ANTIARRHYTHMIC DRUGS: ELECTROPHYSIOLOGICAL AND PHARMACOKINETIC CONSIDERATIONS

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INTRODUCTION

This review of the disposition and electrophysiological effects of antiarrhythmic drugs emphasizes literature published since 1970.[2] We have restricted ourselves to a consideration of those drugs most widely used in the treatment of clinical arrhythmias. Several important advances in cardiac electrophysiology and pharmacology have been made since the last review (1) which has furthered our understanding of the efficacy of these drugs. Progress continues to be made in our understanding of how the cardiac action potential is generated and propagated in the mammalian heart. Advances have been made both at the basic and clinical level in our understanding of the origin of cardiac arrhythmias. It is impossible to include a discussion of the ionic basis of the cardiac action potential and the electrophysiological basis for disturbances in cardiac rhythm in a review of limited length. The reader is referred to several recent reviews and monographs for these basic discussions (2–5). An area of active investigation has been the elucidation of the electrophysiological properties of cells from diseased human hearts and canine hearts subjected to myocardial infarction. The electrophysiological effects of antiarrhythmic drugs on cells surviving infarction have only begun to be investigated, but already it is becoming evident that drug effects on normal tissue may be quite different from drug effects on diseased tissues. In vivo recording and stimulating techniques have been perfected which has allowed assessment of the electrophysiological effects of these drugs in man. Considerable progress has been achieved in analytical and computational methodology allowing some conclusions to be made about the relationship between time course of drug in the body and the time course of pharmacologic effect.

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It is more difficult to be certain that concentrations of drugs that produce certain electrophysiological effects in vitro are in fact similar to drug concentrations in the myocardial interstitial fluid achieved during clinical therapy. It will become apparent as each individual agent is discussed that future research must bear heavily on this problem. The reader is referred to recent reviews on the kinetics of reversible pharmacologic effects for a consideration of pharmacokinetic principles (6–8).

LIDOCAINE

Of the agents under consideration, lidocaine has been the most extensively investigated. The earlier electrophysiological studies on this drug have been reviewed previously (1). Lidocaine has prominent effects on isolated Purkinje fibers. At very low concentrations it markedly depresses phase 4 diastolic depolarization. It is now generally accepted that a decrease of K^+ conductance is the cause of slow diastolic depolarization in Purkinje fibers, and several investigators (9, 10) have presented evidence that lidocaine may exert part of its action by increasing K^+ conductance. The drug increased both the net steady-state outward current (iK_1) and decreased the magnitude and rate of change of the pacemaker current (iK_2). Both of these actions can account for lidocaine's effectiveness against ventricular arrhythmias due to enhanced automaticity. An increase in K^+ conductance may also account for the drug's effect on action-potential duration (APD). Lidocaine shortens all phases of repolarization in Purkinje fibers. Bigger & Mandel (11, 12) reported that moderate concentrations of lidocaine cause a greater abbreviation of the APD than effective refractory period (ERP). The disproportionately greater shortening of the APD has been taken to imply a net prolongation of ERP. These changes in the cardiac action potential together with an enhancement in membrane responsiveness have been regarded as significant actions of this agent in the treatment of reentrant arrhythmias (1).

These concepts have to be reevaluated in the light of recent findings. Studies of Myerburg et al (13) have demonstrated that both APD and ERP increase progressively from the bundle of His to the distal Purkinje fibers. An area of maximal APD occurs a few millimeters before termination of the peripheral Purkinje fibers in muscle. Beyond this region of maximal APD, referred to as the gate, the APD becomes progressively shorter. The gate determines the functional refractory period of the ventricular conducting system under normal conditions and is assumed to play a role in the generation of reentrant arrhythmias. Wittig et al (14) studied the effects of lidocaine on APD throughout the ventricular conducting system. They demonstrated that lidocaine shortened APD to a greater extent in the region of the gate as compared to regions proximal or distal to the gate. The consequence of this effect is that APDs become more uniform throughout the conducting system. By diminishing the nonuniform repolarization that normally exists between Purkinje fibers and ventricular muscle the drug decreases the opportunity for conduction block and reentry to occur. The importance of such a mechanism in the antiarrhythmic action of lidocaine was previously suggested by Davis & Temte (15). Secondary to a depression of automaticity this is probably the most significant electrophysiolog-

ical action of the drug and may be related to its ability to increase the ventricular fibrillation threshold (VFT) (16, 17).

Lidocaine has been shown to have variable effects on the maximal rate of phase 0 depolarization in cardiac fibers. Earlier studies (11, 12) suggested that therapeutic concentrations of drug increased the maximum rate of depolarization and membrane responsiveness and hence improved conduction. These studies have been criticized by Singh & Vaughan Williams (18) who showed that the effects of lidocaine on atrial and ventricular tissue are dependent upon the extracellular K^+ concentration. At K^+ concentrations of 5.6 m*M* (which they consider normal in man) lidocaine depressed action-potential rate of rise which led them to conclude that the action of lidocaine is only depressant. The studies of Bigger et al (11, 12) were done at K^+ concentrations of 3 m*M*. The normal range in man has been reported to be 3.5–5.0 m*M* (19). At this range, lidocaine either does not change responsiveness in canine Purkinje fibers or decreases it (Sasyniuk, unpublished observations). This suggests that alteration of membrane responsiveness in *normal* Purkinje fibers may be a less important antiarrhythmic action of this drug and may not be an ideal property on which to base drug classification. Discrepancies in drug effects found by different laboratories can largely be attributed to the use of various physiological salt solutions and different concentrations of drug. It is now apparent that in order to characterize completely the actions of an antiarrhythmic drug it must be assessed over a wide range of concentrations and at least at several different K^+ concentrations.

It has been postulated by Bigger (20) that lidocaine can control ventricular arrhythmias in the presence of myocardial ischemia or infarction by enhancing responsiveness and improving conduction through the affected area. This hypothesis is not borne out by new data. Several recent studies have helped to elucidate the cellular mechanisms underlying the ventricular arrhythmias that accompany myocardial infarction (21–24). This new approach is based on the electrophysiological study with intracellular microelectrodes of portions of infarcted canine endocardium removed 24 hr after occlusion of a major coronary artery (during the period of in vivo arrhythmias) and perfused in vitro. These studies have revealed the survival of subendocardial Purkinje fibers that are characterized by reduced maximum diastolic potentials, action-potential amplitudes, and maximum depolarization velocities, and an extraordinarily prolonged time course of repolarization. These characteristics have been shown to facilitate the production of reentrant phenomena in vitro. Various types of pacemaker activity were also observed in the infarcted areas. The electrophysiological effects of lidocaine on these surviving Purkinje fibers have been studied by Sasyniuk & Kus (25). They found that lidocaine affected cells in the infarcted area differently from adjacent normal Purkinje fibers. In therapeutic concentrations (1–5 mg/liter) the drug decreased markedly in the amplitude and rate of rise and depressed membrane responsiveness of Purkinje fibers in the infarcted area while causing only small changes in these parameters in normal fibers. This caused a marked slowing of conduction velocity through the infarcted area. Although APD was abbreviated in both normal and infarcted cells, a greater abbreviation occurred in the former. Lidocaine also suppressed pacemaker activity in

the infarcted area. In the presence of lidocaine, early premature beats were often delayed through the infarcted zone resulting in reentry. Higher concentrations of drug caused conduction block. Similar slowing of conduction has been observed by Brennan & Wit (26). Lidocaine has also been shown to slow conduction through infarcted myocardium in dogs in the first few hours following coronary artery occlusion (27, 28).

