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Combination and Monotherapy in Arrhythmia

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ABSTRACT

Cardiac arrhythmia is a disease characterized by abnormal electrical conduction in the heart that results in ineffective pumping. Dysfunctional nodes in the conduction pathway or in the cardiac muscles lead to irregular heartbeat patterns that can potentially induce severe complications such as cardiac arrest.

Anti-arrhythmic agents used (Class IB) for treatment of ventricular

Dysrhythmia however; as monotherapy becomes non inducible in only 10 % - 15 % patients when electrophysiologic techniques are used. (Class IC agents including flecainide, propafenone are also affective for substrate ventricular arrhythmia and is 15 %- 30 % of patients' arrhythmia is non inducible.

As Class IB and Class IC antiarrhythmic agents appears to have different electrophysiologic action of sodium channel and electrophysiologic properties of myocardial, the use of antiarrhythmic drugs in combinations may results in additive or synergistic effects.

I. INTRODUCTION

Arrhythmia is medical condition having improper beating of the heart, whether irregular may be too fast or too slow. Cardiac arrhythmia occurs when electric impulses in the heart does not works properly.

Antiarrhythmic drugs are used to treat ventricular arrhythmias, however in some cases it is not controlled with single drug therapy/monotherapy. Monotherapy in Arrhythmia achieve Target managing the proper rhythms; However, combination therapy on other hand might goes fast or effective with additive effects and synergism.

Combination therapy, a treatment modality that combines two or more therapeutic agents, major benefit of combination therapies is that they reduce development of drug resistance. Results shows only 40%-60% of patients respond to monotherapy. Thus, to manage the ventricular arrhythmicity this approach of combination drug therapy is being used instead of the monotherapy. Several studies have reported that combination drug therapy may enhance antiarrhythmic activity compared to monotherapy (1).

Classification of antiarrhythmic drugs (2)

A] Class I / sodium channel blockers

(a)Subclass IA

Quinidine
Procainamide
Disopyramide

(b)Subclass IB

Lidocaine
Mexiletine

(c)Subclass IC

Propafenone
Encainide

B] Class II / Beta blockers
Propranolol
Esmolol

C] Class III / potassium channel blockers
Amiodarone
Dronedarone
Sotalol
Dofetilide

D]Class IV / calcium channel blockers
Verapamil and Diltiazem

Mexiletine

Efficacy of combination of class IC drugs and Mexiletine therapy

During combination therapy with class IC drug and Mexiletine only one patient had arrhythmia, that was no inducible However, an increase in ventricular tachycardia cycle length that was significant among patients who had further showing tachycardia rate during combination therapy (1).

There is increased effective refractory period is observed which is an antiarrhythmic effect shown

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during combination therapy, compared with the monotherapy of class IC drugs (3).

The significant increase in induction cycle that reported in addition of mexiletine to class class IC is unlikely to be an effect of mexiletine to itself. Multiple studies have reported that mexiletine only insignificantly prolong cycle length.
With combination therapy the further increase in cycle length is unlikely to be effect of mexiletine itself, but it suggests an additive effect to block sodium channel (1).

Pharmacology Mexiletine

It is an oral analogue of Lidocaine; it has similar structure too. It is class IB anti-arrhythmic drug which prolongs the refractory period by delaying the recovery from inactivation of sodium channels responsible for phase 0 of cardiac action potential (4).

The drug has 90% of bio-availability and the peak plasma concentration is reported within 2-4 hours of administration, with mean half-life approximately 11 hours (2).

Mode of Action

Mexiletine is orally active class IB anti-arrhythmic drug, It is effective in suppression of ventricular arrhythmias. It inhibits the inward sodium current, thus reducing the rate of rise of action potential, phase 0. It reduces the effective refractory period (ERP) in purkinje fibers (5).

Pharmacokinetics

It is well absorbed from gastrointestinal tract (GIT) However; it's first-pass metabolism is low and peak blood level is achieved in 2-3 hours (2).

