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Can Antiarrhythmic Agents be Selected Based on Mechanism of Action?

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Contents

Abstract

When selecting an antiarrhythmic agent the clinician needs to be able to accurately predict the probability that a particular drug will serve its intended purpose in a given patient. This is difficult because of the complexity of variables which govern the relationship between drug administration and clinical outcome. The efficacy of a drug may potentially be predicted from its mechanism of action. At least two classifications of antiarrhythmic agents based on mechanism of action have been proposed. The Vaughan Williams classification is based on the predominant electrophysiological effects of a drug on the action potential. In the Sicilian Gambit approach, a number of potential targets ('vulnerable parameters') for drug action are identified and antiarrhythmic drugs or substances that affect cardiac electrophysiology are characterised by their actions on each of these. The usefulness of these classification systems in predicting antiarrhythmic drug efficacy are limited. Furthermore, in the Vaughan Williams classification not all drugs in the same class have identical effects, whereas some drugs in different classes have overlapping actions. The Sicilian Gambit requires in-depth knowledge regarding cellular and molecular targets of antiarrhythmic agents which may make it intimidating or simply impractical for regular clinical use. Surrogate measures such as 24-hour Holter monitoring and programmed electrical stimu-

lation have been used to predict anti-arrhythmic drug efficacy. However, studies such the Cardiac Arrhythmia Suppression Trial (CAST) have shown that suppression of ventricular ectopy on Holter monitoring does not necessarily correlate with improved survival and may in fact be dangerous. Conversely, studies using programmed electrical stimulation to assess drug effect on variables such as tachycardia inducibility, refractory period and ventricular tachycardia cycle length show that suppression of tachycardia inducibility, prolongation of refractory period and prolongation of ventricular tachycardia cycle length, are all associated with reduced recurrence of tachycardia and possibly improved survival. The most practical use of the current classification systems applied to antiarrhythmic agents may be in their ability to predict with reasonable accuracy, the risk and type of proarrhythmia based on the mechanism of action of an agent.

When selecting an antiarrhythmic agent, clinicians generally aim to choose a drug which would achieve efficacy while avoiding adverse effects. The task of accurately predicting the probability that a particular drug will serve its intended purpose in a given patient is difficult. In this, as in many other situations, physicians need to extrapolate from their general knowledge of particular types of patients, the rhythm disturbance in question, and the properties of the antiarrhythmic drug to be prescribed, to the particular circumstances of the individual patient being treated. The conceptual problem of applying information gathered in many patients, whose conditions do not completely resemble those of the patient at hand, to individual patients is not peculiar to the treatment of arrhythmias. However, arrhythmia therapy is complicated by the potential catastrophic consequences of recurrence of the rhythm abnormality and the unpredictable timing of recurrences of the index arrhythmia. Because of this discontinuous and sometimes dangerous nature of recurrences of arrhythmias, the usual therapeutic paradigm of administering a treatment, assessing the results and modifying the treatment based on the clinical response (which can be easily applied to hypertension or osteoarthritis therapies for example) may, therefore, not be easily applied to patients with arrhythmias. Furthermore, as some episodes may be asymptomatic, there may not always be a readily observable event to indicate the efficacy of a drug regimen. Therefore, it is important for clinicians to make as accurate a prediction as possible of whether a drug in a particular patient at a particular time will or will not be effective. 'Effectiveness' needs to be defined according to the clinical circumstance, and may include prevention of recurrent arrhythmias, as in patients with sustained ventricular tachycardia (VT); improvement in symptoms and quality of life (as in atrial fibrillation); or success at preventing sudden death (as in prophylactic studies in patients at high risk of cardiac arrest).

The variables which govern the relationship between drug administration and clinical outcomes are complex. As illustrated in figure 1, they can be broken down into pharmacokinetic variables (which govern the relationship between drug dose and the concentration achieved by that dose at the effector site) and pharmacodynamics (which govern the relationship between effector site concentration and cellular effects). These lead to physiological effects which represent the responses of the tissues affected by the drug as modulated, for example, by interacting drugs or neurohumoral variables, and finally result in a particular clinical outcome. This outcome may, in turn, be modulated by the severity of the underlying illness, time-dependent alterations in the substrate under treatment, and factors external to the patient (for example, the probability of being resuscitated from a serious arrhythmia). It can be readily seen that predicting a particular clinical outcome from a particular drug dose is subject to extraordinary variability and complexity.

