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Review Article

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Pharmacology of Combined Amiodarone Hydrochloride and Ranolazine Therapy in Atrial Fibrillation

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Subject: Pharmacology

ABSTRACT

This review article presents the pharmacology of combined Amiodarone Hydrochloride and Ranolazine therapy specially in Atrial Fibrillation. Amiodarone Hydrochloride is Anti Arrhythmic agent. Ranolazine is a Anti Anginal agent. The Antianginal agent was used in Ischaemia. Amiodarone Hydrochloride is Antiarrhythmic agent and use in Arrhythmia and Atrial fibrillation. If Amiodarone Hydrochloride is administered in large quantities, the condition of patient become worse by occurrence of adverse effect of Thyroid toxicity due to presence of Iodine moiety in Amiodarone. The use of Ranolazine in combination with Amiodarone Hydrochloride has been proved to provide beneficial effect in Atrial Fibrillation. The combination therapy has fewer adverse effect. The mechanism of Amiodarone Hydrochloride and Ranolazine is quite different. Amiodarone Hydrochloride inhibit potassium channel and inactivated-state blocker of cardiac sodium channel while Ranolazine inhibit late inward sodium current(I_{Na}) in cardiac cell and activated-state blocker of cardiac sodium channel. The combination of both have decrease dose dependent side effect of Amiodarone Hydrochloride. Both the drugs were approved by US government and has been used in Atrial Fibrillation in US. The main objective of this review article is to provide pharmacological information of combined therapy of Amiodarone Hydrochloride and Ranolazine to researcher in development of combined dosage form of this.

Key words: Amiodarone Hydrochloride, Ranolazine, Atrial Fibrillation, Pharmacology.

INTRODUCTION(1)

An Arrhythmia is an abnormality of rate, rhythm or site of the cardiac impulse or an abnormality in the impulse conduction. Disturbance of impulse generation may be due to altered normal and abnormal automaticity or after-depolarization. In disturbances of impulse conduction, an impulse may recirculate in the heart and cause repeated activation (re-entry).or there should be conduction block.

➢ **Atrial Fibrillation**: Atrial fibres are activated asynchronously at a rate of 350-550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100-160/min) ventricular response.

➢ **Types** (2):
- Extrasystoles
- Paroxysmal Supraventricular Tachycardia
- Atrial Flutter
- Atrial Fibrillation
- Torsade de points
- Ventricular Tachycardia
- Ventricular Fibrillation
- Atrio-Ventricular Block

Mechanism of Arrhythmia (2)

ENHANCE/ECTOPIC PACEMAKER ACTIVITY

Slope of phase 4 depolarization may be increased in the automatic fibers or appear in ordinary fibers. Ectopic impulse may result from current of injury. Myocardial cells damage by ischemia becomes partially depolarized: current flow between normally polarized fibers and initiate an impulse.

I) AFTER DEPOLARIZATIONS

These are Secondary depolarization accompanying a normal or premature action potential.

Early after depolarization-EADs are frequently associated with long Q-T interval due to slow repolarization and prolonged action potentials.

Delayed after depolarization-After attaining resting membrane potential a secondary deflection which may reach threshold potential and initiate a single premature AP.

II) REENTRY

Due primarily to abnormality of Conduction, an impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated.

Two ways for Reentry:

Circus movement type

Micro reentry Circuit

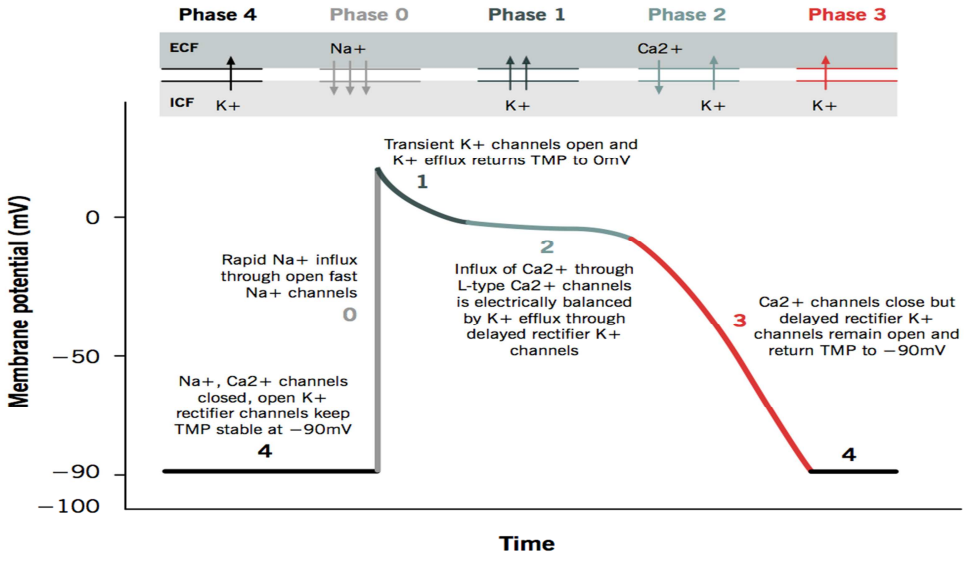

Figure 1: Action Potential (3)

AMIODARONE HYDROCHLORIDE(4-8) :

Chemical name :- 2-butylbenzofuran-3-yl-4-(2-diethylaminoethoxy)-3,5-diiodophenyl ketone hydrochloride(4). Amiodarone Hydrochloride appears as white or almost white crystalline powder. The drug is slightly soluble in

Distilled Water.(3 g/L).Freely soluble in methanol. Amiodarone Hydrochloride melts at 158-165 °C(5). The pKa value of Amiodarone Hydrochloride is 6.56(6). The molecular formula of Amiodarone Hydrochloride is $C_{25}H_{29}I_2NO_3$.HCL.. Its molecular weight is 681.17 g/mol. The structural formula is shown below in fig.2

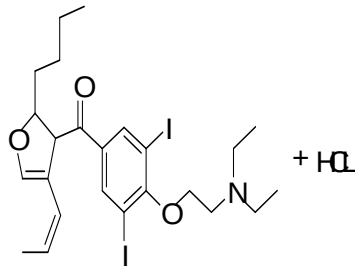

Fig. 2: The chemical structure of Amiodarone Hydrochloride

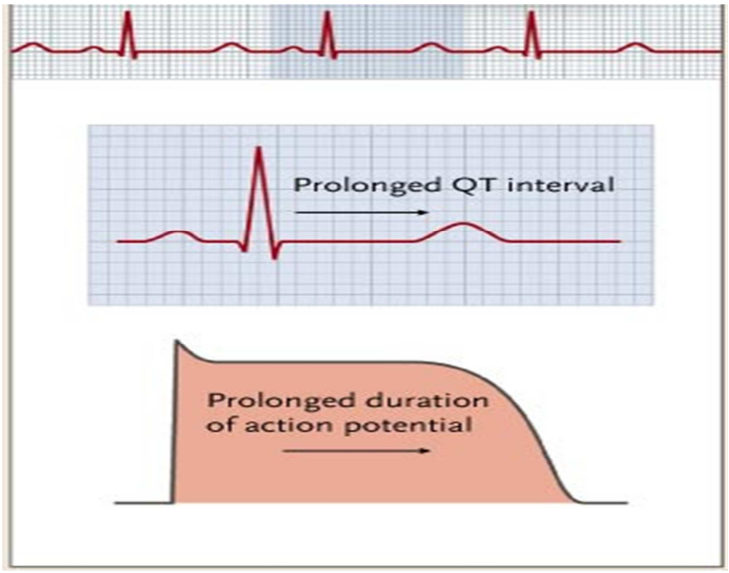

Fig.3 Mechanism of Amiodarone Hydrochloride

Mechanism of Action:

Amiodarone is categorized as a **class III Antiarrhythmic agent** and prolongs phase 3 of the cardiac action potential, the repolarization phase where there is normally decreased calcium permeability and increased Potassium permeability.