It is mainly metabolized in liver by primary pathway CYP2D6 metabolism. 90% of mexiletine is metabolized in liver to its inactive metabolites, pathological changes in liver resist hepatic clearance of its metabolite. Thus, metabolic degradation proceeds via various pathways involving aromatic and aliphatic hydroxylation, dealkylation, deamination and Noxidation. Resulting metabolites are further conjugated with glucuronic acid among these major metabolites are P-hydroxymexiletine, hydroxymethylmexiletine and N-hydroxymexiletine is then excreted unchanged by the kidney (5).

Interactions

Other medications like cimetidine, fluvoxamine, propafenone, rifampin, anti-seizure drugs can affect the elimination of mexiletine.
Mexiletine is a substrate for the metabolic pathway involving CYP2D6 and CYP1A2 enzymes; coadministration of fluvoxamine a CYP1A2 inhibitor decreases the clearance of mexiletine by 8% (5).

Mexiletine does not alter the serum concentration of digoxin but in case of gastrointestinal symptoms coadministration of magnesium-aluminum hydroxide, mexiletine lowers the serum level of digoxin (6).

Concurrent use of mexiletine and theophylline may lead to increased plasma theophylline levels (5).

Precautions

During pregnancy the therapy of mexiletine should carried out only under the supervision of a physician, as there are chances of transfer of the drug to the breast milk however; It is unlikely to harm a nourishing infant (6). Consumption of alcohol and marijuana (cannabis) is strictly avoided and the side effects of drug like blur vision may increase potentially (6).
Before initiating the mexiletine therapy, allergic profile of the patient should be checked (5).

Side Effects (2)(5)(6)

- Nausea
- Vomiting
- Heart Burn
- Dizziness
- Blurred Vision
- Allergic reactions may occurs which includes symptoms like Fever, Swollen Lymph Nodes,Rashes, Itching (Face/Tongue/Throat), Trouble Breathing.

International Journal of Pharmaceutical Research and Applications
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Table 01: Marketed Formulation of Mexiletine

Sr. No.	Form	Brand Name	Pill Image
1	50 mg Capsule	Mexiletine Oral	
2	50 mg Capsule	Mexiletine Oral	
3	150 mg Capsule	Mexiletine Oral	
4	200 mg Capsule	Mexiletine Oral	

Amiodarone

Efficacy of combination Amiodarone and Mexiletine

Amiodarone is most effective antiarrhythmic agent but may be in affective in some patients. The most effective safest combination is not known.

Table 02

Comparison of Electrocardiographic Features, Renal Functions and Amiodarone Dose Before and After Initiating Mexiletine (7):-

	BEFORE	AFTER	P
QRS Width (ms)	120.69+/-28.65	122.93+/-27.43	0.15
QTc (ms)	421.0+/-44.51	414.48+/-38.41	0.25
PR Interval (ms)	165.86+/-27.7	167.75+/-25.34	0.15
Blood Urea Nitrogen (mg/dl)	21+/-9	20+/-8.5	0.37
Serum Creatinine (mg/dl)	1.07+/-0.3	1.17+/-0.6	0.13
Amiodarone Dose/Day (mg)	420+/-60	212+/-50	0.000

International Journal of Pharmaceutical Research and Applications
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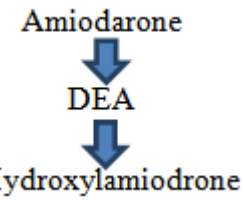
Adding Mexiletine to Amiodarone had no significant effect on QRS width, QTc interval, and PR interval as reported above table.
Clustered episodes of ventricular arrhythmia are difficult to treat.
Intravenous therapy followed by oral Amiodarone therapy together with the beta blocker therapy has been shown to be successful as a short-term management of electric storm.
Combination of Mexiletine and Amiodarone reported to decrease ventricular tachycardia or ventricular fibrillation (7).