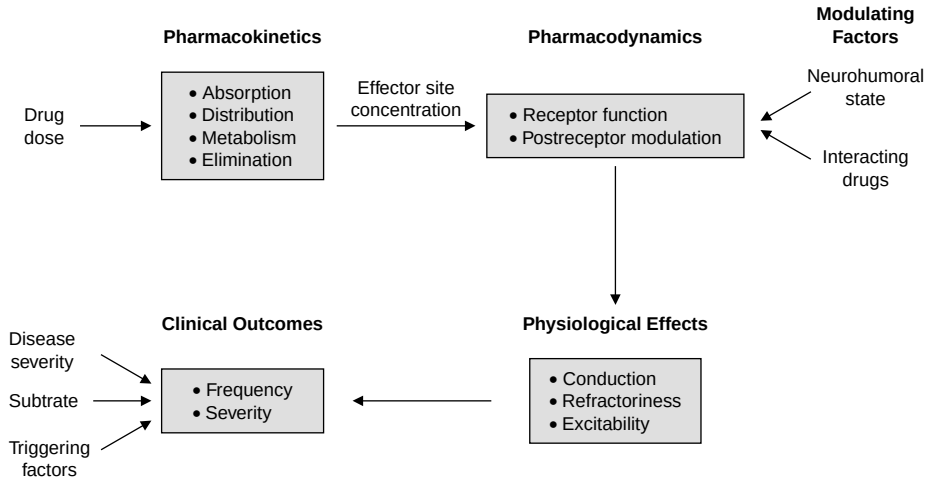

Fig. 1. Predicting antiarrhythmic drug effect.

1. Predicting Antiarrhythmic Drug Efficacy

1.1 Based on Results of Clinical Trials

Antiarrhythmic drug efficacy may be predicted from previous studies which measured clinical effect in a particular subset of patients. If, for example, a drug was shown to be useful in patients with atrial fibrillation, or in preventing sudden cardiac death, then it would be expected, on average, that this particular therapy would be effective in the patient in question. The end-points used in such studies may have been the prevention of sudden death, a decrease in arrhythmia frequency, or other end-points.

Such 'empirical' therapy based on clinical trial results (preferably blinded, randomised, placebo-controlled trials), is clearly the most scientifically valid test of the clinical efficacy of a therapy. However, there are considerable limitations to extrapolating such clinical trial results to individual patients. Patients studied in clinical trials may not be fully representative of the average patient, or of the patient in whom treatment is contemplated. Studies relevant to the patient at hand may not be available or may not be adequate. The dose(s) administered in the clinical trial may not be tolerated, and the effect of a lower dose is often not known. The end-points evaluated in the clinical trials, for example, time to first recurrence of an arrhythmia event, may have unclear relevance to the clinical end-points most often sought by patients and physicians, for example, the total number of severely symptomatic recurrences in a given time-frame. Although time to first recurrence is the most often evaluated end-point for discontinuous outcomes such as arrhythmia events, this end-point relies on the implicit assumption that recurrences are randomly distributed over time. There is considerable evidence that arrhythmia recurrences, at least for ventricular arrhythmias, instead occur in 'clusters',[1,2] and that the true test of drug efficacy requires long term efficacy tests instead of discontinuing the drug at the first recurrence. In addition, although there is ample scientific justification for the primary analysis in clinical trials to be based on 'intention to treat' as opposed to efficacy analysis, there is greater clinical interest in the effectiveness of a drug provided that it can be administered without adverse effects, since the ultimate test of a drug from a clinician's perspective is whether it will be effective if it is taken reliably by the patient.

1.2 Based on the Mechanism of Action of the Antiarrhythmic Drug

1.2.1 The Vaughan Williams Classification

The conventional classification system of antiarrhythmic drugs, initially proposed by Vaughan Williams[3] and later modified,[4-7] was based on their predominant electrophysiological effects on the action potential recorded largely from Purkinje fibres *in vitro* (table I). The slowing of conduction by Na^+ channel blockade, with or without influence on repolarisation, was termed class I action, and blocking of sympathetic stimulation was designated class II action, as typified by β blockers. The class III designation was applied to the prolongation of action potential duration or refractoriness, as exemplified by the prototype drugs sotalol and amiodarone. However, both these latter agents have other properties that were initially thought to be of subsidiary electrophysiological importance. Ca^{2+} channel-mediated effects, as demonstrated by verapamil, were termed class IV action.

Table I. Vaughan Williams classification of anti-arrhythmic mechanisms

Class	General mechanism	Examples
I	Na^+ channel blockade	
Ia	↓↓ phase 0 upstroke rate	Quinidine
	Delay conduction	Procainamide
	Prolong repolarization	Disopyramide
Ib	Little effect on phase 0 in normal tissue	Lidocaine Mexiletine
	↓ phase 0 upstroke rate in abnormal tissue	Tocainide Phenytoin
	Shorten repolarisation or little effect	
Ic	↓↓↓ phase 0 upstroke rate	Flecainide
	Markedly slow conduction	Propafenone
	Slight effect on repolarization	Encainide
		Moracizine
II	β-blockade	Propranolol
		Metoprolol
		Esmolol
		and many others
III	Marked prolongation of repolarization	Amiodarone Sotalol
		Bretylium
		Ibutilide
		Dofetilide
		Azimilide
		Tedisamil
IV	Ca^{2+} channel blockers	Verapamil
		Diltiazem

↓ = slight decrease; ↓↓ = moderate decrease; ↓↓↓ = marked decrease.

