oxygen demand and at the same time decreases oxygen supply because of decreased diastolic flow. **Undrovinas et al, (1992) and Shander et al, (1996)** proposed that ranolazine blocks late INaL ameliorating ischemia induced accumulation of intracellular Na+, preventing Na-induced calcium overload and the subsequent deleterious effects on left ventricular end-diastolic pressure that exacerbates angina and dysrhythmia **(Belardinelli et al, 2004).**

Block of INaL by ranolazine would be expected to shorten action potential duration (APD) and the QT interval on ECG. Ranolazine prolonged APD and increased in the QTc interval, under control conditions, in a plasma concentration-related manner. A minor degree of QT prolongation was observed on taking over dose of ranolazine more than 1000 mg twice daily that may be due to delayed rectifier K+ channels **(Sanguinetti and Jurkiewicz, 1990).** These effects are believed to be caused by ranolazine and not by its metabolites **(Antzelevitch et al, 2004 and Fredj et al, 2006)**.

It is important to note that ranolazine even at high doses does not induce early after depolarizations (EADs) that may underlie triggered tachydysrhythmia **(Hwang et al 2009)** and no torsades de pointes has been observed in experimental tissue models **(Antzelevitch et a, 2004 and Scharm et al, 2004)** or so far in patients **(Fredj et al, 2006).**

Clinical trials

Approval of ranolazine was based on a pair of clinical trials, dubbed **ERICA** (Efficacy of Ranolazine In Chronic Angina) and CARISA (Combination Assessment of anolazine In Stable Angina).

In ERICA Study, data showed that ranolazine significantly decreased frequency of angina attacks (mean 3.3 attacks per week, vs. 4.3 for placebo; p=0.028). The drug showed higher efficacy in male patients **(Stone et al, 2006).**

Other trial, **CARISA** Study, yielded a significant increase in modified Bruce treadmill exercise tolerance ($p<0.05$) and time to angina onset ($p<0.05$) at both peak (4 hours post dose) and trough (12 hours post dose) drug plasma concentrations **(Louis et al 2002).**

The antianginal effects of ranolazine was investigated in the patients with prior chronic angina enrolled in the randomized, double-blind, placebo-controlled **MERLIN–TIMI** (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes) 36 trial of patients with acute coronary syndrome. In patients with prior angina, the primary end point (cardiovascular death, myocardial infarction, recurrent ischemia) was less frequent with ranolazine due to a significant reduction in recurrent ischemia. Ranolazine also reduced worsening angina and intensification of antianginal therapy **(Morrow et al, 2007).**

Indications for use

Ranolazine is indicated for use in the treatment of chronic stable angina in individuals with angina, which is refractory to more standard anti-anginal medications. In addition, it has been shown to both decrease angina episodes and increase exercise tolerance in individuals taking concomitant atenolol, amlodipine, or diltiazem. **(Chaitman et al, 2004a)**

Unlike other antianginal medications such as nitrates and beta blockers, ranolazine does not significantly alter either the heart rate or blood pressure. For this reason, it is of particular use in individuals with angina that is refractory to maximal tolerated doses of other anti-anginal medications.

Drug-Drug Interactions

Studies in healthy volunteers confirm that ranolazine is primarily metabolized by CYP3A. Plasma levels of ranolazine are increased 2 -3 folds by the CYP3A inhibitors such as ketoconazole and diltiazem. Plasma levels of ranolazine is increased about 2-fold by the CYP3A and P-gp inhibitor verapamil. Less potent CYP3A inhibitors such as simvastatin and cimetidine do not increase the exposure to ranolazine in healthy volunteers. Rifampin decreases the plasma concentration of ranolazine by approximately 95%, involving induction of CYP3A and likely of P-gp. Co-administration of ranolazine and rifampin should be avoided. While drug-drug interaction studies with other CYP3A inducers, such as phenytoin, phenobarbital, carbamazepine, and St. John's wort, have not been conducted, they can be expected to reduce the plasma concentration of ranolazine to sub-therapeutic levels and thus should not be given together with it.

Studies indicate that ranolazine is a P-gp substrate. Caution should be exercised when coadministering ranolazine and P-gp inhibitors such as ritonavir and cyclosporine.