Pharmacology of Amiodarone
The IV administration of Amiodarone results in relaxation of vascular smooth muscles Thus peripheral vascular resistance i.e., afterload is reduced. And also decrease cardiac conduction and treats arrhythmias (2).
However, its oral route is not that significant, clinical trials do not confirm oral Amiodarone increases survival.
It is found that increase duration QRS and QTc interval; And decrease SA node automaticity leading to decrease AV node conduction (8).

Mode Of Action
It is class III antiarrhythmic agent, blocks Potassium channels which cause Repolarization of Heart Muscles during 3rd phase of cardiac action potential (2) (8).
It increases the duration of action potential and effective refectory period therefore cardiac muscle cells excitability is reduced Curing abnormal heart rhythms.
In addition to this amiodarone is different from other drugs of class III as also affect the beta-adrenergic receptors, sodium channel, potassium channels. These actions may cause undesirable effect as hypotension, bradycardia (8)

Absorption
Cmax of Amiodarone in plasma is achieved in about 3 -7 hrs. after administration (8).
Onset of action of Amiodarone after one dose if given through IV route is between 1 and 30 minutes, and therapeutic effect lasting for 1-3 hrs. (2).

Metabolism
Amiodarone is Metabolize to desethyleamiodarone (DEA) metabolite by the action of enzyme CYP3A4 and CYP2C8. CYP3A4 is found in Liver and Intestine.
3'Hydroxylamiodarone metabolite of desethylamiodarone (DEA) is found in mammals with unknown clinical significance.



It is eliminated primarily by hepatic and biliary excretion. Small amount of DEA is found in urine (8).

Adverse Effects (2)(8)
- Hypotension (16%)
- Dizziness (3-40%)
- Headache (3-40%)
- Malaise (3-40%)
- Abnormal Gait / Ataxia (3-40%)
- Fatigue (3-40%)
- Impaired Memory (3-40%)
- Photosensitivity (10-75%)
- Hypothyroidism (1-22%)
- Constipation (10-33%)
- Anorexia (10-33%)
- SA Node Dysfunction (1-3%)
- Optic Neuritis (1%)
- Hematology: - Hemolytic anemia, Aplastic anemia, Lupus-like syndrome, Granuloma.
- Musculoskeletal: - Myopathy, Muscle weakness, Rhabdomyolysis, Demyelinating polyneuropathy.
- Psychiatric: - Hallucination, Confusing State, Disorientation, Delirium.
- Genitourinary: - Epididymitis, Impotence.
- Visual Disturbance

Precaution
Avoid excessive exposure to sunlight to reduce chances of photosensitivity.Substitution of Amiodarone therapy with other anti-arrhythmic agents should be done with expert advice, as pharmacokinetics of drug is complex and half-life is more and action is prolonged too. This may cause difficulties like drug interactions.

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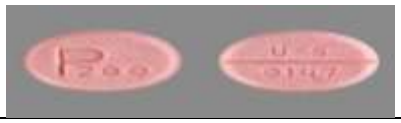
In 2-10 % cases of patients taking Amiodarone therapy may show hypothyroidism, thus there is requirement of either change in dose or discontinue the therapy and need of thyroid hormone supplement (8).

Contraindications
Hypersensitivity.
Severe Sinus Node Dysfunction, 2°/3° AV block or Bradycardia causing syncope (except with functioning artificial Pacemaker), Cardiogenic shock. Avoid during breast feeding as Amiodarone and its metabolites DEA, are excreted in milk causes hypothyroidism, Bradycardia to infants. Thus, breast feeding in such cases is not recommended although it is unclear if these effects are due to Amiodarone (8).