Although the Vaughan Williams classification is physiologically based, it is a hybrid, such that classes I and IV represent blockade of ion channels; class II, blockade of receptors; and class III, a change in an electrophysiological variable (the action potential duration). In addition, many of the antiarrhythmic drugs have actions relating to more than one class or subclass in the classification, a striking example being oral amiodarone which exhibits antiarrhythmic properties from all Vaughan Williams classes.[8] Some antiarrhythmic drugs have metabolites with a different class of action from that of the parent drug, for example, procainamide has class Ia mechanism of action whereas its metabolite, *N*-acetylprocainamide, has little effect on the maximum velocity of phase O (upstroke) of the action potential (V_{max}) of Purkinje fibres but instead prolongs the duration of the action potential, thus having properties of class III drug action.[6] Furthermore, not all drugs in the same class have identical effects whereas some drugs in different classes have overlapping actions. The classification (excluding class II) is primarily based on the effects of drugs on electrophysiological characteristics of isolated, normal cardiac tissues. However, in diseased tissues, where arrhythmias are likely to arise, the electrophysiological milieu is likely to be altered by other variables, for example, interacting drugs, electrolyte abnormalities (see fig. 1), and therefore the action of drugs may be modified as well.

The Vaughan Williams classification has been used to broadly categorise drug actions and relate these actions to clinical outcomes in large clinical trials. For example, clinical trials of drugs with predominantly class I mechanism of action in patients post-myocardial infarction show no benefit or harm compared with placebo.[9] Theoretical and experimental studies indicated that re-entry around

an anatomical or functional obstacle is the cause of most ventricular tachycardias. Prolongation of action potential duration and refractoriness (class III mechanism of action) was thus expected to prevent serious ventricular arrhythmias and reduce mortality. However, clinical trials with agents having 'pure' class III effects have shown no benefit (dofetilide)[10] or even harm (*d*-sotalol).[11] Thus, although the Vaughan Williams classification may guide the clinician in selecting an antiarrhythmic agent based on its physiological mechanism of action, it may fail to help predict efficacy.

1.2.2 The Sicilian Gambit Approach

Another approach to predicting antiarrhythmic drug efficacy is based on the Sicilian Gambit.[12] In this approach, a number of potential targets for drug action are identified and include various ion-conducting channels (Na^+, K^+, Ca^{2+}, Cl^-), receptors (α-, β-adrenergic, muscarinic, purinergic), and pumps ([Na^+/K^+]-ATPase). All antiarrhythmic drugs or substances that affect cardiac electrophysiology are characterised by their actions on each of these channels, receptors or pumps. Actions may be activation or inhibition with varying kinetics and intensity. The Sicilian Gambit attempts to identify the mechanisms of a particular arrhythmia, determine the 'vulnerable parameter' of the arrhythmia most susceptible to modification, define the target most likely to affect the vulnerable parameter, and then select a drug that will modify the target (fig. 2).

This approach may be useful in some cases, for example, the use of β blockers for arrhythmias induced by exercise or ischaemia; the administration of drugs acting directly on the atrioventricular (AV) node (such as adenosine and negatively dromotropic calcium antagonists); for arrhythmias where the AV node is part of the circuit; and possibly in situations where the arrhythmia is caused by a single ion channel abnormality, such as the use of mexiletine to shorten the QT interval in patients with the LQT3 (*SCN5A* gene defect, coding for an abnormal Na^+ channel) form of the congenital long QT syndrome.[14]

Unfortunately, the precise mechanisms of arrhythmias and the clinical consequences of actions on particular channels or receptors are poorly understood. In particular, the subtle and delicate interaction between the trigger for an arrhythmia and its maintenance is usually not well understood. A critical issue is whether the effect of a drug on a particular arrhythmia can be determined by its action on a single electrophysiological parameter, such as the block of a single ionic current, receptor or pump. The available data suggest that the net action of an antiarrhythmic agent may depend on the modulating effect(s) of variables such as neurohumoral state and interacting drugs (fig. 1). For example, antiarrhythmic drug effects are antagonised by catecholamine or sympathetic neural stimulation.[15,16] As a result, β-adrenergic blockade may have additive benefit combined with any antiarrhythmic drug, particularly in states with high adrenergic tone such as sustained VT. This is supported by substudy analysis of both the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) and the European Myocardial Infarct Amiodarone Trial (EMIAT), which showed substantial additive benefits of amiodarone and β blockers compared with amiodarone alone.[17] An additional complicating factor in assessing drug effects or ionic currents is that these currents may be altered in diseased hearts. For example, heart failure or hypertrophy may lead to down regulation of repolarising currents [e.g. transient outward current (I_{to})], and is associated with action potential prolongation.[18] Most studies of drug effects on ionic currents are performed on tissues from nonfailing hearts, and both the magnitude and nature of drug effects in states of altered ion channel function may differ from their effects in healthy cells and tissues.