These results permit a hypothesis concerning the mode of action of lidocaine in postinfarction reentrant arrhythmias. Lidocaine could enhance reentry by depressing conduction through the reentrant pathway without significantly altering conduction in the normal pathway. Because the drug abbreviates the refractory period in the normal tissue, its refractory period will be over by the time the impulse arrives retrogradely at the normal zone and the impulse can reenter. At higher concentrations the drug would abolish reentry by producing bidirectional conduction block. Thus, it may be necessary to maintain a high concentration of drug at the site of action to convert a reentrant arrhythmia. Clinical studies support this view (see below).

Studies in both animals and man have revealed that lidocaine may occasionally be ineffective or detrimental when reentry is a likely mechanism (29–31). Enhancement of ventricular irritability is more likely to occur at lower blood levels (17, 29). Although lidocaine has been reported to reverse the decrease in VFT accompanying acute myocardial ischemia and to restore the multiple response threshold during regional hyperkalemia, it does not consistently prevent degeneration of multiple ventricular responses into ventricular fibrillation (32). Lidocaine may also fail to prevent primary ventricular fibrillation in acute myocardial infarction while having suppressed ectopic beats (30).

Under conditions other than infarction, lidocaine may conceivably convert a reentrant mechanism by enhancing conduction through a reentrant pathway. Arnsdorf & Bigger (9) have found that lidocaine hyperpolarizes fibers with a decreased maximum diastolic potential due to stretch. This tends to restore conduction velocity to normal in stretched fibers. However, these effects occurred at 2.7 m*M* K^+, and lidocaine causes hyperpolarization of normal fibers at external K^+ concentrations of less than 4 m*M*. It would be of interest to determine whether lidocaine hyperpolarizes stretched fibers when K^+ concentration is normal.

Although lidocaine in therapeutic concentrations has little effect on sinus nodal function in normal animals and man (33–35), marked depressant effects have been noted in the human heart with sinus node malfunction (36). Sinoatrial block may be attributed to a greater sensitivity to the drug of sinus perinodal fibers (37). Lidocaine can also produce sinus node depression when administered together with other antiarrhythmic drugs (38, 39).

Lidocaine has variable effects on atrioventricular (AV) conduction. Most human studies (40–43) have shown that therapeutic doses of drug have no significant effect on AV nodal or His-Purkinje conduction time even in the presence of disease or the His-Purkinje system. However, there have been several reports (42, 44, 45) of advanced AV block occurring after therapeutic doses in patients with diffuse in-

traventricular conduction disturbances. Lidocaine can accelerate AV conduction in the presence of atrial flutter, thereby increasing the ventricular rate to alarming levels (46). It is not clear whether this is an anticholinergic effect of the drug or a direct effect on the AV node.

Early attempts to correlate plasma lidocaine concentrations with clinical effects on ventricular arrhythmias led investigators to conclude that the plasma half-life ($t_{½}$) of the drug was in the order of 8–20 min (47–50). Assumption of a single compartment kinetic model together with inadequate assay methodology and termination of sampling times too early after dosing were probably responsible for this conclusion. It has been subsequently demonstrated that the disposition of lidocaine is best described by an open two-compartment kinetic model with an early fast alpha phase ($t_{½}$ 8 min) and a slower beta phase ($t_{½}$ 100 min) (51, 52). According to one report (53) steady-state lidocaine concentrations occurred 10 hr after onset of infusion. One investigator has observed a late third disposition constant with a $t_{½}$ in the order of 10 hr after discontinuing a 24 hr long infusion in patients with acute myocardial infarction (54), but this has not been confirmed. More work is required on the disposition of lidocaine during continuous infusion. In species other than man the beta phase $t_{½}$ of lidocaine is somewhat shorter:
and less than 30 min in rats (55–57).

After an intravenous (iv) bolus dose, peak drug content in peripheral (tissue) compartment is attained in about 25 min (52). However, the time course of lidocaine should be related to myocardial drug concentration rather than to drug content in the total peripheral compartment. Ventricular arrhythmias are often terminated within 1 or 2 min of a bolus infusion only to recur in 10 to 20 min (49). This suggests a high drug concentration in the myocardium soon after the bolus dose followed by a redistribution away from the myocardium as plasma concentrations decrease. Animal studies tend to support this theory. A threefold diminution in myocardial drug content was observed in the rat during the period between 2 and 10 min after administration of bolus doses (56, 58). In another study a tenfold diminution was observed between 1 and 15 min after a bolus dose (59). The need for iv bolus infusions of lidocaine to terminate ventricular arrhythmias has been repeatedly demonstrated, and a threshold plasma drug concentration circulating through the myocardium has been suggested (60).

There is extensive distribution of the drug outside of the circulating volume. In normal individuals, the apparent volume of distribution (AVd) is approximately 1.4 liters/kg with the volume of the central (plasma) compartment in the order of 0.6 liters/kg (51, 52). The AVd is markedly reduced in patients with congestive heart failure and greatly increased in patients with liver disease but unaltered in patients with uremia (61, 62). Elimination is almost entirely by hepatic metabolism, as less than 8% is excreted unchanged in the urine (63). In species other than man, metabolic products of lidocaine have been less active on the cardiovascular system than the parent compound (64). One of the metabolites of lidocaine, monoethylglycinexylidide, may be responsible for CNS toxicity in man after oral administration (51, 56).

The hepatic extraction ratio (65) in normal subjects is 0.7. Approximately 40% of an iv dose is eliminated before distribution is completed (52). Because elimination can occur only if the drug is delivered to the liver, elimination is proportional to the cardiac output and hepatic blood flow (62, 65). Advanced heart failure or liver disease can reduce lidocaine elimination. In spite of evidence to the contrary, some reports (66) state that very little lidocaine is bound to plasma proteins. Estimates of 70–80% binding over the plasma concentration range of 1–10 mg/liter have been reported (63, 67, 68). The relationship of this degree of plasma protein binding to the pharmacokinetics and pharmacodynamics of lidocaine has not been studied.

