Brief Reviews
Mechanisms of Action of Antiarrhythmic Drugs
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An understanding of the manner in which drugs used to treat arrhythmias modify the initiation and the spread of the cardiac impulse must be based in part on an understanding of their effects on the electrical activity of the normal heart and its constituent fibers. However, since these drugs are used to modify abnormalities of impulse initiation and conduction, it is equally important to understand their effects on the abnormal fibers responsible for arrhythmias and conduction disturbances. Although it is possible to study drug action on a variety of preparations of cardiac tissue from normal hearts that have been experimentally modified to produce conduction disturbances or abnormalities of rhythm (1-5), whether the mechanisms responsible for the experimental disturbances of rhythm and conduction are identical to the mechanisms which cause arrhythmias and conduction abnormalities in the diseased human heart is for the most part unknown. Furthermore, the electrocardiographic identification and the classification of arrhythmias and conduction disturbances contribute little if anything to an understanding of the changes in electrical activity of the cardiac cell membrane which may be responsible for the electrocardiographic abnormalities. In the following pages, we shall attempt to review the mechanisms by which some commonly used antiarrhythmic drugs modify cardiac rhythm and conduction, to emphasize the limitations in our understanding, and to indicate some of the types of experiments needed to minimize these limitations.

ORIGIN AND CONDUCTION OF IMPULSES IN THE HEART

It is convenient to consider the physiological basis for disturbances in rhythm and conduction in terms of the passive and the active electrical properties of the cardiac cell membrane (Fig. 1). Cardiac cells are excitable, that is, they respond to a threshold stimulus by developing an action potential. Excitation occurs if a depolarizing stimulus lowers the transmembrane potential of an adequate area of membrane rapidly enough from the resting or maximum diastolic potential to the threshold potential. The latter is a critical level of membrane potential at which regenerative depolarization occurs (6). Normally the spontaneous initiation of the cardiac impulse occurs in the sinoatrial node as a result of gradual depolarization during phase 4 which lowers membrane potential to the threshold level (7). This spontaneous activity, or automaticity, is common to the sinoatrial node, some cells in the specialized atrial fiber paths (8-10), portions (AN and NH regions) of the atrioventricular node (11), and all parts of the His-Purkinje system. Usually in mammalian hearts some part of the sinoatrial node acts as a pacemaker, because the rate of automatic firing is highest in this tissue. If the automaticity of the sinoatrial node is depressed or if the automaticity of some other (latent) pacemaker is enhanced, specialized cardiac fibers other than the sinoatrial node may serve as the pacemaker and initiate single or multiple ectopic impulses.

Disturbances in rhythm also may result from abnormalities in conduction. Rarely, these disturbances arise from the presence of abnormal anatomical pathways which bypass some part of the normal atrioventricular junction, but, more frequently, conduction disturbances are manifested as a localized delay in the propagation of the impulse due to some abnormality in the function of the electrogenic membrane. The velocity with which the cardiac impulse propagates is determined in part by such parameters as the magnitude of the resting potential, the rate of rise of phase 0 of the
Cardiac transmembrane action potential; vertical axis is membrane potential (mV), and horizontal axis is time (msec). In excitable cells an electromagnetically resting membrane potential (RMP) is maintained until a stimulus arrives that is of sufficient magnitude to lower the resting potential to the threshold potential (TP). A sufficiently rapid depolarization to threshold results in excitation. Initially, there is a rapid depolarization (phase 0), often including an overshoot, followed by three phases of repolarization comprising a short, rapid repolarization (phase I), a plateau (phase 2), and a return (phase 3) to the resting membrane potential. The interval of electrical quiescence that follows each action potential is phase 4. In those cells which have the property of automaticity, spontaneous depolarization (thin, broken line) may occur during phase 4 and, on reaching the threshold potential, may result in excitation. The effective refractory period is defined by the earliest prematurely induced action potential (occurring during phase 3) that is able to propagate along the fiber bundle.

The relationship of the maximal rate of phase-0 depolarization for a given action potential to the level of membrane potential at which that action potential arises is referred to as membrane responsiveness.

