A Critical Account of the Pharmacological Agents used to treat Cardiac Dysrhythmias

By
SHAHID RASHID*

INTRODUCTION

The condition of dysrhythmia may be defined as an irregular cardiac rhythm or a heart rate faster or slower than physiological (22). This disturbed rhythm can be caused by an abnormality in the rate, regularity or site of origin or the conduction of the impulse such that the normal physiological sequence of activation of the atria and ventricles is disturbed (7). Most of the cases of sudden early deaths arising from cardiac infarction are due to onset of dysrhythmias.

Rational therapy is based on the recognition of the pathomechanism of the disease. The successful treatment of dysrhthmias also requires a knowledge of the origin of the process involved. Various factors and mechanisms for the genesis of cardiac dysrhythmias have been proposed (7, 16, 17, 22), but no unanimous approach to this problem has so far been developed because none of the existing theories fully explain the phenomenon associated with dysrhythmias and fibrillation and perhaps that is why no particular drug is capable of reverting all the dysrhythmias.

Thus the urgent need for further research into antidysrhythmic drugs and their mode of action is obviously great. But so far a rational basis upon which a systematic investigation into the mode of action of these drugs can be established is confused and there is not even an agreement on the classification of these drugs for example the classifications of Vaughan Williams (48) and, Bassett and Hoffman (1) differ widely.

The other, perhaps the main difficulty, in developing of new drugs is the lack of reliable animal model for the production of dysrhythmia which clearly resembles the clinical situation (49). Due to the lack of reliable animal model for testing potential antidysrhythmic drugs, attempts have been made to study in detail the electrophysiological phenomena involved in the genesis of dysrhythmias (27) and the effects of known antidysrhythmic drugs on these phenomena (1, 14, 18, 19, 24, 28, 29, 30, 42, 48, 49, 50, 52) in the hope of finding some accurately measurable common actions.

The objectives of using electrophysiological phenomena as the basis of antidysrhythmic drug are two fold; (1) a screen for new drugs could be designed because a new compound may possess similar electrophysiological properties to existing antidysrhythmic drug then a tentative assumption could be made that the noval compound was likely to be an antidysrhythmic agent (2) a detailed study of the mode of action of drugs which could control dysrhythmia may be helpful in revealing the fundamental mechanism and cellular basis of dysrhythmias. At this stage a description of electrophysiology of cardiac muscle will be appropriate.

*Chairman, Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi-32, PAKISTAN.

This work was done at Wyeth Institute of Medical Research, Taplow, Nr. Maidenbread Berks.

(ii) Electrophysiology of Myocardial Cell

The basis for the knowledge of electrophysiology has been provided by a variety of techniques, but the use of intracellular microelectrodes has facilitated the study of the transmembrane electrical activity of the single cardiac fibre (45) and has provided much of the recent information on the mechanisms responsible for cardiac dysrhythmia (27).

(*a*) *Cardiac resting membrane potential*:-when the tip of glass microelectrode is advanced into a cardiac cell the potential difference (PD) between intracellular and extracellular space can be recorded. The intracellular space is 80-90 mV negative with respect to the extracellular space in most of the cardiac fibres. This transmembrane potential during a period of electrical quiescence is referred to as the resting membrane potential (RMP) (Fig. 1). This PD between extra and intracellular spaces is due to the uneven distribution of ions between these spaces. Within the cell a high K+ and low Na+ concentration is present while in the extracellular space the concentration of K+is low and of Na+ is high.

(*b*) *Cardiac Action Potential* (AP):-At rest the membrane is permeable mainly to K+. When a stimulus originates either from external source (chemical, electrical) or from internal (natural) source it increases the Na+permeability markedly and a rapid inward flux of Na+ ions (Na+ current) commences and causes the reduction in RMP and a critical point, that is the threshold level of depolarization on AP is generated (—60mV). The rapid depolarization of the membrane or upstroke due to the fast Na+ current is referred to as phase O, the intensity of which as measured by the maximal rate of depolarization (MRD), or maximum dv/dt of the upstroke (Vmax). This phase (Phase 0) is followed by three phases of replolarization, phase I downward slope of the initial spike (relatively rapid phase of repolarization). Phase 2 a plateau and phase 3 a subsequent return to RMP. The period between A.P. is referred to as phase 4 (Fig. 1).

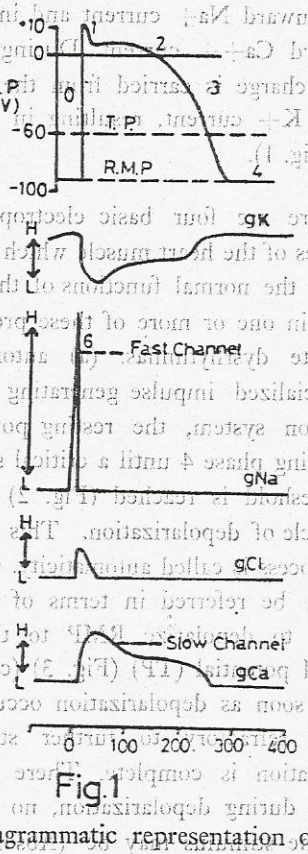

Fig.1

Fig. 1:-Diagrammatic representation of transmembrane action potential (AP) from Purkinje Fibre. The Phases of AP cycle are, 0, 1, 2, 3, and 4. The changes in ionic conductance during AP cycle in Purkinje fibre are also shown.