The minimum effective plasma concentration for the prevention of ventricular arrhythmias is considered to be 1.2 mg/liter with central nervous system and cardiovascular toxicity observed at concentrations over 6–9 mg/liter (47, 60, 69–71). Several dosage schedules have been offered (47, 51, 61, 62, 72). A total loading dose of 150 mg iv followed by a maintenance infusion of 20 μg/kg/min body weight should result in plasma concentrations in the therapeutic range of 1.2–5.5 mg/liter. Because of the reduced AVd and elimination in subjects with heart failure, dose recommendations must be reduced in this group. Lidocaine clearance can also be reduced by drugs such as propranolol that depress cardiac output (73) and increased by drugs that induce hepatic microsomal enzymes (74). The common clinical practice of a bolus dose followed by a maintenance infusion dose results in peak concentrations after the bolus dose exceeding that of the trough concentration by a factor related to the ratio of Kel over beta (75), which for lidocaine is represented by a factor of 3. This has been amply demonstrated in man and could be responsible for the recurrence of arrhythmias in the period 30–120 min after a bolus infusion (76–78).

Alternate routes of administration have been investigated for arrhythmia prophylaxis. Oral doses of 500 mg produce inadequate plasma concentrations due to rapid metabolism in the first pass through the liver with an absolute bioavailability of only 35% (51). Adequate plasma concentrations can be achieved with intramuscular (im) administration. Studies are in progress to determine the suitability of this route of administration (79–85). A quaternary derivative of lidocaine, methyl lidocaine, is presently under investigation. It possesses antiarrhythmic properties similar to those of lidocaine but has a longer duration of action and lacks the CNS toxicity (86, 87).

PROCAINAMIDE

The physiological disposition and cardiac effects of procainamide were studied soon after its institution into clinical therapy (88). However, it was not until 20 years later that more complete knowledge of effective plasma concentrations and dose schedules required to achieve these concentrations had been established (89–91). After parenteral administration, the plasma concentration time curve for procainamide is best described by an open two-compartment kinetic model with a rapid alpha disposition phase ($t_{1/2}$ 5 min) and a beta plasma $t_{1/2}$ of 3.5 hr (range 2.5–4.7) in

subjects with normal renal function (91). Other species have slightly faster rates of elimination (92, 93).

There is considerable variability in the absolute availability of im and oral doses of procainamide as compared to iv doses in man (91). The AVd of procainamide ranged from 1.74–2.22 liters/kg in 8 subjects with normal circulatory function, whereas in 4 subjects with low cardiac indices the AVd was lower (1.48–1.78 liters/kg) (91). One half of the administered drug appears unchanged in the urine. The rest is metabolized in the liver. Metabolites differ in various species but none have been noted to have an antiarrhythmic effect (92, 93). The elimination $t_{½}$ is altered not only by reduced delivery of drug to the sites of elimination, liver and kidneys, but also by renal disease (91, 94). There are no data available on elimination in patients with liver disease. Dose schedules for patients on extracorporeal hemodialysis have not been established, but the drug is dialyzable and the plasma $t_{½}$ is shortened towards normal during hemodialysis (95–97).

Dose schedules to attain and maintain therapeutic plasma concentrations between 4 and 8 mg/liter in patients with normal renal function have been suggested (90, 98, 99). A useful method to terminate ventricular tachyarrhythmia is the administration of 100 mg doses iv every 5 min until either the arrhythmia is abolished, 1 g of drug has been given, or untoward drug effects appear (98, 99). A plot of the R-R intervals of coupled ventricular premature depolarizations (VPDs) or the decrease in number of VPDs against the apparent increase in drug content in the peripheral compartment of an open two-compartment kinetic model for procainamide has shown a good correlation between myocardial response and drug content in the peripheral compartment (98). Peak drug accumulation in the peripheral compartment occurs 15 min after termination of a 1.0 g infusion (20 mg/min) with parallel decay curves of drug in the peripheral and central compartments after this time (Ogilvie, unpublished observations). Maximal effect on H–Q interval and QRS duration have been noted at the termination of a loading dose (100). Greater effects were observed at the same plasma concentration after the infusion as compared to those observed during the infusion. The delay in the time course of maximal effect seen in these clinical studies is in agreement with electrophysiological changes observed in the tissue bath. However, there is a discrepancy in effective concentrations. In vitro studies with procainamide reemphasize the recurrent problem encountered in studies on electrophysiological actions of antiarrhythmic drugs, viz, the relations of drug concentration in the tissue bath to clinical drug levels.

In an attempt to overcome some of these problems, a technique has been developed by Rosen et al (101) to perfuse isolated preparations of cardiac tissue with arterial blood from a donor animal and to evaluate simultaneously the effects of the drug on the heart of the donor and on the isolated tissue. If the K^+ concentrations are comparable, the electrophysiological properties of cardiac cells are similar when perfused with either blood or Tyrode's solution (101). When donor dogs were given single iv injections of procainamide sufficient to produce therapeutic plasma drug concentrations, decreases in Purkinje fiber automaticity regularly preceded other changes in action-potential characteristics. Decreases in action-potential amplitude

and maximal rate of rise and in conduction velocity with simultaneous QRS widening in the donor animal occurred much later when plasma concentrations had decreased to 6 mg/liter (102). In studies of Purkinje fibers perfused in vitro with physiological salt solution, automaticity was also suppressed more rapidly and at a lower procainamide concentration than other drug-induced action-potential changes (103). These results suggest that a lower tissue concentration of procainamide is required to depress automaticity than to depress conduction, implying that the drug may be more rapidly efficacious in suppressing arrhythmias due to altered automaticity than those due to altered conduction. It is not known how procainamide alters automaticity. The drug does not alter K^+ conductance (104).

