Arrhythmia is a general term that refers to an abnormality or irregularity in the heart rhythm. An arrhythmia occurs when there is a disturbance in the conduction system of the heart, which may be due to faulty production of electrical impulses as they pass through the system [1]. Antiarrhythmic drugs are medicine that correct irregular heartbeats and slow down hearts that beats too fast. In modern society these drugs are becoming increasingly important and routine drugs due to increased heart disorders, which are related to increased stress in work place and our modern life style in general. Ions play a vital role in a large number of cellular processes including excitation-contraction and stimulus-secretion [2]. The regulation of the intracellular concentration of these ions makes possible the control of such ion-dependent processes.

1.1 Types of Antiarrhythmic Drugs:
The standard classification of Antiarrhythmic drugs has been developed based on their actions [3]. Example from each class are shown in Fig. 1 and discussed below:

Class I drugs, those act by blocking the sodium channel, are subdivided into 3 subgroups: I A, I B and I C; based on phase-o depolarization and repolarization effects.

- Subclass IA drugs have moderate potency of blocking the sodium channel and also usually prolong repolarization (increase QRS), e.g. Quinidine, Procainamide etc.

- Subclass I B drugs have the lowest potency as sodium channel blockers, produce little if any change in action potential duration, and usually shorten repolarization, e.g. Lidocaine, Phenytoin, tocainide etc.

- Subclass I C drugs are the most potent sodium channel blocking agents and have little effect on repolarization (increasing PR, increasing QRS) e.g. flecainide.

- Marcizine is a class I drug, but has been variously categorized as I A, I B or in its own group.
Quinidine (Class I)

Propranolol (Class II)

Bretylium (Class III)

Nifedipine (Class IV)

Fig. 1 Antiarrhythmic Drugs
Class II drugs act indirectly on electrophysiological parameters by blocking beta-adrenergic receptors (increasing PR), e.g., propranolol etc.

Class III drugs act by mechanism that are not well understood (interference with potassium conductance is one possible mechanism), but act to prolong repolarization (increase refractoriness), with little effect on the rate of depolarization (QT), e.g., Bretylium, Amiodarone, Sotalol etc.

Class IV drugs are relatively selective AV nodal calcium-channel blockers, primarily L-type channels (increasing PR), e.g., Nifedipine, Diltiazem and Verapamil etc.

Class I and Class IV drugs have been the most widely studied and act by blocking Voltage-gated $\text{Na}^+$/Ca$^{2+}$ channels [4].

The importance of these drugs is not only due to their antiarrhythmic action but also due to their usage for safe and effective treatment of hypertension [5]. This has led to extensive research on Ca$^{2+}$ channel blockers [6].

In this study we shall be dealing with class IV antiarrhythmic drugs, which are selective Ca$^{2+}$ channel blockers (c.f. 2).
Fig. 2 Ca^{2+} Channel Blockers
Ca$^{2+}$ is generally present at a concentration of a few mM in the extracellular space, but inside the cell, the cytoplasmic concentration is about 0.1µM, kept low by a number of different pumps and buffering systems, as well as the general impermeability of the plasma membrane to the entry of Ca$^{2+}$ [7].

1.2 Types of Channels:

Ca$^{2+}$ channels are of two types:

a) Voltage dependent calcium channels (VDCCs)

b) Frequency dependent calcium channel

a) Voltage Dependent Calcium Channels:

Voltage dependent calcium channels are heterogenous in structure and regulation. These are transmembrane proteins, which upon membrane depolarization allow selective Ca$^{2+}$ permeation mediating muscle contraction, hormone secretion etc. important cellular processes.

These channels have been classified pharmacologically and biophysically. The channels are designated L-, T-, N-, P-, Q- and R-type. Each channel has different voltage ranges and rates for
inactivation [8]. Low voltage activated (LVA) T-type currents are distinguished from high voltage-activated (HVA) L-, N-, P-, Q- and R- type current based on the relatively hyperpolarized potential at which they are activated [9].

L-type Ca\(^{2+}\) channels (LCC’s) (shown in Fig. 3) are sensitive to numerous agonist and antagonist drugs that modulate Ca\(^{2+}\) flow. The exact mode of action of these drugs is not clear. Three major classes of compounds have been identified as LCC agonists and antagonists, i.e. LCC activators and blockers [10]. These are Phenylalkylamines, Benzothiazepines and Dihydropyridines. All three classes have been widely used as antiarrhythmic drugs for the treatment of cardiovascular disorders [11]. Dihydropyridines however include both activators and blockers of the channel [12]. Phenylalkylamines and Benzothiazepines exist in the protonated form at physiological pH and block the channel by obstructing the pore of the channel.