The potent CYP2D6 inhibitor paroxetine increased ranolazine concentrations 1.2-fold in healthy volunteers. No dose adjustment of Ranolazine is necessary when it is co-administered with drugs inhibiting CYP2D6. Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin **(Song Y, 2004b).**

Studies suggest that ranolazine is a P-gp inhibitor. In vivo ranolazine increases digoxin concentrations 1.5-fold in healthy volunteers. The dose of digoxin may have to be adjusted when ranolazine is co-administered **(Moysey et al, 2008).** Studies indicate that ranolazine and its O-demethylated metabolite are inhibitors of CYP3A and CYP2D6. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP1A2, 2C9, 2C19 or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Concomitant use of ranolazine with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotic, has not been formally studied, but lower doses of the other drug than usually prescribed may be required in the presence of ranolazine **(Song et al, 2006).**

Side effects and Contraindications

The most common adverse events, more frequently on ranolazine than placebo, that led to discontinuation, are dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). The following additional adverse reactions occurred at an incidence of 0.5 to 2.0% in patients treated with ranolazine and were more frequent than the incidence observed in placebo-treated patients **(Hale et al, 2008).**

Ranolazine is contraindicated in patients who are taking strong inhibitors or inducers of CYP3A, or with clinically significant hepatic impairment.

Amiodarone "Cordarone"

Amiodarone is an antidysrhythmic agent, used for various types of tachydysrhythmias both ventricular and supraventricular. Discovered in 1961, it was not approved for use in United States until 1985 **(Porid, 1995).**

Clinical Structure and Doses

(2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl) diethylamine **(David et al, 1983).**

Amiodarone is available in oral and intravenous formulations. Orally, it is available in Egypt under the trade names Cordarone (produced by Global Napi Pharmaceuticals under license of Sanofi Aventis-France) in 200 mg and 400 mg tablets.

Pharmacokinetics

Following oral administration in man, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but has varied between 35% and 65% in various studies **(Woosely et al, 1988).** Maximum plasma concentrations are attained 3 to 7 hours after a single oral dose. The effective plasma concentration is approximately 1-2 mg/ml **(Zipese et al, 1984).** The dose of amiodarone administered is tailored to the individual and the dysrhythmia that is being treated. When administered orally, the bioavailability of amiodarone is quite variable. Absorption ranges from 22 to 95%, with better absorption when it is given with food. **(Siddoway, 2003).**

Amiodarone is fat-soluble, and tends to concentrate in tissues including fat, muscle, liver, lungs, and skin **(Holt et al, 1986).** This confers a high volume of distribution (5000 liters in a 70 kg adult) and a long half-life. Due to the long half-life of amiodarone, oral loading typically takes days to weeks. An oral loading dose is typically a total of 10 grams, divided over one to two weeks but there are many other dosing regimens. Once an individual is loaded, a typical maintenance dose of amiodarone is 100 or 200 mg either once or twice daily. An intravenous loading dose is typically 300 mg in 20-30cc D5W for cardiac arrest due to ventricular fibrillation **(Kudenchuk et al, 1999).** The loading infusion for dysrhythmias is typically 150 mg in a 100cc bag of D5W given over 10 minutes. Both can be followed by a 360 mg slow infusion over 6 hours then a maintenance infusion of 540 mg over 18 hours.

Amiodarone is extensively metabolized in the liver by cytochrome P450 3A4. One major metabolite of amiodarone, desethylamiodarone, it accumulates to an even greater extent in almost all tissues. The pharmacological activity of this metabolite, however it is unknown during chronic treatment, the plasma ratio of metabolite to parent compound is approximately one **(Gill et al, 1992).**

The elimination half life of amiodarone ranges between 40-55 days with a mean approximately 53 days **(McKenna et al, 1986).** For the metabolite (desethlyamiodarone), the mean plasma-elimination half life was approximately 61 days. **(Stark et al, 1991a).** The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. Amiodarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure **(McKenna et al, 1986).** Neither amiodarone nor its metabolite is dialyzable **(Porid, 1995 and Stark et al, 1991a).**