Amiodarone Hydrochloride

↓

Reentry

↓

Automaticity

↓

Amiodarone is highly lipophilic long acting drug.. Amiodarone shows noncompetitive beta blocker-like and potassium channel blocker-like actions on the SA and AV nodes, increases the refractory period via sodium and potassium-channel effects, and slows intra-cardiac conduction of the cardiac action potential, via sodium channel effects.(**8)**

It inhibits potassium channels and voltagegated sodium channels. There is a resulting decrease in heart rate and in vascular resistance.(7)

Pharmacokinetic (9):

Table.1 Pharmacokinetic parameter

Parameter	Observation
Bioavailability	20-55 %
Metabolism	Liver
Biological half-life	58 days(range 15-14 days)
Excretion	Primarily Hepatic and Billary

20-55% of an oral dose is absorbed. Metabolize in liver via CYP2C8,1% unchanged in urine. Major metabolite is Desethylamiodarone, negligible excretion of amiodarone and DEA in urine.

RANOLAZINE (10-11) :

The chemical name:- N-(2,6-dimethylphenyl)-2{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl piprazine-1-yl}acetamide(10). Ranolazine is a white to off-white crystalline powder that is freely soluble in Methanol and slightly soluble in water. Ranolazine melts at 122-124°C(11). The pKa value of Amiodarone Hydrochloride is 13.6(12). The molecular formula of Ranolazine is $C_{24}H_{33}N_3O_4$. Its molecular weight is 427.54 g/mol. The structural formula is shown below:

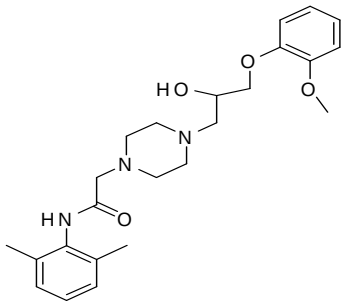

Figure 4: The structure of Ranolazine

MECHANISM OF ACTION [13]

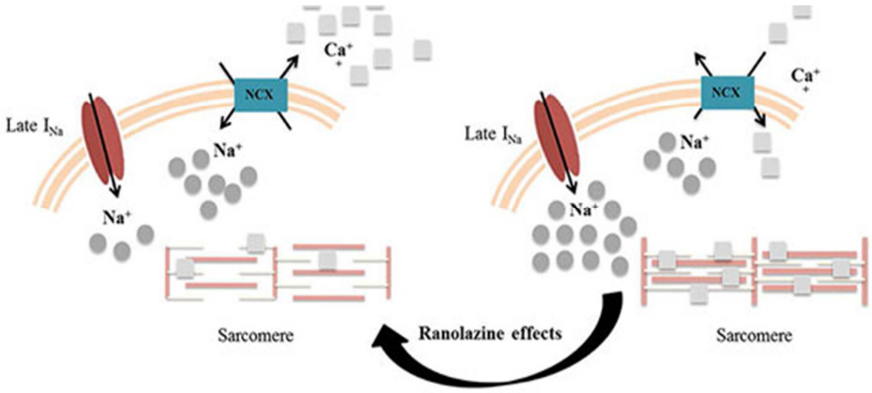

Fig. 5: Mechanism of Ranolazine in Ischaemia

Ranolazine a piperazine derivative is a new anti-ischemic drug for the treatment of angina and atrial fibrillation. The effect of ranolazine to block late I_{Na} has the potential to disrupt this cycle by reducing intracellular calcium accumulation and the accompanying decrease in ventricular wall tension. Two beneficial Effect- First, the reduction in wall tension during diastole should reduce the consumption of oxygen and ATP for contractile work, and thus oxygen demand. Secondly, the reduction of wall tension should reduce vascular compression. Because vascular compression causes closure of small vessels and reduction of blood flow, a reduction in compression may lead to increased myocardial nutritive blood flow and oxygen supply to the myocardium during diastole.(14)

As a late INa inhibitor, ranolazine was also shown to increase action potential duration and thus modestly QT interval by 2–5 ms. This effect, however, is not heart rate-dependent and cannot be exaggerated during bradycardia.