Abbreviations: H—High L—Low
M.P.—Membrane Potential
R.M.P.—Resting membrane potential
T.P.—Threshold potential

Ionic exchange between membranes takes place during repolarization process. Phase I repolarization as been attributed to an inward current carried by chloride ion. During the plateau two ionic currents maintain a fairly steady membrane potential. These are the decreasing inward Na+ current and in some cells an inward Ca++ current. During phase 3 a positive charge is carried from the cell by an outward K+ current, resulting in a return to RMP (Fig. 1).

There are four basic electrophysiological properties of the heart muscle which are responsible for the normal functions of the heart and changes in one or more of these properties can precipitate dysrhythmias. (a) automaticity:-In the specialized impulse generating cells of the conduction system, the resting potential (RP) rises during phase 4 until a critical spike genration threshold is reached (Fig. 2) inducing a fresh cycle of depolarization. This spontaneous firing process is called automaticity. (b) excitability:-may be referred in terms of the current required to depolarize RMP to the level of threshold potential (TP) (Fig. 3) (c) refractoriness:-as soon as depolarization occurs, the cell becomes refractory to further stimuli until repolarization is complete. There will be no response during depolarization, no matter how strong the stimulus may be (Absolute Refractory Period, A.R.P.). Depolarization may be initiated at —55 to —60 mV (Relative Refractory Period, R.R.P.), if the stimulus is stronger than normal. The earliest time interval after the onset of a previous action potential when a propagated response will develop to a physiological stimulus is termed as Effective Refractory Period, (E.R.P.). This E.R.P. is of considerable importance (Fig. 4).

(d) Conductivity:-Conductivity is an electrical property of excitable tissue wich ensures that if one area of a membrane is excited, then the excitatory wave should propagate to excite adjacent area. There are three variations which have profound effect on the conductivity (a) the amplitude of the A.P. (b) the maximum rate of of changes of the depolarization (Max dv/dt) of the AP and (c) the level of RMP at the time of AP initiation (35).

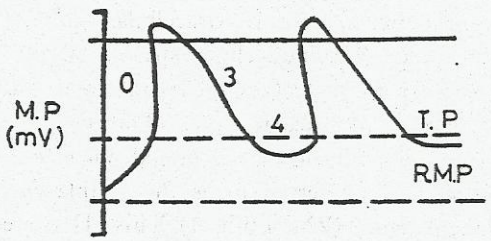

Fig 2

Fig. 2:-Automaticity:-Diagrammatic representation of transmembrane action potential from automatic fibre, showing spontaneous diastolic membrane depolarization during phase 4, reaching to the level of threshold potential.

There is another important electrophysiological parameter of cardiac membrane i.e. membrane responsiveness (MR) which could be defined as the relationship of the Vmax of an A.P. to the level of membrane potential at which the A-P is initiated (51) (Fig. 5).

(iii) Dysrhythmogenesis

After explaining the major electrophysiological parameters of the cardiac cell, it is important to discuss the factors which are responsible for

the genesis of dysrhythmias. Although the pathophysiological mechanisms responsible for this phenomena are not completely understood (24) it is generally agreed (16, 17) that there are three primary factors involved in the initiation of dysrhythmias, these are (1) disorders of impulse formation (altered automaticity) (2) disorders of impulse conduction (decreased conductivity) and (3) temporal dispersion of the refractory period, often a combination of two or more of these mechanisms is involved in the genesis of dysrhythmia.

Altered automaticity refers either to the accelerating of the firing rate of the sinus node or enhanced or depressed firing of latent pacemaker activity in specialized conductive tissue. It is assumed that production of such ectopic impulses involves a defect of the normal mechanism of automatic function, that is spontaneous phase 4 diastolic depolarization (Fig. 2a).

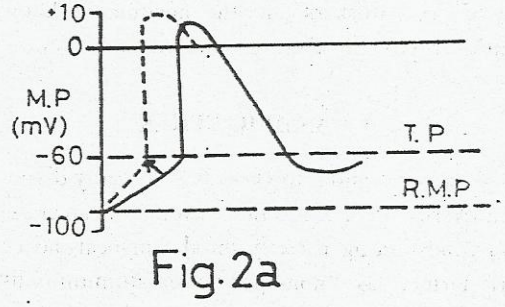

Fig. 2a

[*Fig.* 2*a*:-is showing diagrammatically that auto maticity is increased by increasing the slope of the diastolic depolarization (↑) in abnormal condition. (Antidysrhythmic drugs can control this abnormal process by slowing automaticity (1) by decreasing the slope of diastolic depolarization (2) by raising threshold level at which depolarization occurs (Krikler, 1974).]