Transmembrane action potential, and the value of the threshold potential. Any factor will slow conduction if it increases the time required for the propagating impulse to move the transmembrane potential from its resting value to its threshold value or decreases the distance along the membrane over which the propagating impulse can move membrane potential from the resting value to the threshold value. Impairment of conduction, if severe, is often associated with local failure of excitation and unidirectional or bidirectional block. Marked slowing of conduction can permit an impulse to linger long enough in some part of the heart so that it might reexcite other parts after they have recovered excitability. If the slow conduction is accompanied by unidirectional block, restraint excitation and arrhythmias do occur (2) (Fig. 2).

As a general rule, a decrease in the magnitude of the transmembrane potential at the moment of excitation causes a decrease in the maximum slope of phase 0 and a decrease in the conduction velocity. Exceptions to this rule include small depolarizations which bring membrane potential somewhat closer to the threshold potential without having a significant effect on the maximum slope of phase 0 (12, 13); under these conditions the speed of conduction may increase. Because the rate of rise and the amplitude of the action potential are a function of the level of membrane potential at the moment of excitation, impulses which arise as a result of phase-4 depolarization will have a decreased amplitude and rate of rise of phase 0, and often they will conduct abnormally. Impulses that are sufficiently premature to arise at a time during
MECHANISMS OF ACTION OF ANTIARRHYTHMIC DRUGS

Model for unidirectional block and reentrant arrhythmias: pictured are the anterior (AD) and posterior (PD) divisions of the left bundle branch. The posterior division supplies the posterior papillary muscle (PPM) where it arborizes into smaller branches, two of which are depicted here. Under normal conditions, depolarization (solid arrows) proceeds in an retrograde fashion through the His-Purkinje system (1-3), resulting ultimately in a radial activation of the ventricular myocardium (4). In instances such as infarction which lends to cell injury and depolarization (shaded area) anterograde activation may be slowed or blocked (5). However, the wave front proceeding through the normal Purkinje system and propagating sequentially along the normal papillary muscle (6) may, to a variable degree, enter and activate the depressed segment (broken lines). If the resultant membrane depolarization spreads slowly and reaches adjacent more normal tissue after the end of the effective refractory period, it may reenter the cardiac conducting system (7) and, with subsequent propagation, result in an ectopic beat. It is conceivable that drugs might be effective in the treatment of such reentrant arrhythmias if they enhanced conduction to the point that transmembrane activation proceeded normally or if they further decreased conduction, establishing bidirectional block in what was previously a reentrant loop. See text for further discussion.

Phase 3 when membrane potential is markedly decreased will conduct slowly and will be likely to block. If a stimulus falls sufficiently early during phase 3, when membrane potential is less than -50 to -55 mv, excitation normally will not occur (14). This level of membrane potential defines the end of the absolute refractory period. At slightly higher values of membrane potential, a premature response can propagate, and this level of membrane potential defines the end of the effective refractory period. It is clear that changes in the duration of the action potential ordinary will result in changes in the duration of the refractory periods. However, since the voltage-time course of the membrane potential during phase 3 and the relationship between the membrane potential and the reactivation of the sodium-carrying system (14) (membrane responsiveness [15, 16]) may change, alterations in the duration of the action potential need not be the same as alterations in the duration of refractoriness. If automatic activity gives rise to a premature impulse which spreads in fibers that are not fully repolarized, this impulse will propagate abnormally. Alterations in automaticity thus are frequently associated with abnormalities of conduction (1, 17).

CLASSIFICATION OF DRUG ACTION

In terms of these observations it appears that agents which increase the slope of depolarization during phase 4 or move the threshold potential closer to the resting potential should increase the rate of automatic firing or cause ectopic automatic impulses. Conversely, drugs which decrease the slope of phase-4 depolarization or increase the voltage difference between the resting potential and the threshold potential should have the opposite effect and slow the rate of automatic firing, thereby suppressing ectopic automatic activity.