There is a discrepancy between effective concentrations of procainamide in isolated preparations perfused with blood versus physiological salt solution. Under the latter conditions the only consistent electrophysiological change observed at concentrations less than 30 mg/liter was a depression of phase 4 diastolic depolarization in spontaneously beating Purkinje fibers. Thirty to 40 min were required to produce this effect, in contrast to 5 to 10 min during blood perfusion. Concentrations greater than 30 mg/liter produced progressive alterations in action-potential configuration and in conduction time which were not readily reversible. Lesser concentrations produced similar effects only after several hours. Yet, this drug is not significantly bound to plasma proteins (15%), and its metabolites have no antiarrhythmic action (88, 92, 93). The myocardial:plasma concentration ratio in the dog has been reported to be 3:1 one hour after a parenteral dose (88). The discrepancy in concentration may be related to the mode of administration of the drug to the donor animal. If the drug had been administered to the animal by constant iv infusion, perhaps effects comparable to perfusion with artificial media would have been obtained. If it is assumed that uptake of drug by the heart is related to plasma concentration, the high plasma concentration obtained immediately following a bolus injection may mean that a much greater amount of drug is concentrated in the heart in a shorter period of time than occurs during a constant infusion. Thus, the isolated preparation perfused with blood is exposed to a much higher initial concentration of drug than that perfused with a constant amount of drug dissolved in a physiological salt solution. Hence, the two experiments are not strictly comparable. An alternative explanation may be that other components in blood may alter the electrophysiological effects of the drug. One undesirable feature of blood perfusion is the alteration of the electrophysiological properties of antiarrhythmic drugs by extracellular K^+ concentration requiring monitoring of plasma K^+ levels. Changes in voltage-time course of repolarization in Purkinje fibers are extremely sensitive to changes in external K^+ concentration. At physiological K^+ concentrations, therapeutic levels of procainamide decrease the duration of the plateau phase of the action potential without altering total action-potential duration. At K^+ concentrations in the low physiological range or below, procainamide lengthened all phases of the action potential (102). The drug has variable effects on repolarization-time course of Purkinje fibers located at different sites within the conducting system. Although there is a tendency toward equalization of action-potential durations throughout the ventricular conducting system, at physiological K^+ concentrations, the changes

produced are not as marked as those seen with lidocaine (103). Changes in phase 0 characteristics in the presence of altered K^+ concentrations are less well defined.

It was originally suggested by Weidmann (105) that a principal mode of action of procainamide is a prolongation of the ERP of Purkinje fibers out of proportion to any increase in APD. All subsequent references to the mechanism of action of this drug have stressed this property. The greater increase in ERP than drug-induced lengthening of the APD has been attributed to a decrease in membrane responsiveness. Because of reduced responsiveness, repolarization has to proceed to a more negative value before excitation can occur resulting in a prolongation of refractoriness independent of any change in APD. However, this will only be true in those fibers (located at the gate) whose APD is not altered by procainamide at physiological K^+ concentrations. In blood-perfused Purkinje fibers Rosen et al (102) found that the increase in ERP tended to lag behind the increase in APD at therapeutic concentrations of drug and that membrane responsiveness was not altered. These authors do not account for this apparent discrepancy. It is likely that blood perfusion is not without its problems, and various discrepancies may be due to continuously changing drug and ion concentrations. This would make interpretation of results somewhat more difficult. One wonders whether more consistent and useful information could not be achieved with physiological salt solution containing an adequate amount of albumin to account for plasma protein binding of the drug.

In any event, it seems apparent that alteration of ERP may not be as consistent a mechanism of abolition of reentrant arrhythmias by procainamide as are changes in conduction. Giardina & Bigger (98) showed that in patients with coupled VPDs, procainamide, in increasing plasma concentrations, progressively increased the coupling interval until the arrhythmia was abolished. They suggested that procainamide terminates reentrant arrhythmias by prolonging conduction in the depressed portion of the reentrant pathway until bidirectional block occurs. Giardina et al (99) have also found that lower plasma procainamide concentrations were effective in terminating ventricular arrhythmias following myocardial infarction than other types of ventricular arrhythmias. This suggests that cells within the infarcted area are more sensitive to the actions of the drug than normal areas as has been shown with lidocaine. Yoon et al (106) showed that procainamide increased the VFT in both the normal and ischemic ventricle. This increase was maintained at a high value while plasma concentrations decreased. However, the change in VFT in the ischemic ventricle was not as pronounced as that in the normal ventricle, and the drug failed to reverse completely the decreased fibrillation threshold accompanying ischemia. In contrast, lidocaine can revert the decreased VFT well above the normal value during coronary occlusion (17). Yet, Lown & Wolf (107) and Weisse et al (108) reported that procainamide offers a greater degree of protection than lidocaine against ventricular fibrillation in dogs during coronary occlusion, and Gamble & Cohn (29) showed that procainamide was more effective than lidocaine in abolishing repetitive premature beats in cats following coronary artery ligation. However, this discrepancy may be related to measurements of VFT at inadequate plasma concentrations of lidocaine. The action of procainamide on VFT may be responsible for

its effectiveness in reducing the frequency of premature beats and ventricular fibrillation in patients with myocardial infarction (107). Because of the relatively rapid elimination of procainamide in man and the narrow range between therapeutic and toxic concentrations, doses to maintain plasma concentrations within the therapeutic range must be administered every $t_{1/2}$ of the drug (90). Consequently, there is difficulty in maintaining adequate plasma concentrations overnight unless the subject is awakened. It is a less than ideal agent for chronic prophylaxis against arrhythmias due to the high incidence of lupus-like syndrome (109). Other aspects of procainamide therapy were recently reviewed by Miller et al (110).

QUINIDINE

The antiarrhythmic effect of quinidine has often been explained in terms of its ability to depress automaticity, excitability, and conduction velocity and to prolong refractoriness. These actions have been attributed to a direct depressant activity on sodium current and membrane responsiveness in cardiac muscle. As a result of laboratory and clinical studies, a controversy has arisen as to whether changes in conduction or alterations of refractoriness are the primary antiarrhythmic properties of quinidine against reentrant arrhythmias. The earlier literature (111) supports the view that prolongation of refractoriness is the more important action of the drug and that slowing of conduction is an undesirable effect. This view is based on the circus-movement hypothesis of arrhythmia generation, which suggests that any agent that prolongs refractoriness will close the gap between activation wave fronts and thereby abolish the circus movement. Slowing of conduction would tend to keep this gap open and perpetuate the arrhythmia. Thus, prolongation of the QT interval was regarded as the therapeutic effect of quinidine, whereas widening of the QRS complex was considered potentially toxic.

Experiments utilizing microelectrode recordings of cardiac action potentials have shown that concentrations of quinidine between 1 and 12 mg/liter cause a significant decrease in the rate of phase 0 depolarization of transmembrane action potentials recorded from atrial muscle (112, 113), ventricular muscle (114–116), and Purkinje fibers (105, 117). It is difficult to assess from these in vitro experiments the degree to which the drug alters refractoriness. Studies in the intact heart show that quinidine significantly prolongs intraatrial, His-Purkinje, and intraventricular conduction time (118–121). Wallace et al (118) did not find a consistent alteration of the refractory period of ventricular muscle in the intact heart, although conduction was consistently slowed. Heissenbuttel & Bigger (122) have shown a significant increase in both QRS duration and QTc interval in patients following antiarrhythmic doses of quinidine. There was a positive but weak correlation between the increases in QRS duration and QTc interval and increases in plasma concentration. They suggested that QRS prolongation more accurately reflected an early quinidine effect. Bloomfield et al (123) did not find any appreciable widening of the QRS complex in patients given quinidine after acute myocardial infarction. In a more recent clinical study (124) there was consistent prolongation of the QTc interval, whereas

QRS duration increased in only half of patients given quinidine im, supporting the earlier view that prolongation of refractoriness is a more characteristic quinidine effect. Similarly, Cho (125) found a high correlation between increases in QT interval and increases in plasma concentrations, whereas there was a significant but poor correlation between QRS duration and quinidine concentration.