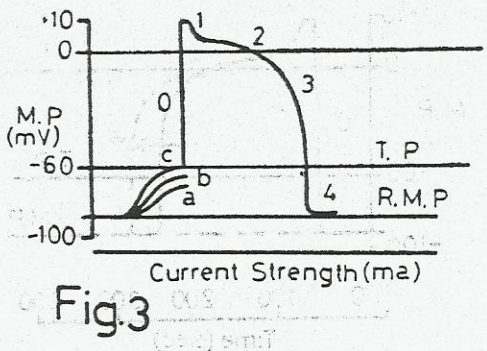

Fig.3

Fig. 3:-Diagrammatic representation of excitability, a, b represent depolarizing pulses of sufficient strength to displace membrane potential (MP) but not strong enough (like impulse C) to displace MP to threshold potential. Impulse C as a result propagates action potential.

Increased automaticity with increased phase 4 depolarization is the underlying mechanism which has been observed with hypokalemia (43) and endogenous and exogenous catecholamine stimulation (8). It is most desirable that the disorders of impulse formation are best treated with drugs that have the ability to suppress spontaneous phase 4 diastolic depolarization.

Disturbance in conduction may be categorized into two forms (17); (i) gradually decreasing conduction and (ii) the presence of block to conduction in a given direction (unidirectional block). Decremental conduction could be defined as a process due to changes in the properties of the cardiac muscle fibre, as a result of which the A.P. spreading lengthwise, becomes gradually less able to activate still unstimulated part of the fibre. The process may continue until the conductivity ceases completely (Fig. 6).

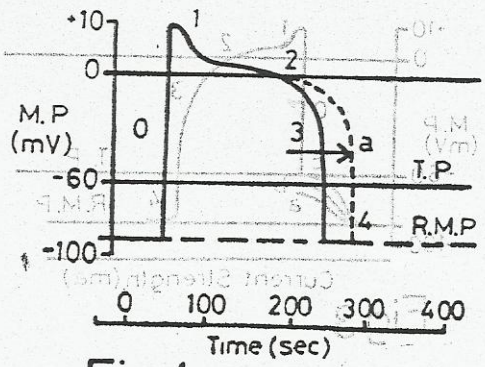

Fig 4

Fig. 4:-Diagrammatic representation of the lengthening (a) of the refractory period.

Although any cardiac muscle fibre may show decremental impulse conduction, but it is significant if it appears in specialised conduction tissues such as sino-atrial node, atrioventricular node and the His-purkinje system. This decremental conduction may cause a functional block in any part of the impulse conducting system. The block may be unidirectional e.g. the conduction may be arrested at the junction of the purkinje fibre and the working muscle, yet retrograde propagation from this point may be possible, which could cause re-entry, re-excitation and self sustaining dysrhythmia.

Another factor which could disturb the co-ordinated function of the heart is refractory period .For co-ordinated function of the heart relatively long refractory period is needed which is the result of long A.P. and any alteration in refractory period will produce dysrhythmia. Conduction velocity and duration of refractory period are the electrophysiological properties most critical in dysrhythmias of the re-entrant type and pharmacological intervention is based upon alteration of these two properties. Although three separate initiating mechanisms in the genesis of dysrhythmia have been identified, a complex functional interrelationship does exist.

It is evident from the foregoing discussion that in the presence of cardiac disorders, certain electrophysiologial properties of cardiac tissue may be altered with potential dysrhythmic effects. From electrophysiological consideration the actions of commonly used dysrhythmic drugs may be separated into various groups (1, 18, 24, 42, 48). Overlap in secondary pharmacological properties between groups is possible.

From the clinical point of view it appears helpful to construct a pharmacological classification of the drugs on the basis of major electrophysiological determinants of antidysrhythmic actions (41). In the following attempts will be made to appraise the classification put forward by various workers and the position of known antidysrhythamic drugs in the classification.

CLASSIFICATION

Szekeres and Papp (44) have broadly divided antidysrhythmic drugs into two major categories; (1) drugs acting directly on the myocardial cell are termed as "non-specific or quinidine like agents" (interesting enough, same compound may belong to both groups), (2) compounds which exert their antidysrhythmic action specifically via adrenergic or cholinergic influence and are designated as "specific antidysrhythmic compounds".

The effect of non-specific agents can be best understood on the basis of their action

on the electrophysiological parameters of myocardial cells. From microelectrode studies a substantial amount of electrophysiological data has been accumulated on the effects of well known antidysrhythmic drugs, such as quinidine, procainamide, propranolol, diphenylhydantoin (D.P.H.) and lidocaine and this data provided the basis for the classification of these agents.

Bassett and Hoffman (1) divided these drugs into two groups (Table 1). Quinidine and procainamide decrease membrane responsiveness (MR), increase action potential duration (APD) and ERP while lidocaine and DPH may increase responsiveness and decrease APD and ERP. Hence first two drugs constitute group I and last two drugs make group II.

Propranolol decreases MR, APD and ERP. All these drugs decrease automaticity (slow the rate of depolarization in purkinje fibre (PF).