The targeting of 'vulnerable parameters' on a rational basis with drugs with known properties in terms of the Sicilian Gambit may be an unrealistic goal at present. Furthermore, the complexity of this approach requires in-depth knowledge regarding cellular and molecular targets of antiarrhythmic agents which may make it intimidating or simply impractical for regular clinical use. Nevertheless, the Sicilian Gambit is a useful conceptual framework for describing the currently known effects of

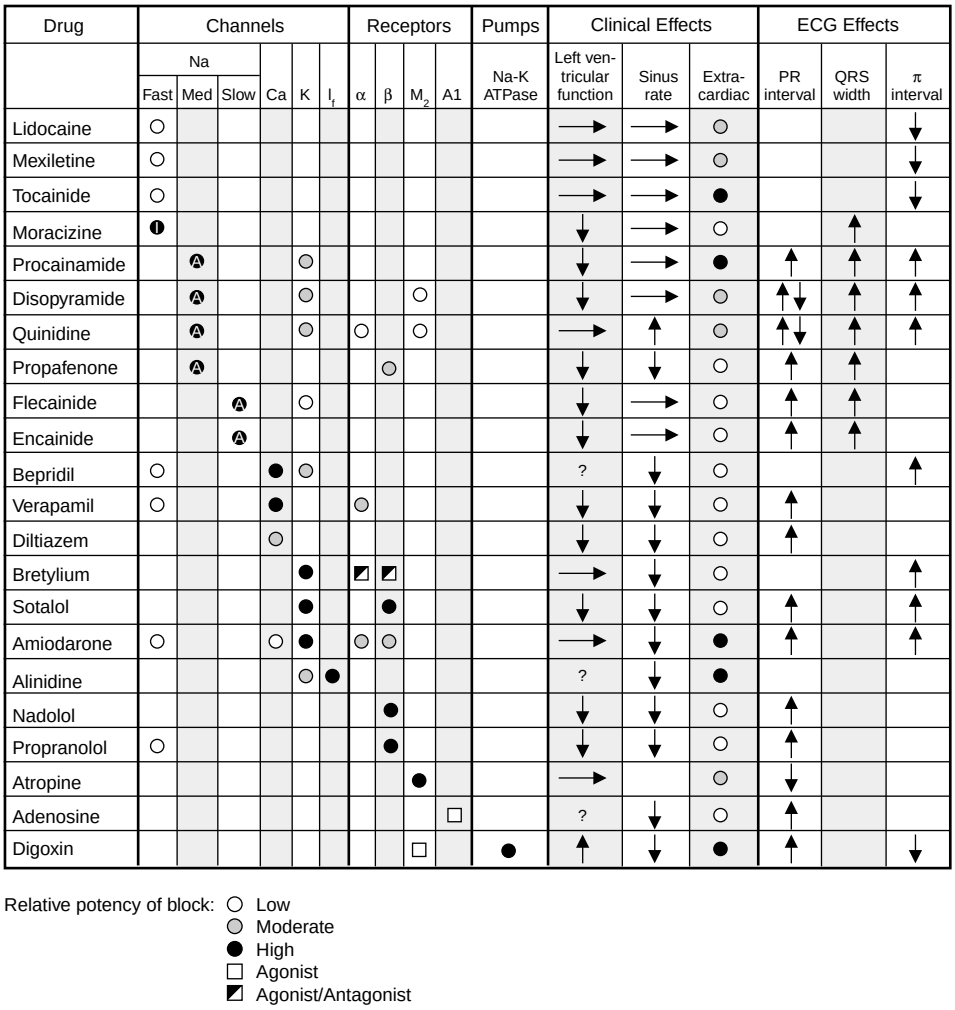

Fig. 2. Actions of antiarrhythmic drugs (reproduced from Rosen,[13] with permission). **A** = activated state blocker; **I** = inactivated state blocker; → = no effect; ↑ = increase; ↓ = decrease; **?** = uncertainty concerning effect.

antiarrhythmic drugs and aids in the understanding of the multiplicity of drug actions.

2. Surrogate Measures to Predict Antiarrhythmic Drug Efficacy

A potentially complementary approach to predicting drug efficacy employs the use of surrogate measures, which assess the effect of the drug on variables other than the clinical occurrence of the arrhythmia in question. Tests such as Holter monitoring and programmed electrical stimulation (PES) give additional information which can be used to help predict if a drug will be effective. Conceptually, if the antiarrhythmic drug has particular effects on some arrhythmia-related variable, it may be predicted with greater confidence that the drug will prevent clinical recurrences of the arrhythmia to be treated.