Mechanism of action

In animals, amiodarone is effective in prevention or suppression of experimentally induced dysrhythmias. The antiarrhythmic effect of amiodarone is due to non-competitive alpha and beta adrenergic inhibition , class II activity, in addition, amiodarone is a very effective blocker of sodium channels, class I activity, moreover, it has a week calcium channel blocking effect, class IV activity. Therefore, amiodarone has a broad spectrum of antidysrhythmic actions on the heart **(Du et al, 1995).**

Amiodarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of prepotential is reduced, generally reducing automaticity **(Varro and Rabloczky, 1986).** Amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (after load) and slightly increases cardiac index **(Singh, 1970).**

After oral dosing, however, amiodarone produces no significant changes in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF **(Twidale et al, 1993).** After acute intravenous dosing in man, amiodarone may have a mild negative inotropic effect **(Gangol et al, 1985).** Amiodarone does not alter vagal reflexes or the responsiveness of cardiac cholinergic receptors but it causes some non competitive alpha and beta adrenergic blockade **(Biggera and Hoffman, 1992).**

Amiodarone has also a selective inhibition of the effect of T3 on myocardium that may contribute to prolongation of the action potential duration and refractoriness **(Melmed et al, 1981).**

Indication for use

Because amiodarone has a low incidence of pro-arrhythmic effects, it has been used both in the treatment of acute life-threatening dysrhythmias as well as the chronic suppression of dysrhythmias. It is useful both in supraventricular and ventricular dysrhythmias.

Ventricular fibrillation

The treatment of choice for ventricular fibrillation (VF) is electrical defibrillation. However, amiodarone can be useful in shock-refractory VF. In the ARREST trial, amiodarone was shown to improve survival in hospitalized patients, when compared to placebo, in individuals who suffer cardiac arrest with shock-refractory VF **(Kudenchuk et al, 1999).**

It is on the basis of this study that the guidelines created by the American Heart Association for the treatment of VF include amiodarone as a second line agent, after epinephrine **(Jaffe, 1993).**

Ventricular tachycardia

Amiodarone may be used in the treatment of ventricular tachycardia in certain instances. Individuals with hemodynamically unstable ventricular tachycardia should not initially receive amiodarone as amiodarone is a second line agent after epeniphrrine. These individuals should be cardioverted out of their unstable rhythm.

Amiodarone can be used in individuals with hemodynamically stable ventricular tachycardia. In these cases, amiodarone can be used regardless of the individual's underlying heart function and the type of ventricular tachycardia; it can be used in individuals with monomorphic ventricular tachycardia , but is contraindicated in individuals with polymorphic ventricular tachycardia as it is associated with a prolong QT interval which will be made worse with antidysrhythmic drugs **(Rosenbaum et al, 1976).**

Atrial fibrillation

Individuals who have undergone open heart surgery are at an increased risk of developing atrial fibrillation (or AF) in the first few days post-procedure. In the ARCH trial, intravenous amiodarone (2 grams administered over 2 days) has been shown to reduce the incidence of atrial fibrillation after open heart surgery when compared to placebo. The benefit of amiodarone in the treatment of atrial fibrillation in the critical care population has yet to be determined but it may prove to be the agent of choice where the patient is haemodynamically unstable and unsuitable for DC cardioversion **(Guarnieri et al, 1999).**

However, clinical studies have failed to demonstrate long-term efficacy and have shown potentially fatal side effects such as pulmonary toxicities. While Amiodarone is not approved for AF by the FDA, it is a commonly prescribed off-label treatment due to the lack of efficacious treatment alternatives.

So called 'acute onset atrial fibrillation', defined by the North American Society of Pacing and Electrophysiology (NASPE) in 2003, responds well to short duration treatment with amiodarone. This has been demonstrated in seventeen randomised controlled trials, of which five included a placebo arm. The incidence of severe side effects in this randomized clinical trial was low.