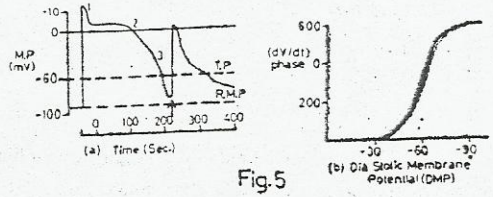

Fig. 5

Fig. 5 :-Membrane responsiveness is the relationship between the maximum rate of rise in A.P. (dV/dt phase 0) and the level of diastolic membrane potential (D.M.P.) at the time of excitation. (1) shows that if a stimulus (↑) activates the fibre during phase 3, the upstroke of this premature action is slow. (b) showing the relationship between dV/dt phase 0 and D.M.P. which is in the shape of sigmoid curve.

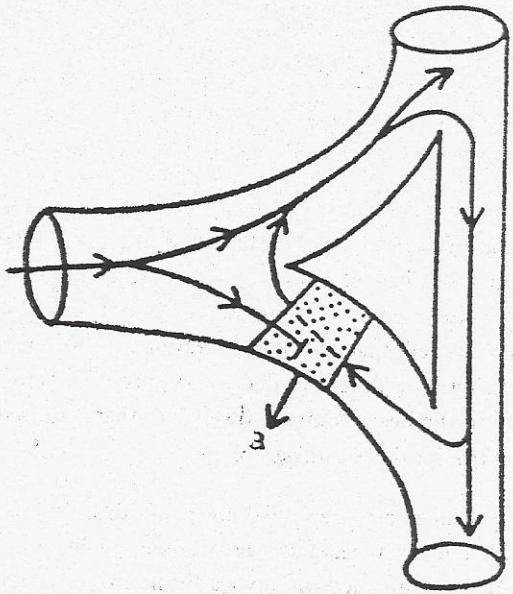

Fig. 6

Fig. 6.-Diagrammatic representation of unidirectional block produced in an area (a) due to decremental conduction.

Vaughan Williams (48) classified such drugs (quinidine, procainamide) in Class I due to their direct membrane action and showed that MRD had been reduced by these drugs while APD and ERP have been increased. The classification of quinidine and procainamide seems to be agreeable with the clasification of Bassett and Hoffman (1), Mason et al. (24) and Singh and Hauswirth (42), but, differ in the case of lidocaine and DPH.

Recently Vaughan Williams (49) argued the inclusion of DPH and lidocaine in Class I (Table 2) while these compounds were classified in group II by Bassett and Hoffman (1) and

Mason et al. (24). Singh and Hauswirth (42) took a cautious view and classed them in subclass B of Class I. In the following discussion the nature of the controversy which exists in these two schools of thought will be discussed.

As it has been discussed that quinidine and procainamide reduce MRD and increase APD and ERP, it is also shown that these compounds are local anaesthetics on nerve, but it must be emphasized that the concentration of the antidysrhythmic drugs needed to suppress excitability in the heart is much lower than that required for the local anaesthesia of nerve.

Lidocaine is a well known antidysrhythmic and a local anaesthetic agent, one might think that it would act on myocardium in the same way as other local anaesthetics (procaine, procainamide and quinidine). But Davis and Temte (4) and Bigger and Mandel (2) suggested that the antidyrhythmic actions of lidocaine and DPH are fundamentally different, although these authors agreed that both drugs do depress MRD like quinidine, but higher concentrations were required.

Bigger, Bassett and Hoffman (4) ,for example, reported that DPH up to 13.8 ug/ml concentration (thereapeutic 5 to 25 ug/ml) neither decreased MR and conduction velocity (CV) nor elevated the electrical threshold of excitability. However, Sano, Suzuki, Sato and Iidas (32) found that DPH in concentrations between 1-10 ug/ml had actions on the cardiac muscle not dissimilar to those of quinidine, producing a marked reduction in CV and in MRD in ventricular muscle.

Table 1. Classification of antidysrhythmic drugs based on their action on electrophysiological parameters of purkinje fibre. From Bassett and Hoffman (1971).

Electrophysiological Properties (purkinje fibre)	*GROUP I*		*GROUP II*	*Comments*
	Quinidine, P.A.	*Propranolol*	*D.P.H. Lidocaine*	
Automaticity	↓	↓	↓	*Contradictory to further findings
Membrane Responsiveness	↓	↓	→OR ↑ +	of Sano et al., 1968 in the case of
Conduction velocity	↓	↓	→OR ↑ +	DPH.
E.R.P.	↑	↓	↓	+contradictory to the finding of
A.P.D.	↑	↓	↓	Singh and Vaughan Williams
ERP relative to APD	↑	↑	↑	1971.
Excitability	↓	↓	→*	

A.P.D. Action Potential Duration
D.P.H. Diphenylhydantoin
E.R.P. Effective Refractory Period
P.A. Procainamide.

Singh and Vaughan Williams (38) confirmed the findings of Bigger and his colleagues (4) after repeating these experiments with low K+ perfusate and mentioned that at abnormally low K+concentrations (3.0 mM) higher concentrations of the drugs are needed to depress MRD (as was the case with the experimentation of Bigger and his colleagues) but pointed out that at a normal K+ concentration (5.6 mM) in perfusate, however both lidocaine and DPH depress MRD at concentrations well within the therapeutical range.

Singh and Vaughan Williams (38) concluded therefore that lidocaine and DPH are probably antidysrhythmic because they depress MRD in common with other local anaesthetic drugs, and so these drugs are classified with Class I by Vaughan Williams (49).