In the 1980s, frustration with empirical drug therapy for sustained ventricular arrhythmias led to the development of two techniques for predicting the response to long term therapy on the basis of acute responses in serial drug testing. These techniques were based on arbitrary degrees of suppression of either spontaneously occurring arrhythmias documented on 24-hour Holter monitoring or those inducible by PES of the heart. The fundamental premise was that drug-induced suppression of either the artificial triggering of the clinically relevant arrhythmia, as in the case of PES, or suppression of a spontaneous but different arrhythmia, as in Holter monitoring, was predictive of long term responses. It is important to note that arrhythmias elicited by PES and those documented by Holter monitoring might at best define the arrhythmogenic potential of a given substrate at the time the test is performed. The 'vulnerable substrate' is known to be subject to the influences of a wide variety of physiological and pathophysiological changes. For example, major anti-arrhythmic actions of drugs are often markedly attenuated by catecholamines.[16,19] Temporal fluctuations in adrenergic tone might be expected to directly or indirectly alter the net efficacy of anti-arrhythmic or anti-fibrillatory compounds. Moreover, the efficacy of anti-arrhythmic compounds varies with the severity of cardiac disease and ventricular dysfunction.[20] Drugs are both more likely to prevent VT inducibility and recurrence of spontaneous arrhythmias in patients with less severe left ventricular (LV) dysfunction.[20] In addition, the proarrhythmic action of most antiarrhythmic agents, especially class I drugs, increases with increasing severity of cardiac disease, and there is a corresponding fall in efficacy.

It was long believed that a marked reduction in the frequency of premature ventricular complexes (PVCs), or near-complete or complete elimination of runs of nonsustained VT on Holter monitoring, would confer a high likelihood of a drug effectively preventing arrhythmia recurrence. The results of the Cardiac Arrhythmia Suppression Trial (CAST), in which antiarrhythmic drug therapy with encainide, flecainide, or moracizine (moricizine) resulted in higher mortality than therapy with placebo despite effective ectopy suppression,[21] suggest that this approach is ineffective and may be dangerous. Nevertheless, it has not been proven that the paradigm of ventricular ectopy suppression is invalid for all drugs and all patients, simply that it is not applicable for particular drugs, and in all likelihood, drugs with class I antiarrhythmic action. For example, patients in whom ectopy was suppressed by sotalol had a significantly higher probability of having inducibility of VT at electrophysiological study suppressed and of remaining free of their arrhythmias, compared with patients in whom PVCs were not eliminated.[22] Observational evidence suggests that in patients with persistent nonsustained VT despite amiodarone therapy, the recurrences of arrhythmias are more frequent than in those in whom the ectopy is eliminated, although the tolerance of VT may be improved as a result of slowed tachycardia rates. The prognostic value of Holter monitoring during treatment of sustained VT with amiodarone is controversial. Some studies have reported improved prognosis in patients with significant suppression of premature ventricular complexes during amiodarone therapy,[23,24] whereas others have shown no such relationship.[25-27]

2.1 Correlating Efficacy with Effects on Electrophysiological Variables

2.1.1 Inducibility at Electrophysiological Study

Inducibility of VT at electrophysiological study as a method to predict efficacy of an antiarrhythmic drug has possibly fallen out of favour, but has been extensively studied. Original observations by Mason et al.[28] suggested that patients in whom inducibility of sustained VT at electrophysiological study was suppressed by the prior administration of an antiarrhythmic drug had a markedly lower likelihood of VT recurrence or sudden death than patients in whom a drug failed to suppress inducibility but who continued to take the drug.[28]

The usefulness of this electrophysiological paradigm was questioned by the results of the Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) trial, in which patients were

randomised to antiarrhythmic drug therapy selected ('predicted') on the basis of the invasive method (electrophysiological studies) or the non-invasive method (Holter monitoring combined with exercise testing). Results showed similar predictive accuracy between the two methods of assessing drug efficacy with respect to arrhythmia recurrence.[29] However, high rates of recurrence with both methods of efficacy prediction in this study (25 to 40% on the average) may have been in part due to the predominant use of drugs with primarily class I mechanism of action. In contrast, in a smaller study with up to 10 years of follow-up, Mitchell and colleagues[30] showed that treatment directed by the electrophysiological study approach led to significantly lower risk of VT or ventricular fibrillation (VF) recurrence than the Holter monitoring approach.[30]