Voltage-gated Ca\(^{2+}\), Na\(^{+}\) and K\(^{+}\) channels share a similar topology [13]. Therefore some Ca\(^{2+}\) channel blockers may also act as Na\(^{+}\)/K\(^{+}\) channel blockers.
b) Frequency Dependent Ca$^{2+}$ Channel (use-dependent blockade):

The enhancement of sodium or calcium or calcium channel block seen in rapidly depolarizing tissue has been termed as "use-dependent blockade" and is thought to be responsible for the efficacy of these drugs in slowing and converting tachycardias with minimal effects on conduction in normal tissues stimulating at normal physiological rates.

This use-dependent blockade has been explained by a proposed theory termed as "modulated receptor theory (MRT)" [14]. The theory is based on a three state model for the calcium channel originally proposed by Hodgkin and Huxley [15].

The three normal channel states are: Resting, Open (or activated), and Inactive (Fig. 4): Under normal resting conditions, the calcium channels are predominantly in the resting state and are nonconducting. When the membrane is depolarized the calcium channels open and conduct calcium resulting in the inward calcium current that makes the major contribution to phase-0 of the action.
Fig. 3 L-type Ca\(^{2+}\) ion Channel

Fig. 4 Three States of the Channel
potential. The inward calcium current rapidly decays as channel moves to the inactive state. The return of inactive channel to the resting state is termed ‘reactivation’ and it is voltage and time dependent.

The theory assumes that channel blocker drugs bind different channel states with different affinities and that drug binding alters the transition rates between different states.

Use-dependent blockade is also known as frequency dependent calcium channel, because in this type of blockade frequency of depolarization is increased.

We have selected L-type calcium channel for the study of affinity of drug to receptor, because this is abundantly found in cardiac muscle, and hence it can explain the selective effects on the cardiovascular system.

1.2.1 Bioactive Conformational Aspects of Calcium Channel Blockers:

Conformational preference of 1,4 dihydropyridines and its derivatives have been widely studied utilizing a combination of NMR
studies, X-ray crystallographic and theoretical techniques [16]. Theoretical studies have mostly been of semiempirical type. There have been lots of studies on the bioactive conformation of dihydropyridines [17]. Dihydropyridines have been the main focus of conformational studies. Benzothiazepines and Phenylalkylamines have been relatively less studied [13,18].

1.2.2 Effect of Substituents:

Effect of different ester substituents at the 3,5 position of the pyridyl ring and effect of substitution at o-, m-, and p- position on the phenyl ring has been studied in 1,4 dihydropyrines. Bulky alkoxy substituents on phenyl ring are better blocking agents. Activity is independent of their electronic character. It only depends on their size [17,19]. Experimental binding energies have been studied for various substituents at 3,5 positions [20].

1.2.3 Receptor Aspects:

Earlier it was believed that all class IV antiarrhythmic drugs bind to the same receptor on the Ca$^{2+}$ channel. Now experimental
studies have proved that these drugs bind to 3 different allosterically related sites on the Ca$^{2+}$ channel [21]. Experiments have helped in identifying the important drug sensing residues in the Ca$^{2+}$ channel [22-29]

1.2.4 Receptor Models:

Some receptor models for voltage gated calcium channels have recently been proposed based on available information about dihydropyridine sensing residues in the channel and also based on Monte Carlo minimizations towards lowest ligand-receptor energy conformation [30].

1.3 Aim of this Study:

In this study we will work on selected calcium channel blockers from the three major categories: Phenylalkylamines, Benzothiazepines and Dihydropyridines. Energy minimized conformations will be studied. If bioactive conformation has not been conformed via receptor bound X-ray data then conformational surface will be thoroughly scanned. Complete MESP maps will be studied for
the charge environment of the drugs. Receptor models will be studied based on available information. Unprotonated/Protonated drug-receptor interactions will be studied. The ability of drugs to bind Ca$^{2+}$ ion and the ability of receptor to bind Ca$^{2+}$ ion will be studied separately. These studies will highlight the mode of action of these drugs. These studies may also throw some light on use-dependent blockade of Ca$^{2+}$ channel.
References:


   b) S. Nattel, Drugs 41, 672, 1991.


    


    