Other agents which may be included in Class I are mexilitine and disopyramide. Mexilitine is an orally active agent with local anaesthetic properties equal to lignocaine (39). Electrophysiological investigations showed that mexilitine reduced MRD, CV and depressed contractions. It did not effect RMP (like quinidine) or APD (Singh and Vaughan Williams (39).

The mode of action and electrophysiological effects of disopyramide appear to be very similar to those of quinidine, such as, causing little change in RMP or APD, but reducing the overshoot potential and slowing the rate of rise of action potential (34).

The overall findings in this groups with different level of external K+, though resolved some of the reported discrepancies, but also brought into a sharp focus the importance of the levels of extracellular K+ concentration in determining the mode of action of major class of antidysrhythmic drugs.

Among the group of drugs which exert their antidysrhythmic effect specifically via adrenergic or cholinergic influence (44) sympatholytic drugs would naturally be expected to reduce the incidence of these dysrhythmias which are associated with sympathetic activity. These sympatholytic drugs such as B-adrenoceptor blocking agents like propranolol or those which interfere with the release of sympathetic transmitters such as bretylium and guanethedine would be more effective in dysrhythmias associated with sympathetic hyperactivity.

Table 2. Recent Classification of antidysrhythmic drugs. From Krikler (1974), Singh and Hauswirth, (1974), and Vaughan Williams (1970, 1974).

Classes	*I*	*II*	*II*	*IV*	*Comments*
Main antidysrhythmic actions	Slowing of rate of rise of depolarization	Antisympathetic	Prolongation of action potential	Calcium Antagonism	
Antidysrhythmic angents.	Quinidine Procainamide Lignocaine Phenytoin Mexiletine Disopyramide (B blockers)*	B blockers* Bretylium Guanethidine	Amiodarone (Sotalol) (INPEA) (Quinidine) (Procainamide) (Disopyramide)	Verapamil Prenylamine+	*Proportionate action varies with different agent. Agents possessing more than one action are in brackets. +Quoted from Krikler, 1974.

All these agents can be put togther in one group as antisympathetic (Class II) by virtue of their action on sympathetic system. But on careful examination, some of the compounds have more than one mode of action in reversing the dysrhythmias.

It has been reported that pronethalol, propranolol and several other B-receptor blocking agents were powerful local anaesthetics, more potent than procaine (46) and reduced the rate of rise of action potential like other antidysrhythmic drugs with local anaesthetic properties (49). This property of these drugs may help to classifiy them in Class I as it has been shown by Morales-Aguilera and Vaughan Williams (25).

The B-adrenergic receptor blocking and direct membrane effects of propranolol can be related to its stereoisomeric forms, d-propranolol has little B-blocking action when compared with l- propranolol and is less effective against catecholamine induced dysrhythmias . (24) while l-propranolol with greater B-blocking property was much more effective in protecting against ouabain-induced dysrhythmia than dextro compound (10).

These observations with propranolol make this compound to be classified in both Classes I and II. But it depends on the drug concentrations attained in plasma. In very low drug concentrations in plasma competitive antagonism of B-receptors can be demonstrated. The sole electrophysiological effect in these blocking concentrations is the reduction in the slope of pacemaker potential. Much higher concentration of B-blockers produce local anaesthesia and the characteristic memberane depressant effect on heart muscle (42).

The other sympatholytic drugs like bretylium, when studied for its electrophysiological properties showed that it has not class I activity (26). These findings of Papp and Vaughan Williams have been substantiated by Bigger and Jaffe (3). But on other the hand it has been reported that bretylium increases APD and functional refractory period, (24), though the increase in APD was not accompanied with significant changes in MRD, MR or CV. Thus it seems likely that bretylium may be placed in Class II due to its antiadrenergic properties.

The above mentioned drugs follow the criteria of the classification based on the electrophysiological studies in one way or another, but recent studies show that some other active antidysrhythmic drugs failed to show such electrophysiological properties on the basis of which they could be classified in either Class I or Class II. These drugs are Amiodarone and Verapamil.

Amiodarone is an antianginal agent which causes coronary dilatation and decreases myocardial O2 consumption (6). It has no local anaesthetic activity and thas no effect on RMP or action potential amplitude (APA). Only small effect was detected on RMD on isolated rabbit atrial and ventricular muscle fibre when given I.P. for six weeks (36). It has no B-blocking properties.

During the course of studies it was found that amiodarone prolonged the action potential duration (APD) in isolated rabbit atrial and ventricular preparations, when given daily I.P. for three weeks (36). It shows that this drug interferes with repolarization to much greater extent than its effects on depolarization, where

as quinidine, procainamide and other antidysrhythmic drugs produce the reverse. It was also demonstrated that the same alterations in cardiac potentials caused by amoidarone could be demonstrated in rabbit after thyroidectomy (12).