Therefore, it is at least plausible that there is information content in the electrophysiological study result which may help predict the likelihood of drug efficacy. In addition, the clinical outcome may be predicted by the specific rhythms induced, not only the binary outcomes of 'inducible' or 'not inducible'. Waller et al.[31] studied a large group of patients, most of whom were on amiodarone, in whom VT was inducible and not modified, inducible but modified (i.e. with a longer cycle length and better haemodynamic tolerance), or non-inducible. In their study, patients who still had inducible but modified VT had equally good outcomes, with respect to freedom from sudden death, as patients who were non-inducible, and substantially better outcomes than patients who had no modification of inducibility. In a study by Rodriguez et al.,[32] patients in whom sustained monomorphic VT was persistently inducible following amiodarone, or in whom there were no inducible arrhythmias, both had substantially better survival than the smaller subgroup in whom VF was induced at electrophysiological study on amiodarone. Two other studies reported that if the cycle length of induced VT in patients receiving amiodarone was slowed by more than 100ms and if the arrhythmia was haemodynamically stable and well tolerated, the survival rate was identical to that observed among patients in whom arrhythmia was no longer inducible.[33,34] Similarly, patients with spontaneous and inducible VT whose induced VT was slowed by the combination of sotalol with quinidine or procainamide, had as good an outcome as those in whom VT was rendered non-inducible.[35]

These studies suggest that clinical outcomes can be predicted not only on the basis of whether arrhythmias are inducible or not, but the type and the haemodynamic tolerance of the arrhythmias induced.

2.1.2 Electrophysiological Parameters

Electropharmacological studies of VT have demonstrated the importance of lengthening of repolarisation and prolongation of refractoriness in predicting a favourable response to drug therapy.[36-39] In contrast to the more empirical approach of administering drugs which generally prolong refractoriness, these studies examine the benefits of class III action therapy, in particular, in those patients in whom refractoriness is actually prolonged, and relate efficacy to the extent of refractoriness prolongation. Drugs that prolong cardiac refractoriness by delaying repolarisation, such as sotalol or amiodarone, have been shown to be superior to sodium channel blocking agents (which primarily slow cardiac conduction) for management of recurrent VT or sudden death.[40,41] Suppression of VT induction at electrophysiological study is correlated with relatively greater prolongation of refractoriness, whereas the extent of conduction slowing (estimated clinically from QRS duration) is not related to inducibility of VT.[38,39,42,43] In patients treated with sotalol plus quinidine or procainamide, greater prolongation of refractoriness was associated with a smaller risk of VT inducibility and slower rates of VT where it was inducible.[35] An increase in the ventricular effective refractory period on amiodarone correlates with an increase in VT cycle length.[44,45] Thus, prolonging refractory periods slows the rate of VT, and with certain drugs (e.g. amiodarone) or drug combinations (e.g. sotalol plus quinidine or procainamide), refractoriness is the best indicator of VT cycle length during treat-

ment. Slowing of VT may be an important facet of antiarrhythmic therapy, making the arrhythmia more likely to be tolerated haemodynamically.[31,33,34]

Although this review deals mainly with ventricular arrhythmias, the above principles appear to apply to common atrial arrhythmias as well. In the atria, efficacy in conversion of atrial flutter with ibutilide has been shown to be correlated with an increase in atrial refractory period and decreased conduction velocity in the isthmus, compared with propafenone which predominantly depressed conduction velocity, or amiodarone, which had fewer effects on atrial refractory period and conduction velocity.[46] In another study, enhanced conversion efficacy of ibutilide compared with procainamide in atrial flutter was correlated with a relatively greater prolongation of atrial monophasic action potential duration than atrial cycle length.[47] Furthermore, conversion of atrial fibrillation by ibutilide was enhanced by a longer mean atrial cycle length or monophasic action potential duration at baseline during atrial fibrillation.[48] These data suggest that effect on electrophysiological variables may also be useful clinically to predict efficacy in conversion of atrial arrhythmias.

2.1.3 Use-Dependence and Reverse Use-Dependence

If prolongation of refractoriness predicts a favourable response to drug therapy, one would expect that all agents with class III mechanism of action should be effective at suppressing arrhythmias and improving mortality. However, studies such as Survival with Oral *d*-sotalol (SWORD)[11] and Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND)[10] have shown us that this is not uniformly the case. The lack of uniformity of class III effect in predicting antiarrhythmic efficacy may be due to reverse use-dependence, a phenomenon whereby a drug exerts greater effects at slow rates, with a progressive loss of antiarrhythmic effect at rapid rates,[48] or loss of efficacy with sympathetic stimulation.[16] If the former were true, we would expect that drugs or drug combinations which result in attenuation of reverse use-dependence should be more effective. In support of this, amiodarone shows a lack of reverse use-dependence.[44] The combination of sotalol, which prolongs ventricular repolarisation and has β blocker properties, and quinidine or procainamide, which prolong refractoriness and slow cardiac conduction modestly, has been shown to be useful in suppressing VT inducibility and arrhythmia recurrence.[35] Reverse use-dependence, as judged by an attenuation of refractory period prolongation with successive extrastimuli, which is characteristic of sotalol alone, was attenuated by its combination with quinidine/procainamide[49] (fig. 3). It is possible that block of a slowly activating outward potassium current (I_{Ks}) may result in action potential and refractoriness prolongation which is less attenuated at fast rates (attenuated reverse use dependence) than block of a more rapidly activated repolarising current (I_{Kr}).[50] For example, azimilide, a drug which blocks both I_{Kr} and I_{Ks} currents, loses less of its efficacy at rapid rates than dofetilide, an I_{Kr} blocker, in a model of atrial arrhythmias.[51] Combining β blockers with drugs that prolong ventricular refractoriness appear to confer increased benefit over the antiarrhythmic drug alone. For example, adding β blockers to amiodarone increases the reduction in mortality (over placebo) in the CAMIAT and EMIAT studies[52] and increases the likelihood of non-inducibility of sustained VT at electrophysiological study.[49] Sympathetic activation, or administration of catecholamines experimentally, augments the I_{Ks} current which can contribute to loss of class III effects especially at high rates of stimulation.[53] *In summary*, drugs (or drug combinations) which can be shown *in vivo* to maintain their effects on refractoriness at rapid rates may be expected to be more effective than those which lose their class III effects as rates increase.