In relation to disturbances of conduction, it is necessary to specify the condition of the tissue to indicate the expected effect of pharmacological agents. If the resting potential is decreased enough to impair the response of the tissue, a drug which increases resting potential and thus improves responsiveness would be expected to improve conduction (18). Similarly, a drug which improves the response elicited at an abnormally low level of membrane potential, thereby improving membrane responsiveness, also would be expected to improve conduction. Conversely, drugs which cause a significant decrease in the resting potential or in the magnitude and the rate of rise of the action potential would depress conduction as would drugs which decrease the responsiveness of a tissue at any given level of membrane potential (18). Thus, a drug might eliminate an arrhythmia due to reentry either by improving conduction in a depressed area or by further depressing conduction to the point of complete block (Fig. 2).
Although this general description of expected drug effects seems clear and more or less reasonable, the action of a drug is more complex at times. For example, quinidine and procaine amide decrease membrane responsiveness and in high concentrations markedly slow conduction (15, 17). Nevertheless, when phase-4 depolarization is present over considerable lengths of the conducting system, these same agents in low concentrations may increase conduction velocity, because they diminish the slope of phase-4 depolarization and thus permit the impulse to be initiated at a higher level of membrane potential (19). An agent which increases the duration of the transmembrane action potential might be expected to block the appearance or the propagation of a premature impulse. Although this expectation generally is true, again there are exceptions. A local or an inappropriate prolongation of refractoriness might delay the propagation of a premature impulse enough to permit reentrant excitation. In the same context, if an impulse is delayed in some area because of a local increase in action potential duration, a drug which accelerates repolarization might exert an antiarrhythmic action.

These concepts led to a classification of antiarrhythmic drugs based primarily on their effects on conduction, action potential duration, and responsiveness of the cardiac fiber (Table 1) (18). Quinidine (20), procaine amide (18, 20), propranolol (21), diphenylhydantoin (16), and lidocaine (22, 23) all decrease the slope of phase-4 depolarization and all thus might be effective against automatic rhythms. Quinidine and procaine amide in sufficient concentrations, increase the action potential duration of several types of cardiac fibers, but propranolol (21), diphenylhydantoin (16), and lidocaine (22, 23) have the opposite effect. Quinidine, procaine amide, and propranolol decrease conduction velocity in concentrations comparable to therapeutic levels (18), but lidocaine (24) and diphenylhydantoin (16) at therapeutic levels either fail to change conduction velocity or actually cause it to increase. In low concentrations, quinidine and procaine amide decrease the responsiveness of cardiac fibers, although diphenylhydantoin and lidocaine do not; indeed, there is some evidence that the latter two drugs may actually improve the responsiveness of depressed fibers (16, 24). Drugs which depress conduction and responsiveness were placed in one class and those which do not depress and which might improve conduction and responsiveness were placed in another.

This division of antiarrhythmic drugs into only two major groups is not generally accepted. Vaughan Williams (25), using different experimental techniques and criteria, has proposed four classes of antiarrhythmic drugs. This classification discriminates between the ability of a drug to decrease the action potential amplitude and the maximum rate of rise of phase 0, to cause sympathetic blockade, to increase the duration of the transmembrane action potential, or to modify a postulated inward calcium current which is activated during depolarization (26).

It is quite likely that further experimentation will result in other attempts to classify antiarrhythmic
MECHANISMS OF ACTION OF ANTIIARRHYTHMIC DRUGS

Drugs and to identify the components of these effects which actually are responsible for their antiarhythmic action. Clearly what is needed is additional information on the electrophysiological basis for the arrhythmias and the conduction disturbances which are treated and a demonstration of specific effects of the agents on the particular abnormalities in electrical activity responsible for the arrhythmia or the conduction disturbance being treated. In addition it will be important to characterize the effects of each agent on each of the tissues of the heart, including the sinoatrial node, the atrial myocardium and specialized atrial fibers, the atrioventricular node, each segment of the His-Purkinje system, and the ventricular muscle. Finally an attempt must be made to describe the effects of a drug when it is administered by the usual route to an intact animal, is carried in the blood variably bound to plasma proteins and tissue constituents, acts at varying electrolyte concentrations, and interacts with different constituents of the plasma. Some recent work on each of these problems may indicate the direction that future studies will take.