In summing up, amiodarone does not show the electrophysiological features which could justify its inclusion either in Class I or Class II. On the other hand, its antidysrhythmic properties have been established and can be referred to prolongation of APD by the drug. Question arises whether to give it a separate class or to leave it afloat. Perhaps a new class for this kind of property (prolongation of the APD) will be more suitable for the inclusion of the other potential antidysrhythmic drugs possessing this quality and a clinican can see the exact mode of action of these drugs. Vaughan Williams (48, 49, 50) provided Class III for this kind of electrophysiological action as shown by amiodarone. As it has been discussed earlier, bretylium also increass APD in ventricles and may be grouped with amiodarone (22). It is very interesting to know that two of the B-adrenoceptor blocking drugs MJ 1999 (Sotalol) and INPEA also had this III class antidysrhythmic action in prolonging the duration of the action potential (37).

Another drug which falls out from the above mentioned classification is verapamil. Verapamil is a coronary dilator drug and has been shown in experimental studies (20, 33) as well as in clinical studies (23) to be a very potent antidysrhythmic drug.

Garvey (13) proposed that the mode of action of verapamil seems likely to be that of quinidine, but Singh and Vaughan Williams (40) demonstrated that in electrophysiological studies MRD was hardly effected by verapamil except at higher concentrations, though it is 1.6 times more potent than procaine. Verapamil does not effect the relative and effective refractory periods (30), nor APD even at higher concentrations (40). B-adrenoceptor blocking activity of verapamil has not been detected (15, 20, 31).

The observations that verapamil markedly depresses contractility of ventricular muscle fibre without altering the transmembrane AP suggested that this drug interferes with Ca++ mobilization (11). Earlier Vaughan Williams (46) suggested that there might be an inward slow current carried by ions other than Na+ in addition to the fast current which is responsible for depolarization.

Voltage clamp studies on cat's ventricular trabeculae using verapamil showed that verapamil caused a complete disappearance of the later slow inward current which may be carried by Ca++ with minor suppression of rapid Na+ current (21). Singh and Vaughan Williams (40) suggested that verapamil interferes with Ca++ conductance with the implications that Ca++ currents may contribute to abnormal impulse formation.

In the absence of a definite action of verapamil on electrophysiological parameters of myocardial fibres, as already has been discussed, it seems unrealistic to group verapamil into any class, but again it is desirable to classify this drug and other drugs such as prenylamine (22) separately due to its unique mode of action unrelated to other antidysrhythmic drugs.

CONCLUSIONS

Many workers beleive that if the precise mechanisms of dysrhythmia were known, it

would be easier to select a therapeutic agent with the specific effect necessary to correct the abnormality. Unfortunately, the basic knowledge of precise mechanism involved in the genesis of dysrhythmia is still lacking in most of the cases and therefore unanimity of opinion has yet to be reahed regarding the pathomechanism of dysrhythmias.

Recent electrophysiological studies with the help of microelectrode technique have proved very helpful in elucidating the pathomechanism of dysrhythmias and on the other hand helped to classify the antidysrhythmic drugs into groups which do or do not have certain clearly definable pharmacological actions.

A rational framework for interpreting the mode of action of the conventional as well as the newer antidysrhythmic agents assuming increasing importance is needed, and, perhaps the clasification of these drugs, may provide that rational basis. But nevertheless judgement of the clinicain to use an appropriate antidysrhtyhmic drug should be final.

Classification which has been discussed above is based on the effect of antidysrhythmic drugs on electrophysiological parameters of cardiac muscle fibre (these parameters assumed to be responsible for precipitating dysrhythmias) may be useful but may not be free from controversy.

Perhaps the situations of the genesis of dysrhythmias in isolated tissues and in intact animals may not be the same. In intact animals various factors, such as autonomic reflexes compensating mechanism may play a part in producing or terminating dysrhythmias, which are lacking in isolated tissues. Secondly the side effects of the drugs cannot be evaluated in isolated preparations and that is why a drug assessed by pharmacologists as the most potent of its group for desirable properties may have dangerous side effects. If the classification based on the observations which were mentioned above were accepted, the physician would still wonder whether he is any nearer in practical terms to a rational approach to the treatment of clinical abnormalities of cardiac rhythms.

These electrophysiological studies seem to provide a sufficient basis for the classification of antidyrhythmic drugs but the importance of other factors such as extracellular electrolyte concentrations cannot be ignored as it has been shown that the actions of DPH and lidocaine on electrophysiological parameters can be modified by the levels of K+ in perfusate. Singh and Hauswirth (42) have pointed out that discrepancies in the electrophysiological actions of DPH and lidocaine on heart muscle brought into focus the importance of the levels of extraceullular K+ ion concentrations, in determining the mode of action of major antidysrhythmic drugs. Therefore it could be suggested that a record be kept of electrolyte concentrations in extracellular fluid during the experiments for evaluating the properties of antidysrhythmic drugs.

Another factor which should be taken into consideration during the evaluation of these drugs, is the concentrations of the drug. As it has been reported that propranolol does not produce any change in AP at the concentration of 0.1 mg/l but at 0.3 mg/l APD and ERP in Purkinje fibre (14) are decreased.

In summary, the classification of the antidysrhythmic drugs based on their actions on the electrophysiological parameters of the myo-

cardium could provide an appropriate framework from which a process may emerge to rationalize the mode of actions of established or potential antidysrhythmic drugs, provided a cautious view may be taken of changes in the serum electrolytes concentrations, pH, interactions with serum proteins or other extracardiac factors at the time of evaluation, as these factors could modify considerably the primary actions of these drugs.