Table 03: Marketed Formulation of Amiodarone

Sr.No.	BRAND	FORM	PILL IMAGE
1	Pacron Oral	200 mg Tablet	
2	Duron Oral	200 mg Tablet	
3	Tachyra Oral	200 mg Tablet	
4	Amiodon Oral	200 mg Tablet	
5	Amipace Oral	200 mg Tablet	
6	Cordarone IV	150 mg /3 ml Injection	

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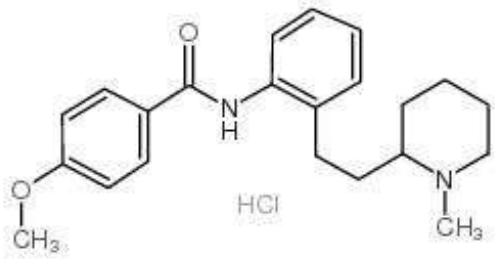
7	Tachyra IV	150 mg Injection	
8	Duron IV	150 mg / 3 ml Injection	

Encainide

Structure (9)



Efficacy of combination of class IB and class IC antiarrhythmic agents

Electrophysiological effects and efficacy of Encainide administered along with lidocaine to patients with sustained monomorphic ventricular tachycardia and with Encainide treatment alone reported; Administration of Encainide with addition of lidocaine, to patient with sustained ventricular tachycardia results, tachycardia remained inducible but the effective refractory period and induction cycle get prolonged significantly compared to Encainide monotherapy. No serious side effects were reported in combination therapy (10).

Encainide and Quinidine each produced a statistically significant reduction in total premature ventricular complex frequency compared with base line values; Encainide produce a grater reduction than that of Quinidine. Suppression of ventricular tachycardia was also significantly better during Encainide therapy than Quinidine therapy (11).

The Efficiency class IB and class IC sustained ventricular tachycardia inducible during therapy with class IC anti-arrhythmic agents alone; reported in only one patient arrhythmia was no inducible during combination therapy. Remaining patients reported prolonged induction cycle (12).

Pharmacology of Encainide

It is potent class IC anti-arrhythmic agent (11), used to treat irregular heartbeats (13).

It reduces the excitability, conduction velocity and automaticity thus causing the prolongation of atrio-ventricular Node (AV Node), His-Purkinje and intra-ventricular conduction (11) (13).

It has no significant negative ionotropic effect, thus useful for patient suffering from severe left ventricular dysrhythmia (11).

It leads to slight and significant lengthening of refractory periods with the major effects on His-Purkinje (13).

Placebo controlled studies reported Encainide is effective in 70-80 % of patients with ventricular arrhythmia (11).

The effective dose appears to be between 25 and 50 mg three to four times / day (11). It reduces the rate of rise action potential without markedly affected its duration (13).

Mode of Action

Encainide is a sodium channel blocker, it binds to voltage gated sodium channel. It stabilizes the neural membrane by inhibiting the ionic fluxes required for the initiations and conductions of

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impulsers.
Ventricular Excitability is depressed and the stimulation threshold of the ventricle is increased during diastole (13).

Metabolism

Metabolism of Encainide is occurs in the liver (13), 90 % of patients are extensive metabolizers with only 30 % of oral bioavailability of Encainide due to first-pass metabolism. With half-life of 2.5 hrs. and systemic clearance about 1.8 ltr. / min.

Metabolites of EncainidesOdesmethyl-encainide (ODE) and 3-methoxy-Odesmethy-encainide (3-MODE) have higher plasma concentration than Encainide and have anti-arrhythmic activity.
Less than 10 % patients are poor metabolizers with 88 % of oral bioavailability. With 8-11 hrs. of half-life period (t1/2) and systemic clearance of about 0.2 ltr. / min.
But the concentration of ODE and 3-MODE is less observed however the concentration of N-desmethyl-encainide (NDE) is found to be similar in both groups of metabolizers (14).

Encainide exhibited a short half-life consist with its high clearance. The average half-life after IV administration ranges 2.05-6.91 hrs. After oral dosing the half-life tends to be shorter in most patients ranges about 1.573.72 hrs. (15).
The radio-labeled dose of Encainide is excreted in approximately equal amounts in the urine and feces (13).