RECENT STUDIES ON THE ELECTROPHYSIOLOGICAL BASIS FOR ARRHYTHMIAS

As stated above, an understanding of the mechanism of action of drugs used to treat disturbances of rhythm and conduction in the heart is dependent on an understanding of the electrophysiological and the possible anatomical abnormalities responsible for or contributing to the electrical disturbance. Recent studies have provided strong support for this argument. Several groups of investigators (27-29) have studied the sequential changes in electrical activity and transmembrane potentials which accompany myocardial infarction. Wint (unpublished observation) has shown that in the dog, within the first 24 hours, many myocardial cells and Purkinje fibers within the ischemic area show low resting potentials and abnormally small action potentials. Conduction block is prominent and areas of parasystolic automatic firing frequently are found. By 48 hours, almost all of the myocardial cells in the infarct are electrically quiescent, although the subendocardial Purkinje fibers have regained an almost normal resting potential. These fibers generate action potentials of good amplitude but unusually prolonged duration. At this stage a premature impulse often blocks in the areas where action potential duration is long and, as a result, reentry occurs.

Early after infarction, an antiarhythmic drug might be effective if it suppresses automatic firing or decreases responsiveness of partially depolarized cells, thus eliminating them as possible reentrant paths. Alternatively, an agent like diphenylhydantoin, which appears to improve responsiveness of depressed fibers, might be effective by this action. At a later stage, when action potentials of subendocardial Purkinje fibers are abnormally prolonged, a drug like lidocaine might prevent multiple reentrant excitations because of its ability to shorten the action potential and the refractory period. In this context, it clearly is essential to know the relative sensitivity of the normal and the abnormal Purkinje fibers to the antiarhythmic drug. If the abnormal fibers are the more sensitive at the stage when Purkinje fiber action potentials are prolonged, then lidocaine might reduce temporal inhomogeneity of recovery. At the same time the relative spontaneous arrhythmia and that in animals which appear to improve responsiveness of normal fibers and simultaneously shorten action potential duration in ischemic fibers because of their increased sensitivity to low or therapeutic concentrations of the drug. These observations reinforce the argument made quite some years ago (30) that an understanding of the mechanism of action of antiarhythmic drugs can be obtained only from studies in which the drug is used to treat the spontaneously occurring arrhythmia and that information obtained from studies of drug action on normal fibers may be quite misleading.

Cranefield and his associates (4, 5) have studied the types of conduction disturbances and arrhythmias which may result when mammalian Purkinje fibers are partially depolarized so that the strong inward sodium current normally responsible for phase-0 depolarization is greatly attenuated or eliminated and a weak depolarizing current (perhaps carried by calcium) is primarily responsible for the generation of action potentials. In these experiments, suitably depressed preparations of Purkinje fibers demonstrated all of the conduction abnormalities typically associated with the atrioventricular junction of the mammalian heart. They also permitted the demonstration of both reentrant excitation as a result of either reflection or circus movement and parasystole with entry and exit.
ties intermediate between those of sinoatrial nodal perinodal fibers (34) which have electrical properties of mammalian heart have been identified. Between the sinus node and the atrium there is a group of various groups of functionally unique fibers in the ventricular myocardium and specialized atrial fibers, each of which might occur in the diseased human heart. An elevation of extracellular potassium concentration (14-15 mM) and the action of a catecholamine such as epinephrine or norepinephrine are sufficient to elicit slow responses and an infinite variety of conduction disturbances and arrhythmias. It seems quite likely, therefore, that some abnormalities of rhythm and conduction in the human heart result from slow responses of the sort demonstrated in these isolated tissues. If this speculation is so, it is completely unreasonable to attempt to explain the mechanism of action of antiarrhythmic drugs solely in terms of their demonstrated effects on the normal electrogenic mechanism. Preliminary studies have shown that the slow response is suppressed by alpha-receptor blockade (33) and perhaps also by drugs which may modify inward calcium current (30). In addition, the slow response seems not to be influenced by otherwise effective concentrations of conventional antiarrhythmic drugs such as quinidine.