Any increase in QRS duration that is obvious on the standard electrocardiographic trace is probably indicative of approaching toxicity. Bigger (20) has arbitrarily chosen an increase in QRS duration of greater than 25% to be indicative of approaching toxicity and an increase of 50% to be definitely toxic. The lack of consistent results may be attributed to different serum K^+ concentrations that alter the effects of quinidine on conduction and refractoriness. Low extracellular K^+ concentrations antagonize the depressant effects of the drug on phase 0 characteristics in atrial and ventricular muscle but cause further prolongation of APD and refractory period (116, 121). High K^+ concentrations cause further depression of conduction. There is also some evidence that hyperkalemia may modify quinidine distribution (126). Alterations in serum K^+ concentration may modify other electrophysiological effects of the drug. Sasyniuk & Kus (unpublished observations) have found that therapeutic concentrations of quinidine decrease the dispersion of refractoriness in the ventricular conducting system at normal K^+ concentrations. The drug lengthens APD of Purkinje fibers proximal to and ventricular muscle distal to the gate without altering APD of gate cells. However, at low K^+ concentrations (less than 3 m*M*) the drug lengthens all action potentials to the same degree, thereby maintaining the inhomogeneity. This may explain why hypokalemic patients are often unresponsive to quinidine therapy.

The electrophysiological effects of quinidine are also modified by heart rate. The drug has a greater depressant action at higher rates of stimulation (113, 115, 118). At extremely slow rates the drug causes little change in phase 0 characteristics at therapeutic concentrations. In studies on intact hearts it has been shown that the degree of intraventricular conduction delay as well as the magnitude of changes in end diastolic threshold are substantially greater at rapid rates of stimulation than at slower rates. These observations suggest that tachycardia renders the heart more sensitive to the electrophysiological effects of the drug. Quinidine has been shown to have a greater depressant effect on atrial pacemakers than on ventricular pacemakers (127). This difference may be a pure rate effect.

In toxic concentrations, quinidine can increase the slope of phase 4 diastolic depolarization and further depress conduction velocity. High doses also cause extracellular acidosis. Toxic actions of the drug can be reversed with molar sodium lactate or isoproterenol. Although administration of molar sodium lactate may reverse quinidine toxicity, it will also delay the excretion of quinidine and might prolong the duration of toxicity. Isoproterenol antagonizes the effects of quinidine on conduction velocity without altering the effect of the drug on refractory period (128).

The pharmacokinetic disposition of quinidine has not been well studied, although there are reports of plasma concentrations observed after single or multiple doses

(129). The use of assay methods of questionable specificity and the reluctance of investigators to administer quinidine iv because of cardiovascular toxicity have contributed to the paucity of kinetic information in man. A one-compartment kinetic model has been applied to studies with iv administration in various animal species and a plasma $t_{1/2}$ of 6 hr has been observed in dogs (130). In man, the late phase plasma $t_{1/2}$ after oral or im doses has also been reported to be 6 hr in subjects with normal renal function (131–134). Approximately 80% of plasma quinidine is bound to albumin (135). At least one half of the administered dose is metabolized in the liver and the metabolites eliminated in the urine (136, 137); 10–50% is recovered unchanged in the urine within 24 hr (134, 138). A prolonged plasma $t_{1/2}$ has been observed in patients with congestive heart failure or renal insufficiency (134, 138–140). However, a recent study by Kessler et al (132) shows unimpaired quinidine elimination in patients with either congestive heart failure or poor renal function. They attribute the prolongation of $t_{1/2}$ found by others to the use of a nonspecific assay method that does not differentiate impaired quinidine biotransformation from impaired excretion of inactive metabolites. However, one patient with heart failure showed virtually no decrease in drug concentration over a 10 hr period. There is decreased quinidine elimination in alkaline urine (141).

There have been several studies of the myocardial:plasma quinidine concentration ratios in dogs (125, 142–144). Cho (125) has observed a linear relationship between atrial and ventricular muscle quinidine content and plasma quinidine concentration in anephric dogs given quinidine iv. He reported a ventricular muscle:plasma ratio of 20 and an atrial muscle:plasma ratio of 10 with quinidine sulfate. The concentration ratios for the gluconate salt were one half of those observed with quinidine sulfate. Others have obtained ratios between 4 and 12, the differences being attributable to different measurement techniques and sampling times (142–144).

The effective plasma concentration range for treatment of arrhythmias is stated to be 3–6 mg/liter with the assay method of Brodie & Udenfriend (145–148). A lower range (1–4 mg/liter) has been reported with the assay method of Cramer & Isaksson (149–154). The latter method and the method of Armand & Badinand (155) are apparently more specific for the parent compound. Correlation between efficacy or toxicity and plasma quinidine concentrations has been complicated by the different analytical methodology used in the various studies. Bloomfield and co-workers (123, 156) have studied the efficacy of oral quinidine in prophylaxis against cardiac arrhythmias using double-blind techniques. Plasma quinidine concentrations >4 mg/liter [method reference Brodie (145)] were achieved within 9 hr of initiating oral therapy with a loading dose. Concentrations >2.5 mg/liter were effective in patients with acute myocardial infarction, whereas concentrations >4 mg/liter were required in patients with acute coronary insufficiency without infarction. There is an increasing interest in the prophylactic use of antiarrhythmic drugs to prevent sudden death in patients following acute myocardial infarction. Quinidine has demonstrated effectiveness in decreasing the incidence of arrhythmias in patients with acute coronary insufficiency or uncomplicated acute myocardial infarction (123, 156).