Other surrogate measures of predicting antiarrhythmic drug efficacy have been proposed. For example, QT interval dispersion during antiarrhythmic drug therapy has been shown to be an independent predictor of antiarrhythmic drug response assessed by electrophysiological studies in patients with spontaneous VT or VF late after myocardial infarction.[54] Suppression of VT inducibility by

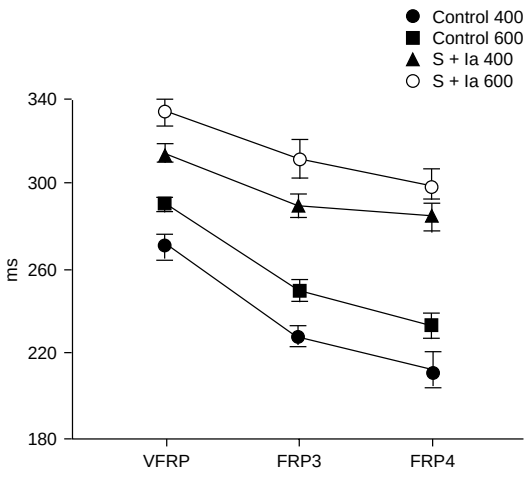

Fig. 3. Effect of sotalol plus a class Ia agent in combination on ventricular refractoriness in humans. 32 patients with spontaneous sustained ventricular tachycardia (VT) were studied using programmed electrical stimulation (PES) in the drug-free state and after treatment with sotalol and a class Ia agent (quinidine or procainamide). The curves show ventricular functional refractory period (VFRP, V1 upstroke to V2 upstroke) and shortest intervals for the V2 to V3 upstroke (FRP3) and V3 to V4 upstroke (FRP4) on no antiarrhythmic drug regimen and cycle lengths of 400ms (control 400) and 600ms (control 600); and during therapy with sotalol and a class Ia agent at cycle lengths of 400s (S + Ia 400) and 600ms (S + Ia 600). Progressive shortening of FRP with repetitive extrastimuli, seen in the control groups, is attenuated with therapy (reproduced from Lee et al.,[49] with permission).

sotalol is correlated with shortening of the signal-averaged QRS duration whereas persistent inducibility correlates with lengthening of this parameter.[55,56]

In summary, the electrophysiological effect of a drug may be used to predict clinical efficacy more reliably than can be done by mere knowledge of the mechanism of action of a drug.

3. Can Adverse Effects be Predicted Based on Mechanism of Action?

The results of studies such as CAST,[21] Stroke Prevention in Atrial Fibrillation (SPAF)[57] and SWORD,[11] and meta-analyses of agents with class I mechanism of action[9,58] have taught us that therapy with antiarrhythmic drugs is not without its risks, that of proarrhythmia being of paramount importance. Proarrhythmic reactions can take a variety of forms, including an increased number of premature atrial or ventricular complexes, an increase in the ventricular response rate to atrial fibrillation or atrial flutter, the induction or facilitation of sustained ventricular tachyarrhythmias, and the alteration of ventricular tachyarrhythmia properties such that they become very resistant to direct current electrical cardioversion. Perhaps the most disturbing manifestation of proarrhythmia is one in which overt tachyarrhythmias may not even be evident, specifically, an increase in the mortality rate in treated patients. In studies involving patients after myocardial infarction or with atrial fibrillation, an excess in sudden and/or presumed arrhythmic death rates were responsible for increases in mortality, pointing directly to proarrhythmic mechanisms.[59]

The mechanisms of proarrhythmia are now better understood, and in fact can be predicted to a reasonable extent based on the mechanism of action of a drug, either at a physiological or cellular level. Postulated mechanisms include excessive slowing of conduction, and excessive action potential prolongation.[59,60] A major effect of Na^+ channel blockade is conduction slowing, which is usually more prominent in diseased or abnormal tissue than in normal tissue. In patients with ventricular scarring due to remote myocardial infarction (a substrate with depressed conduction), the addition of a sodium channel blocker may facilitate re-entrant VT by further depressing conduction especially in the presence of superimposed ischaemia. Such VT can manifest as incessant very wide complex VT which is resistant to electrical cardioversion. Similarly, in patients with atrial flutter, conduction slowing by sodium channel blocking drugs can slow the flutter rate. With slowed atrial flutter, 1 **:** 1 AV nodal conduction may result in a net (apparently paradoxical) increase in ventricular response.