Drug-Drug Interactions

The Pharmacokinetic of numerous drugs, including many that are commonly administered to individuals with heart disease, is affected by amiodarone. Particularly, doses of digoxin should be halved in individuals taking amiodarone since amiodarone decreases renal and nonrenal clearance of the digitalis glycosides and increases its bioavailability. These effects appear related to the dose of amiodarone, with higher doses of amiodarone being associated with the greatest increase in digoxin concentration **(Achilli and Serra, 1981).**

Amiodarone potentiates the action of warfarin. Individuals taking both of these medications should have their warfarin dose halved and their anticoagulation status, measured as prothrombin time (PT) and international normalized ratio (INR), measured more frequently. Amiodarone decreased the total body clearance of warfarin in normal subjects but did not change volumes of distribution. Amiodarone is a general inhibitor of the cytochrome P450 catalyzed oxidation of warfarin. **(Larry et al, 1991).**

The FDA revised the labels of amiodarone and simvastatin in 2002 to warn of increased risk of rhabdomyolysis, the most severe form of myopathy, when the two drugs are taken concomitantly in doses greater than 20 mg per day of simvastatin **(Karimi et al, 2010).** There are many other drugs should not be taken with amiodarone: cimetidine, clopidogrel, cyclosporine, dextromethorphan, diclofenac, loratadine, a beta-blocker, potentiation, and Ca2+ channel blockers **(Singh et al, 1989).**

Side effects and contraindications

Amiodarone has numerous side effects. Most individuals administered amiodarone on a chronic basis will experience at least one side effect **(Vanerven and Schalij, 2010).**

- Decrease heart rate and increase incidence of heart block.
- The most serious reaction that is due to amiodarone is interstitial lung disease. Some individuals developed pulmonary fibrosis after a week of treatment, while others did not develop it after years of continuous use.
- The most specific test of pulmonary toxicity due to amiodarone is a dramatically decreased DLCO noted on pulmonary function testing.
- Amiodarone is structurally similar to thyroxin, which contributes to the effects of amiodarone on thyroid function, both under and over activity of the thyroid may occur on amiodarone treatment. Thyroid-stimulating hormone (TSH) should therefore also be checked every 6 months. The radioactive iodine uptake, nuclear thyroid uptake test, may still be helpful in the diagnosis and management of amiodarone-induced hyperthyroidism **(Batcher et al, 2007).**
- Corneal micro-deposits, Corneal verticillata, also called vortex keratopathy, are almost universally present (over 90%) in individuals taking amiodarone for at least 6 months. Bilateral optic disk swelling and mild and reversible visual field defects can also occur.
- Abnormal liver enzyme results are common in patients on amiodarone. Much rarer are jaundice, hepatomegaly and hepatitis **(Flaharty et al 1989).**
- Long-term administration of amiodarone is associated with a blue-grey discoloration of the skin. Individuals taking amiodarone may become more sensitive to the harmful effects of UV-A light.

Contraindications

- The only absolute contraindications to the administration of amiodarone is allergic reaction (i.e.: anaphylaxis) to the compound. However, because of the wide spectrum of the mechanism of action of amiodarone and the numerous side effects possible, there are a number of groups for which care should be taken when administering the drug.
- Individuals who are pregnant or may become pregnant are strongly advised to not take amiodarone. Since amiodarone can be expressed in breast milk, women taking amiodarone are advised to stop nursing.
- It is contraindicated in individuals with sinus nodal bradycardia, atrioventricular block, and second or third degree heart block who do not have an artificial pacemaker.
- Individuals with baseline depressed lung function should be monitored closely if amiodarone therapy is to be initiated.
- The injection should not be given to neonates, because the benzyl alcohol it contains may cause the fatal "gasping syndrome".
- Amiodarone can worsen the cardiac dysrhythmia brought on by Digitalis poisoning as amiodarone decreases renal and nonrenal clearance of the digitalis glycosides, reduces digitalis glycoside volume of distribution, and increases digitalis glycoside bioavailability **(Strocchi et al, 2009).**

Conclusion

Ranolazine showed a powerful prophylactic antidysrhythmic effect comparable to that exerted by amiodarone with less recorded drug-drug interactions and less adverse effects. This would outline a dual benefit of ranolazine as an anti-ischemic as well as antidysrhytmic agent in ischemic heart disease patients for further investigations.

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