REFERENCES

1. Bassett, A.L. and Hoffman, B.F. Antiarrhythmic drugs. Electrophysiological action. Ann. Rev. Pharmac. 11:143-170, 1971.
2. Bigger, J.T. Jr. and Mandel, W.J. Effect of lidocaine on electrophysiological properties of ventricular muscle and Purkinje fibres. J. Clin. Invest. 40:63-77, 1970.
3. Bigger, J.T. Jr. and Jaffe, C.C. The effect of bretylium tosylate on the electrophysiological properties of ventricular muscle and Purkinje fibres. Am. J. Cardial 27: 82-92, 1971.
4. Bigger, J.T., Basset, A.L. and Hoffman, B.F. Electrophysiological effects of diphenylehydantoin in canine Purkinje fibres. Circulation. Res. 22:221-236, 1968.
5. Charlier, R. Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive blockade of adrenoceptors. Br. J. Pharmac. 39:668-674, 1970.
6. Charlier, R., Deltour, G., Baudine, A. and Chaillet, F. Pharmacology of amiodarone, an antianginal drug with a new biological profile. Arzneimittelforsch. 18:1408-1417, 1968.
7. Cranefield, D.P.F., Wit, A.L. and Hoffman, B.F. Genesis of cardiac arrhythmias. Circulation XLVII:190-204, 1973.
8. Daggett, W.M. and Wallace A. Vagal and sympathetic influences on ectopic impulse formation in" Mechanism and therapy of cardiac arrhythmias" Ed:—Driefus, L.S. and Likoff, W. Grune and Stratton, New York. pp 64-75, 1966.
9. Davis, L.D. and Temte, J.V. Electrophysiological actions of lidocaine on canine ventricular muscle and Purkinje fibres. Circulation Res. 24:639-655, 1969.
10. Dohadwalla, A.N. Freedberg, A.S. and Vaughan Williams, E.M. The relevance of B-receptor blockade to ouabain induced cardiac carrhythmias. Br. J. Pharmac 36:257-267, 1969.
11. Fleckenstein, A. Specific inhibitors and promoters of the excitation contraction coupling of heart muscle and their role in the prevention or production of myocardial lesions. In press. New York, 135-188, 1971. (Quoted from Rosen et al. 1975).
12. Freedberg, A.S., Papp, J.G.Y. and Vaughan Williams, E.M. The effect of altered thyroid state on atrial intracellular potentials. J. Physiol (Lond); 207:357-370, 1970.
13. Garvey, H.L. The mechanism of action of verapamil on the sinus and A-V nodes. Eur. J. Pharmac. 8:159-166, 1969.
14. Getts, L.S. The electrophysiologic effect of antiarrhythmic drugs. Am. J. Cardiol. 28:526-355, 1971.
15. Hills, E.A. Iproveratril and bronchial asthma. Br. J. Clin. Pract. 24:116-117, 1970 (Quoted from Singh and Vaughan Williams 1972).

16. Hoffman, B.F. The genesis of cardiac arrhythmias. Prog. Cardiovasc. Dis. 8:319-329, 1966.
17. Hoffman, B.F. and Cranefield, P.F. The physiologic basis of cardiac arrhythmias. Am. J. Med. 37:670-684, 1964.
18. Hoffman, B.F. and Bigger, J.T. Jr. Antiarrhythmic drugs. in: Drills' pharmacology in Medicine Ed. J.R. Di Palma. McGraw Hills New York. 824-852, 1971.
19. Hoffman, B.F., Rosen, M.R. and Wit A.L. Electrophysiology and Pharmacology of cardiac arrhythmias VII Cardiac effects of quinidine and procanimaide B. Am. Heart. J. 90:117-122, 1975.
20. Kaumann, A..J and Aramendia, P. Prevention of ventricular fibrillation induced by coronary ligation. J. Pharmac. Exp. Ther. 164:326-332, 1968.
21. Kohlhardt, M., Bauer, B., Krause, H. and Fleckenstein, A. New and selective inhibitors of transmembrance Ca Conductivity in mammalian myocardial fibres. Studies with the voltage clamp technique. Experientia 28:288-289, 1972.
22. Krikler, D.M. A fresh look at cardiac arrhythmia "Therapy". Lancet, I: 1034-1037, 1974.
23. Krikler, D.M. and Spurrell, R.A. Verapamil in the treatment of paroxymal supraventricular tachycardia. Postgrade. Med. J. 50: 447-453, 1974.
24. Mason, D.T., Demaria ,A.N., Amsterdam, E.A., Zelis, R. and Massumi, R.A. Antiarrhythmic agents I Mechanisms of action and clinical pharmacology Drugs. 5: 261-291, 1973.
25. Morales-Aguilera, R. and Vaughan Williams E.M. The effect on cardiac muscle of B-receptor antagonists in relation to their activity as local anaesthetics. Br. J. Pharmac. 24:319-331, 1965.
26. Papp, J. Gy and Vaughan Williams, E.M. The effect of bretylium on intracellular cardiac action potentials in relations to its antiarrhythmic and local anaesthetic activity. Br. J. Pharmac. 37:380-390, 1970.
27. Rosen, M.R., and Hoffman, B.F. Mechanisms of action of antiarrhythmic drugs Circulation. Res. 32:1-8, 1973.
28. Rosen, M.R., Wit, A.L. and Hoffman, B.F. Electrophysiology and pharmacology of cardiac arrhythmias I Cellular electrophysiology of the mammalian heart. Am. Heart. J. 88:380-385, 1974.
29. Rosen, M.R., Hoffman, B.F. and Wit, A.L. Electrophysiology and pharmacology of cardiac arrhythmias V Cardiac antiarrhythmic effects of lidocaine. Am. Heart J. 89:526-536, 1975.
30. Rosen, M.R., Wit A.L. and Hoffman, B.F. Electrophysiology and pharmacology cardiac arrhythmias VI Cardiac effects of Verapamil. Am. Heart J. 89:665-673, 1975.
31. Ross, G. and Jorgensen, C.R. Cardiovascular actions of iproveratrial J. Pharmac. Exp. Ther. 158:504-509 1967.
32. Sano, T., Suzuki, F. Sato, S. and Iidas. Mode of action of new antiarrhythmic drugs. Jap. Heart J. 9:161, 1968. (Quoted from Singh and Hauswirth, 1974).
33. Schmidt, J.R. and Hannah, C. A comparison of antiarrhythmic actions of two new synthetic compounds iproveratrial and M.J. 1999 with quinidine and propranolol. J. Pharmac. Exp. Ther. 156:331-338, 1967.
34. Sekiya, A. and Vaughan Williams, E.M. Comparison of the antifibrillatory actions and effects of intracellular cardiac poten-