Adverse Effects (16)

- Dizziness
- Nausea
- Postural Hypotension
- Anxiety
- Ataxia
- Encephalopathy
- Memory Impairment
- Slurred Speech
- Gastro-intestinal Toxicity
- Hyperglycemia

Contraindications (16)

Encainide should not be used for the treatment of post-myocardial infraction patients who are asymptomatic or who have only mild symptoms of premature ventricular contractions or either it should be employed only for the treatment of life-threatening arrhythmia.
Hypersensitivity to Encainide and Pre-existing second- or third-degree AV block.
Precautions for its use include congestive heart failure, electrolyte abnormality, hepatic disease (16).

II. CONCLUSION

We conclude that if therapy with mexiletine is carefully evaluated and individualized, the drug is effective and well tolerated during long-term use and Amiodarone, a unique antiarrhythmic agent with many pharmacologic actions, is effective in the treatment of a wide range of rhythm abnormalities.

Encainide is not indicated in patients with symptomatic ventricular arrhythmias and structural heart disease. In patients without structural heart disease and symptomatic ventricular arrhythmias, the benefit and risks of encainide therapy should be carefully considered before it is prescribed.

REFERENCES

[1]. ChemSrc. (2020, 01 31). Encainide hydrochloride. Retrieved 01 28, 2022, from https://www.chemsrc.com/en/cas/66794-74-9_831856.html
[2]. DRUGBANK. (n.d.). Encainide. Retrieved 01 28, 2022, from https://go.drugbank.com/drugs/DB01228
[3]. Frederique Chezalviel-Guilbert, P.-M. D.-M. (1995, september). Mexiletine Antagonist Effects of sotalol on OT
[4]. Interval Duration and it's Proarrhythmic Effects in a canine MOdel of torsade de pointes. 26, 787-792.
[5]. JAILLON., P. (1990). Pharmacokinetics and Metabolism of Encainide.
[6]. JOEL MORGANROTH, M. F.-H. (1986, 01). Comparative Study of Encainide and Quinidine in the Treatment of Ventricular Arrhythmias. 07.
[7]. Lisa Mendes, M. P. (1991, May). Roll of Combination Drug Therapy with a Class IC Antiarrhythmic Agent and Mexiletine for Ventricular Tachycardia, 17, 1396-1402.
[8]. ROGER A. WINKLE, M. F. (1981, 08). Clinical Pharmacology and Antiarrhythmic Efficacy of Encainide in Patients With Chronic Ventricular Arrhythmias. 64, 290-296.
[9]. Ross DL. Sze DY, K. D. (1982).

Antiarrhythmic drug combinations in the treatment of ventricular tachycardia: efficacy and electrophysiologic effects. 66, 1205-1210.

[10]. RxList. (2017). rxlist.com. Retrieved January 28, 2022, from https://www.rxlist.com/mexitil-drug.htm

[11]. ScienceDirect. (n.d.). Encainide. Retrieved 01 28, 2022, from https://www.sciencedirect.com/topics/chemistry/encainide

[12]. ShabnamMadadi, M. N. (2019). Clinical Results of Combined Amiodarone and Mexiletine Therapy in Refractory Ventricular Tachycardias, 8(1), 11-13.

[13]. Tripathi, K. (2013). In K. Tripathi, Essential of Medical Pharmacolgy (7 ed.). Jaypee Brothers Medical Publishers (P) Ltd.

[14]. WebMD. (n.d.). Retrieved January 28, 2022, from webmd.com: https://www.webmd.com/drugs/2/drug4500/mexiletine-oral/details

[15]. WebMD. (n.d.). Retrieved January 2022, from webmd.com: https://www.webmd.com/drugs/2/drug4521/amiodarone-oral/details

[16]. Wharton 1M, P. D. (1989). Combined therapy with IC and IB agents: Is it effective for ventricular tachycardia. 13, 141A.

[17]. Wikipedia. (2020). Mexiletine. Retrieved January 28, 2022, from Wikipedia: https://en.m.wikipedia.org/wiki/Mexiletine