DIPHENYLHYDANTOIN

The electrophysiological actions of diphenylhydantoin (DPH) have recently been the subject of considerable controversy which is still not adequately resolved (1, 18, 157, 158). Two aspects of the electrophysiological actions of DPH appear to be fairly well defined. The drug suppresses spontaneous depolarization in normal and depressed Purkinje fibers as well as in fibers exposed to digitalis glycosides (159). In normal Purkinje and ventricular muscle fibers, DPH abbreviates all phases of repolarization (159). There are no studies indicating whether this drug has actions similar to lidocaine on distal Purkinje fibers. As with lidocaine, the significance of the net prolongation of ERP is still unclear. The controversy concerns the effects of this agent on phase 0 characteristics in cardiac fibers. One group of investigators (159–161) maintains that the significant antiarrhythmic action of DPH is to enhance action-potential rise time, membrane responsiveness, and conduction velocity in cardiac tissues, particularly when these parameters are depressed. A second group of investigators (18, 157, 162, 163) believe that the significant action of this drug is largely a depression of depolarization. All investigators have demonstrated that low concentrations of DPH can enhance action-potential rise time, membrane responsiveness, or conduction velocity and decrease electrical threshold in cardiac tissues. This effect is more marked when the extracellular concentration of K^+ is low, and is particularly evident in preparations that have been depressed by cooling, stretch, hypoxia, or toxic concentrations of cardiac glycosides. Higher concentrations of drug (10–20 mg/liter) which correspond to "therapeutic plasma concentrations" in man are uniformly depressant. The effects of DPH on phase 0 characteristics are also frequency dependent (162). It appears then, that DPH may have a dual action whose expression is determined by the concentration of drug, the extracellular K^+ concentration, and the stimulation frequency. As has already been pointed out, a major difficulty in any in vitro study of drug action is deciding which concentration of drug in the perfusing fluid corresponds to therapeutic and toxic levels of the drug in man. It is even more difficult when a drug is highly bound to plasma proteins and its actions are highly concentration dependent. Greater than 90% of DPH is bound to plasma proteins (see below). Thus, less than 10% of the plasma concentration is presumed therapeutically active. Should one then consider tissue bath concentrations of 1–2 mg/liter (which enhance responsiveness) as representative of therapeutic effectiveness in man? Further studies are needed to resolve this problem, but recent data in man are consistent with a lack of depression of conduction. Caracta et al (164) found no effect of DPH (at therapeutic plasma concentrations) on His-Purkinje conduction time in most patients during sinus rhythm and over a wide range of paced atrial rates. The only consistent effect was a shortening of the effective refractory period of the His-Purkinje system. Damato et al (165) also found no change in intraventricular or His-Purkinje conduction in human subjects. Administration of DPH may alter intraventricular conduction in man by decreasing the relative refractory period of the His-Purkinje system. This has the effect of preventing aberrant conduction and normalizing the H–V interval

following the introduction of atrial premature beats (166, 167). Clinical evidence also confirms that DPH is able to improve His-Purkinje conduction when it is impaired by digitalis intoxication (168). It would be of interest to determine whether DPH improves responsiveness of subendocardial Purkinje fibers surviving infarction.

The effect of DPH on AV conduction has been the subject of numerous studies. DPH has been variably reported to decrease, increase, and not change conduction time through the AV node (164, 169–171). Both in intact animals (170) and man (164, 165, 172, 173), a decrease in AV conduction time has usually been observed. In denervated preparations, DPH causes a prolongation of conduction time (174–176). These results would be interpreted to mean that DPH accelerates conduction through the AV node by an indirect action, probably an anticholinergic effect. However, Bigger et al (172) have shown that neither pretreatment with propranolol nor atropine abolishes the accelerating effect of DPH in man. Data in man also show that the effect of DPH in enhancing conduction through the AV node is dependent upon atrial rate, a lesser enhancement of conduction occurring at faster rates (173). In fact, DPH can further depress AV conduction and slow ventricular rate in the presence of atrial flutter and fibrillation. Further studies are needed to define the direct effects of this drug on AV nodal cells and its modification by rate and K^+ concentration.

In spite of the variable effects on AV conduction in normal animals and man, both clinical and experimental studies have shown that DPH uniformly reverses the AV prolongation induced by digitalis. The mechanism whereby DPH causes enhancement of AV conduction in this setting is still uncertain. Part of this effect is probably related to a direct membrane action. Preliminary studies have shown that DPH reverses the decreased amplitude and rate of rise of N cells of the node induced by toxic doses of acetylstrophanthidin (Sasyniuk, unpublished observations). The exact nature of this effect requires further characterization.

The efficacy of DPH in treating ventricular arrhythmias due to digitalis toxicity is well established (177–181). A number of recent investigations have been concerned with elucidating the mechanism of the interaction of DPH with the cardiac glycosides. It was suggested by Scherlag et al (182) and Helfant et al (183) that the antiarrhythmic action of DPH represents a specific antagonism of the toxic actions of digitalis. They reported a reversal of the myocardial K^+ venoarterial difference induced by toxic doses of the glycosides. More recent studies do not support the earlier work. Miller & Gilmore (184) have reported that DPH fails to alter K^+ efflux induced by acetylstrophanthidin. They suggested that the myocardial K^+ loss demonstrated by Scherlag & Helfant and their colleagues was largely secondary to the tachycardia induced by digitalis and that reversal by DPH was due to abolition of the tachycardia and not a specific reversal of the digitalis effect. Spain & Chidsey (185) showed that DPH administration did not reverse Na^+–K^+ ATPase inhibition in animals made toxic with ouabain. Nor did DPH reverse enzyme activity when it was added in vitro to ouabain-inhibited enzyme. Gibson & Harris (186) found no effect of DPH on Na^+–K^+ ATPase activity in the microsomal fraction from human myocardium or any reversal of the inhibitory effects of ouabain. DPH also had no

effect on the activity of Na^+–K^+ ATPase isolated from cultured heart cells (187) and guinea pig atria (188). More recently, Goldstein et al (189) reported that perfusion of the isolated canine heart preparation with DPH combined with digoxin delayed the development of toxic arrhythmias but resulted in an even greater degree of inhibition of Na^+–K^+ ATPase. A recent study in man also demonstrated a lack of effect on DPH on ouabain-induced K^+ loss (190). The existing evidence then supports the view that DPH alters digitalis arrhythmias by some mechanism other than stimulation of Na^+–K^+ ATPase.

DPH has central nervous system actions. At least part of its antiarrhythmic effect in digitalis-induced arrhythmias may be due to altered nervous system function. Several groups have shown that activation of the sympathetic nervous system may be involved in the arrhythmogenic effects of the cardiac glycosides (191, 192). Gillis et al (191, 192) have provided direct evidence from nerve recordings that ouabain can influence preganglionic cardiac sympathetic nerve activity in diurethane-anesthetized cats. At toxic doses, sympathetic nerve activity was substantially augmented and high intensity activity had a temporal correlation with ventricular tachyarrhythmias. Administration of DPH depressed the glycoside-induced enhanced nerve activity and converted ventricular tachycardia to sinus rhythm. DPH increased the lethal dose of ouabain in spinal cats with high adrenergic neural activity but did not alter it in animals in which spinal cord transection resulted in a substantial reduction in adrenergic activity (193). Thus, DPH reduces adrenergic neural activity in digitalis-induced arrhythmias when this activity is enhanced. However, digitalis glycosides, in larger doses, can still produce arrhythmias in animals in which the sympathetic response is removed. An area of substantial progress in recent years has been the further delineation of the direct electrophysiological effects of the glycosides (194–197). The effects of DPH in reversing these electrophysiological actions of digitalis on cardiac Purkinje fibers remain to be determined. The relative importance of the neurodepressant effects as opposed to direct myocardial effects require further investigation.