Furthermore, ranolazine does not induce early after depolarization and does not increase dispersion of repolarization across the left ventricular wall.(13)

PHARMACOKINETICS (15) :

Pharmacokinetic:

After oral administration of ranolazine as a solution, 73%of dose is systemically available. , metabolize mainly by CYP3A and to a lesser extent by CYP2D6. excreted unchanged in urine, feces

Parameter	Observation
Bioavailability	35 to 50 %
Protein binding	62%
Metabolism	Hepatic, CYP extensively involved
Biological half-life	7 hours
Excretion	Renal-75 % ,Fecal-25 %

Table.2 pharmacokinetic parameter

COMBINATION THERAPY OF AMIODARONE HYDROCHLORIDE AND RANOLAZINE (17)

The combination provides the remedy for prevention of Atrial Fibrillation with less adverse effect , safety and having high clinical effects**.(16)**

Combination of ranolazine with Amiodarone demonstrated efficacy superior to amiodarone alone. Combination treatment is safe and more effective and faster restoration of sinus rhythm.(18)

Amiodarone is toxic drug and its undesirable side effect like thyroid toxicity are dose dependent and so methods of increasing the efficacy of amiodarone to enable a reduction of dose are highly desirable. Combination of Chronic amiodarone and relatively low concentration of Acute ranolazine produce a synergistic use-dependent depression of sodium channel-dependent parameters lead to a potent effect of drug combination to prevent induction of AF. Both the drugs were approved by the US Government, and have frequently been used for the treatment of atrial fibrillation in US. This study will test the safety and efficacy of the combination therapy with these agents in patients with atrial fibrillation.(17,19)

Mechanism of Action of Combined Therapy (17,19)

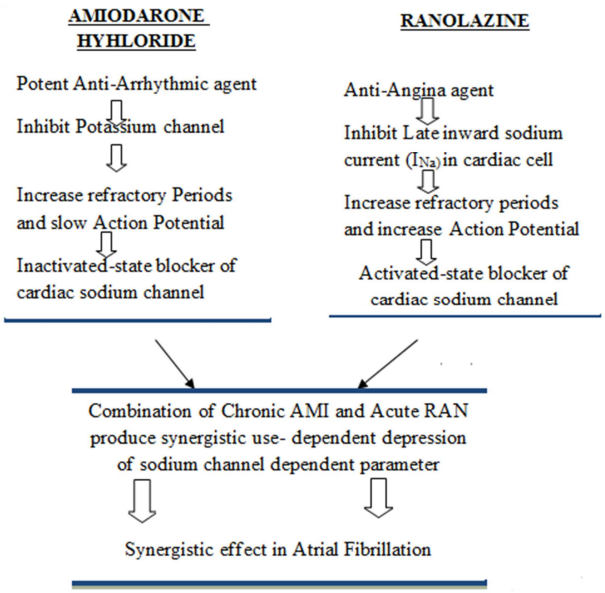

Fig. 6 combination mechanism action

CONCLUSION

By reviewing the all literatures, the combination therapy was found to be effective in treatment of atrial fibrillation. This review represents individual pharmacology and pharmacokinetic of Amiodarone Hydrochloride and Ranolazine as well as mechanism of action of combination of Amiodarone Hydrochloride and Ranolazine in treatment of atrial fibrillation. This review will helpful for researcher in future studies and also for development of combined formulation of Amiodarone Hydrochloride and Ranolazine as there no formulation is available.

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