tial of pronethalol, disopyramide and quinidine. Br. J. Pharmac. 21:473-481, 1963.

35. Singer, D.H., Lazzara, R. and Hoffman, B.F. Interrelations-ships between automaticity and conduction in Purkinje fibres. Circulation. Res. 21:537-558, 1967.
36. Singh, B.N. and Vaughan Williams, E.M. The effect of amiodarone, a new anti-anginal drug on cardiac muscle. Br. J. Pharmac. 39:657-668, 1970.
37. Singh, B.N. and Vaughan Williams, E.M. A third class of antiarrhythmic action. Effect on atrial and ventricular intracellular potentials and other phamacological actions on cardiac muscle, of MJ 1999 and AH 3474. Br. J. Pharmac. 39:675-687, 1970.
38. Singh, B.N. and Vaughan Williams, E..M Effect of altering potassium concentraction on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. Circulation Res. 29:286-295, 1971.
39. Singh, B.N. and Vaughan Williams, E.M. Investigations of the mode of action of new antidysrhythmic drug KO 1173. Br. J. Pharmac. 44:1-9-,1972.
40. Singh, B.N. and Vaughan Williams, E.M. A fourth class of antidysrhythmic action? Effect of verapamil on oubain toxicity on atrial and ventricular intracellular potentials, and on other features of cardiac function. Cardiovasc. Res. 6:109-119, 1972.
41. Singh, B.N. and Norris, R.M. The clinicians' approach to antiarrhythmic therapy. Drugs, 4:257-260, 1973.
42. Singh, B.N. and Hauswirth, O. Comparative mechanisms of action of antiarrhythmic drugs. Am. Heart. J. 87:367-382, 1974.
43. Surawicz, B. Role of electrolytes in etiology and management of cardiac arrhythmias. Prog. cardiovas. Dis. 8:364-386, 1966.
44. Szekeres, L. Papp, J. Gy. Antiarrhythmic drugs: Prog. Drug Res. 12:292-369, 1968.
45. Trautwein, W. Generation and conduction of impulses in the heart as effected by drugs. Pharmac. Rev. 15:277-332, 1963.
46. Vaughan Williams, E.M. The mode of action of quinidine on isolated rabbit atria interpreted from intracellular records. Br. J. Pharmac. 13:276-287, 1958.
47. Vaughan Williams, E.M. Mode of action of Beta receptor antagonists on cardiac muscle. Am. J. Cardiol. 18:444-449, 1966.
48. Vaughan Williams, E.M. Classification of antiarrhythmic drugs in symposium on "cardiac arrhythmia". Ed. Sandoe, E. Jensen, E.F. and Olesen, K.F. AB Astra Sodertalje, Sweden, P. 449-472, 1970.
49. Vaughan Williams, E.M. Electrophysiological basis for rational approach to antidysrhythmic drug therapy. Ad. Drug. Res. 9:69-101, 1974.
50. Vaughan Williams, E.M. Classification of antidysrhythmic drugs. Pharmac. Therap. B. 1:115-138, 1975.
51. Weidmann, S. The effect of the cardiac membrane potential on the rapid availability of the sodium carrying system. J. Physiol. 127:213-224, 1955.
52. Wit, A.L., Rosen, M.R. and Hoffman, B.F. Electrophysiology and Pharmacology of cardiac arrhythmias VIII Cardiac effect of diphenylhydantoin B. Am. Heart J. 90: 397-404 , 1975.

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