The kinetic disposition of DPH is best described by an open two-compartment model (198, 199). Earlier studies assumed a first order elimination process from the central compartment but more recently a zero order process has been accepted assuming saturation of the hepatic biotransformation process for DPH (200). These and other authors have demonstrated dose-dependent changes in the plasma $t_{1/2}$ of DPH. The elimination of DPH doses in common clinical use is likely a mixed zero and first order process approaching first order at lower plasma concentrations. This may explain in part the various K_m and V_{max} values that have been reported for man (201, 202). With single or chronic oral dosing, the plasma $t_{1/2}$ (or more correctly, the t 50%) have averaged 22–28 hr (range 7–42) (198, 200, 203–207), whereas after iv dosing it has been considerably shorter in the order of 9–14 hr (range 3–29) (198, 204, 205, 207, 208). Less than 10% of an oral dose is excreted unchanged in the feces and less than 5% in the urine (209). Glazko (210, 211) has observed that the major metabolite 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH) acts as an inhibitor of DPH hydroxylation by competing for a binding site on the liver enzyme complex. This may be an explanation for the difference in

plasma $t_{1/2}$ after oral and iv dosing because of a greater "first pass" hepatic uptake of DPH with large amounts of HPPH being formed early after oral administration. However, total recovery of HPPH after oral or iv doses is similar (204).

The AVd for DPH in normal individuals has been estimated to be 0.64–0.72 liters/kg (202, 208) with a volume of the central compartment of 0.20 liters/kg (198, 208). The effect of cardiac failure on the disposition of DPH has not been studied. A larger AVd, lower plasma concentrations, and a shorter plasma $t_{1/2}$ have been observed in uremic subjects (202, 208, 212–214). The binding of DPH to plasma proteins of uremic subjects is reduced from the normal 92% at effective plasma drug concentrations (215, 216) to 43% (208, 213, 217). This is probably due to a qualitative change in the plasma proteins or uremic subjects (218). Although HPPH accumulates in patients with renal disease (209, 214), it does not displace DPH from plasma proteins (219). The antiarrhythmic effect of DPH in uremic subjects has not been studied. An increased incidence of adverse effects due to DPH has been observed in patients with decreased concentrations of serum albumin (220). The binding of DPH to plasma proteins is also significantly decreased in hepatic disease (221). The effect of displacement from plasma proteins by other drugs on the kinetic disposition of DPH has not been studied. However, certain drugs such as salicylate and phenylbutazone could cause significant displacement even at therapeutic concentrations resulting in a potentiation of the effects of DPH. The bioavailability and metabolism of DPH has been recently reviewed by Glazko (210, 211).

Bigger et al (222) observed that the majority of cardiac arrhythmias terminated by DPH were abolished at plasma concentrations of 10–18 mg/liter. In most subjects this range can be achieved by oral doses of 4–5 mg/kg per day with peak plateau concentrations observed after 6–12 days. Either single or divided daily doses may be used (203). However, a greater daily fluctuation in plasma concentration is observed with a single daily dose. More rapid attainment of plateau is obtained with a loading dose of 12 mg/kg in divided doses over the first day. A single bolus dose of 300 mg administered iv over several minutes can produce concentrations in the range associated with CNS toxicity (>20 mg/liter) followed by a rapid decrease to values below the minimum effective concentration after 20 min when the arrhythmia frequently recurs (204, 222). Doses greater than 20 mg/min iv should be avoided because of the higher incidence of cardiovascular toxicity associated with higher rates of infusion (222). After a single iv dose of DPH (300 mg over 15 min) peak drug content in the peripheral compartment is not observed until 30 min after the infusion has been terminated (Ogilvie, unpublished observations). It is likely that the clinical effect of DPH more closely parallels the amount of drug in the peripheral compartment rather than that in the central compartment, but this has not been adequately studied. Pharmacokinetic studies that take into account the high degree of plasma protein binding have not been carried out.

An area of active investigation concerns the effectiveness of antiarrhythmic drugs in the long-term prevention of arrhythmias. Some of the divergent results concerning the effectiveness of DPH in arrhythmia prophylaxis may be due in part to differences in doses used and plasma concentrations achieved. Because of the wide variations of steady-state DPH plasma concentrations between patients taking the

same dose of drug, any prophylactic study should take into account measurement of plasma drug content. Vajda et al (223) found that only one third of patients given either 300 or 400 mg/day of DPH had plateau plasma concentrations exceeding 10 mg/liter. Only those patients who had achieved these plasma concentrations had a significantly lower incidence of ventricular premature beats and a significantly lower mortality. A multicenter clinical study showing ineffectiveness of DPH as a prophylactic agent in postmyocardial infarction arrhythmias did not measure plasma drug content (220). DPH in chronic doses sufficient to produce blood concentrations between 10 and 20 mg/liter also improved survival following myocardial infarction in the farm pig (224), while no protection was afforded in dogs with coronary occlusion (107). Plasma drug concentrations were not measured in the latter study. On the other hand, Stone et al (225) found DPH to be uniformly ineffective in preventing recurrence of ventricular tachycardia in patients with a documented history of infarction despite the presence of adequate plasma concentrations. The relative effectiveness of DPH in preventing arrhythmias due to coronary artery disease thus remains to be determined.

PROPRANOLOL

The pharmacokinetic disposition of propranolol has been studied extensively. After iv administration of a single dose to man, the plasma concentration time curve is best described by an open two-compartment kinetic model with an alpha phase $t_{1/2}$ of 6 min, a beta phase $t_{1/2}$ of 2.5 hr, and a volume of distribution of 200 liters (226, 227). In other species (dog, monkey, and rat) the plasma $t_{1/2}$ is shorter (40 min) (227, 228). In man, over 95% of an administered dose is metabolized in the liver to at least seven metabolites, several having pharmacological activity (226, 229). After oral administration the major metabolite formed is 4-hydroxypropranolol (230) which has the same beta adrenoreceptor antagonist activity as propranolol (231) and is not measured by the usual assay method for the parent compound (226). This has complicated correlation of plasma concentrations with clinical effects during oral propranolol therapy. The beta phase plasma $t_{1/2}$ after single oral doses (3.5 hr) is slightly longer than that reported after iv doses, but there is considerable variation between individuals. A single oral dose less than 30 mg results in only trace plasma concentrations because of virtually complete hepatic extraction (232–236). There is a disproportionate increase in plasma concentrations during chronic administration of doses greater than 160 mg/day due to saturation of hepatic binding sites, altered hepatic extraction and metabolism of the drug, and a drug-induced decrease in hepatic blood flow (237, 238). A dose-dependent retardation of elimination has been observed, as the plasma $t_{1/2}$ after discontinuation of chronic oral doses of this size ranged from 3.4–6.0 hr. The effects of chronic dosing on the human myocardium are completely abolished 48 hr after cessation of propranolol therapy (239). In man, 91–96% of plasma propranolol is bound to proteins (227). In renal failure, the plasma $t_{1/2}$ of propranolol or 4-hydroxypropranolol is unaltered, but there can be significant retention of other metabolites and perhaps a degree of delayed gas-

trointestinal absorption after oral dosing (240). The AVd of propranolol may be reduced in patients with chronic renal disease (241).