Differences in Sensitivity of Cardiac Fibers to Antiarrhythmic Drugs

There are many convincing demonstrations that comparable concentrations of the same drug exert quite different effects on the electrical activity of fibers from different parts of the heart (13). To characterize fully the actions of a single agent, its effects on fibers of the sinoatrial node, the atrial myocardium and specialized atrial fibers, each of the cell types in the atrioventricular node, each segment of the His-Purkinje system, and the fibers of the ventricular myocardium should be examined. Even this listing of sites to be studied probably is incomplete, because it is not certain that all of the various groups of functionally unique fibers in the mammalian heart have been identified. Between the sinus node and the atrium there is a group of perinodal fibers (34) which have electrical properties intermediate between those of sinoatrial nodal and atrial fibers and which probably play an important role both in the transmission of excitation between the sinus node and the atrium and in the production of arrhythmias due to abnormal sinoatrial conduction.

Studies by Myerburg et al. (35, 36) have demonstrated quite clearly that the fibers in the bundle branches and the Purkinje system of the canine heart cannot be treated as a system with uniform properties. Action potential duration and effective refractory period increase progressively with distance from the His bundle to a point just proximal to the junction of the terminal Purkinje fibers with the ventricular muscle. This area of maximal action potential duration limits the propagation of premature impulses from the conducting system to the ventricular muscle and from the ventricular muscle back to the conducting system. Normally the maximum duration of the effective refractory period is the same in all the terminal branches of the conducting system. However, when there are local differences in this duration the likelihood of reentrant excitation is enhanced. Other studies have shown that there may be quantitative differences in the effects of antiarrhythmic drugs such as lidocaine (37), propranolol (38), and procaine amide (39) on different parts of the His-Purkinje system. In the case of procaine amide, we have found that when the extracellular potassium concentration is 4.0 mM, reasonable concentrations (30 μg/ml) of drug alter the effective refractory period in the ventricular conducting system to a lesser extent than they do when the potassium concentration is lower (2.5 mM). These results suggest that the effects of procaine amide on the propagation of premature impulses might be quite different at different plasma potassium levels in man and that the mechanisms of antiarrhythmic action also might vary with the extracellular environment of the fibers.

Information about drug effects on the electrophysiological properties of cardiac tissues should be obtained wherever possible from studies on the human heart and, if the results are to be related to the clinical efficacy of a drug, such studies should not be restricted to normal tissues. Recent work (40) has demonstrated that human atrium contains two types of fibers, resembling those described as specialized and nonspecialized for other mammalian atria, and that these fibers show quantitative differences in response to drugs and changes in extracellular ionic concentrations. In addition, it has been shown that the electrophysiological properties
of diseased atria are quite different from those of normal atria (41, 42).

REPLACEMENT OF STANDARD STYX'S SOLUTION WITH MORE PHYSIOLOGICAL SOLUTIONS

Almost all studies on the effects of antiarrhythmic drugs on the transmembrane potentials of isolated preparations of cardiac tissue are limited by the fact that the tissues are not perfused through their arterial vessels. Although techniques are available for arterial perfusion of an isolated papillary muscle (43), and for the selective in situ perfusion of the atrial and the atrioventricular nodes (44), they have not been generally employed for studies in electrophysiology or pharmacology of antiarrhythmic agents. Most investigators have employed isolated tissues perfused with an aqueous salt solution containing glucose and various other additives and more or less arbitrary concentrations of drug. Recently several groups have begun to appreciate the importance, in relation to drug action, of small changes in the ionic composition of the perfusate (39, 45, 46), and it now seems likely that the actions of lidocaine, diphenylhydantoin, and procaine amide, like the action of digitalis, are strongly dependent on extracellular potassium and calcium concentrations. Nevertheless, perfusion with artificial media still fails to approximate in a satisfactory manner the conditions which occur when the drug is administered to the intact animal and when drug binding and metabolism and changes in the composition of the blood may strongly influence one or more of the effects of the agent administered. A technique has been developed to perfuse isolated preparations of cardiac tissue with arterial blood from a donor animal and to evaluate simultaneously the effects of a drug on the heart of the donor and on the isolated tissue (47). Use of this method to study the effects of procaine amide has modified our understanding of the changes in electrical activity of Purkinje fibers which are induced by therapeutic and toxic blood levels of this agent (48), and we anticipate that further application of this technique will permit a greater appreciation of the effects of known plasma concentrations of various drugs on cardiac electrophysiology.

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