There is less information correlating the pharmacokinetic disposition with effects due in part to the wide individual variability in plasma concentrations after specific doses and variability in response. After oral dosing, the plasma concentration required to produce a given reduction in exercise tachycardia has been stated to be between one half and one third of that required after iv administration because of the formation of 4-hydroxypropranolol (242, 243). Oral doses of 40–80 mg every 6 hr are required to produce plasma concentrations consistently greater than 0.07–0.11 mg/liter which will result in maximal or near maximal reductions in exercise-induced tachycardia. At these concentrations the doses of isoproterenol required to induce tachycardia are increased 30-fold (237, 242–245). Plasma propranolol values associated with suppression of ventricular premature beats in patients without a history of acute myocardial infarction or digitalis intoxication have been reported to range between 0.04 and 0.085 mg/liter and seldom over 0.150 mg/liter (246). These concentrations are 100 times less than those required in vitro to demonstrate "quinidine like" effects on isolated cardiac fibers (247–249) but are similar to the plasma levels required to produce β-blockade (242). This difference is further accentuated by the significant degree of binding to plasma proteins. Dextropropranolol, which lacks β-blocking activity, was ineffective at much higher concentrations in patients who had previously responded to racemic propranolol concentrations of less than 0.075 mg/liter. These results suggest that β-blocking activity is important for antiarrhythmic action.

Recent studies of Harrison et al (250) have demonstrated an increase in the functional refractory period of distal Purkinje fibers with a marked delay in the propagation of early premature beats in the presence of norepinephrine. Propranolol, in concentrations approximately 10 times greater than those required for β-blockade, abbreviated APD and, like lidocaine, had its greatest effect at the region of the gate resulting in attenuation of the spatial discrepancy of APD along the peripheral conducting system and between Purkinje and muscle. No effects were seen on phase 0 characteristics at these concentrations. They proposed that abbreviation of refractoriness rather than a "quinidine like" action is related to propranolol's antiarrhythmic action in vivo. However, it is not completely clear from their data whether the degree of shortening they describe is due only to a direct action of propranolol or partly to its β-blocking action. They do not present data showing the effects of the two agents administered together. Furthermore, Giotti et al (251) have shown that in the presence of β-blocking concentrations of propranolol, norepinephrine causes a lengthening of the plateau phase and an increase in APD in sheep Purkinje fibers. The lengthening induced by norepinephrine is antagonized by α-blocking agents, suggesting that this effect is mediated by α-receptors. Further studies are needed to clarify the action of propranolol on refractoriness.

Studies in man (252, 253) have not been able to demonstrate any significant effect on conduction or refractoriness in the His-Purkinje system and ventricles. Significant effects were noted only on AV nodal conduction and refractoriness. Similar

results were obtained in dogs with implanted electrodes at multiple sites within the conducting system (254). Consideration of these human, animal, and isolated tissue studies suggest very strongly that the direct "quinidine like" actions of propranolol are not relevant to the antiarrhythmic actions of this drug in man. In fact, the use of "quinidine like" in reference to propranolol's action is a misnomer, and its use should be abandoned because the direct actions of propranolol are quite different from those of quinidine, particularly on APD in Purkinje fibers and ventricular muscle.

CONCLUSION

The pharmacokinetic disposition of most antiarrhythmic drugs can be best described by an open two-compartment model with the antiarrhythmic effects best correlated with drug content in the peripheral compartment. Maximal drug effects occur only when peak drug content at the site of drug action has been achieved. The time to achieve equilibrium between the central compartment and the tissue compartment depends upon the rate constants for drug distribution. Because of the high perfusion rate of the heart, equilibrium between concentrations of most drugs in the plasma and the myocardium usually occurs within one half hour of iv drug administration. The importance of loading doses of these agents has been long recognized and dose schedules have been developed in order to rapidly achieve and maintain therapeutic concentrations. Most agents in clinical use have a narrow therapeutic/toxic ratio underlining the importance of knowledge of volumes of distribution as well as the routes and rates of elimination from the body. Knowledge of the disposition of these drugs is essential for a proper assessment of their pharmacologic effects not only in man but also in animal models and in vitro systems. Controversial results concerning their electrophysiologic actions are attributed in part to disagreement over which drug concentrations in vitro are comparable to effective plasma concentrations in man and to lack of information on effective drug content in myocardial tissues. Interpretation of the electrophysiological actions is also complicated by several factors: 1. comparable concentrations of drug exert different effects on electrical activity of fibers from different parts of the heart; 2. abnormal or diseased tissues respond differently from normal tissues; 3. small changes in ionic concentrations can markedly influence tissue response, and, 4. important actions of the drug may be absent in experimental models. There is little information on electrophysiological interactions of drug combinations. One cannot assume that drugs with certain electrophysiologic properties will produce specific effects when administered together.

We have not attempted to reclassify these drugs based on their electrophysiological actions, as we feel there is insufficient information on which to base a meaningful classification. Two actions appear to be common to all the drugs. All five are effective in suppressing automaticity in Purkinje fibers. However, there is no information on the relative ability of each agent to depress automaticity. Only lidocaine has been shown to alter the ionic conductances responsible for slow diastolic depolarization. Perhaps lidocaine is the agent of choice when enhanced automaticity is

the likely mechanism of a ventricular arrhythmia. A second action that may eventually be found common to all of the drugs is the ability to produce uniformity of action-potential duration and refractory period throughout the ventricular conducting system. This has already been demonstrated for lidocaine, procainamide, quinidine, and propranolol. Agents that abbreviate action-potential duration have their greatest effect on the longest Purkinje fiber action potentials. Agents that prolong action-potential duration have a tendency to lengthen the shorter Purkinje fiber and ventricular muscle action potentials without altering total action-potential duration of the gate cells. The importance of such an action in terminating reentrant arrhythmias will have to await future studies.

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