Organic heart disease, particularly in association with coronary artery disease, was found to be an important risk factor for the development of pro-

arrhythmias with class Ic antiarrhythmic drugs.[61] In canine models of myocardial infarction, preferential conduction slowing in the ischaemic zone facilitated the occurrence of circus movement tachycardia, with block or very slow conduction in the direction transverse to fibre orientation causing re-entry.[62-64] Acute myocardial ischaemia produces a variety of important electrophysiological derangements, including profound alterations in excitability and impulse propagation, that greatly predispose to malignant ventricular tachyarrhythmias.[65,66] There is a great deal of evidence which suggests that sodium channel blockers may promote ischaemic VF by their effects on cellular excitability and impulse propagation.[67-70] It has also been suggested that spatially heterogeneous effects on action potential repolarisation may result from the combination of acute ischaemia and Na^+ channel blockade, and contribute significantly to the genesis of ventricular tachyarrhythmias.[71] Acute ischaemia may be the central factor promoting class I drug-associated mortality in studies like CAST. This speculation is supported by an analysis of nonfatal ischaemic events and sudden death in CAST,[72] which found that patients treated with encainide or flecainide had the same number of end-point events as patients receiving placebo when nonfatal ischaemic events and sudden death were combined as end-points. The excess of sudden death in patients receiving active treatment was accounted for by a reduced presentation of nonfatal ischaemic events, suggesting that encainide and flecainide transformed what would otherwise have been nonfatal acute myocardial ischaemia into lethal ischaemic arrhythmias.

Action potential prolongation may be proarrhythmic by generating triggered arrhythmias arising from early afterdepolarisations (EADs),[73] contributing to increased intracellular Ca^{2+} which then causes triggered automaticity from delayed afterdepolarisations (DADs),[74] and accentuating repolarisation heterogeneity across the ventricular wall and in the Purkinje system promoting the development of re-entry.[75] Our understanding of the cellular mechanisms that cause EADs has improved recently. Studies demonstrating the dependence of EADs on the availability of L-type (slow) Ca^{2+} current[73,76] support a central role for L-type Ca^{2+} channels as the charge carrier for the depolarisation of plateau EADs. A proposed model for induction of plateau EADs involves two overlapping phases: *phase 1* is the conditioning phase where the action potential plateau must lengthen within a range of voltages to permit, in *phase 2*, the time- and voltage-dependent recovery from inactivated to closed states of L-type Ca^{2+} channels, and (re)-opening of a small portion of these channels within their 'window' voltage range to initiate the EAD depolarisation phase.[77] This hypothesis is supported by direct demonstration of L-type Ca^{2+} 'window' currents in isolated heart.[78-80] This highly arrhythmogenic current can arise from genetically normal and drug-unmodified Ca^{2+} channels that are reactivated by another intervention (e.g. I_{Kr} block) that prolongs action potential duration. Alternatively, any channel, exchanger or pump that influences action potential duration can modulate the EAD conditioning phase.

EADs are easily induced with bradycardia or following pauses, and are thought to initiate torsades de pointes, the most common proarrhythmic syndrome for drugs whose major effect is the prolongation of cardiac action potentials, specifically antiarrhythmic agents with class Ia and class III mechanism of action. Isochronal mapping studies in experimental animal models have shown that drug-induced nonsustained torsades de pointes is consistently initiated first as subendocardial focal activity, with subsequent beats due to re-entrant excitation in the form of rotating single wavefronts.[81] Termination of the rhythm was usually associated with the bifurcation of a wavefront into two fronts with functional block present. Thus, the clinical arrhythmia of torsades de pointes may be initiated by triggered automaticity from EADs but sustained by a re-entrant mechanism.

Patients with a history of heart failure or ventricular hypertrophy appear to be at increased risk of proarrhythmia from excessive action potential prolongation, possibly because of the disease-induced

action potential duration prolongation which predisposes to further prolongation in the presence of K^+ channel blockade, especially at slow heart rates.[18]

The rate-dependent effects of action potential prolonging drugs may exacerbate the risk of EADs, triggered activity, and torsades de pointes. Many action potential prolonging drugs appear to exert their greatest effects at very slow rates (where torsades de pointes is a risk) and to exert much less effect at rapid rates (where the action potential prolonging, refractory period prolonging effect is desirable). Drugs which have less reverse use-dependence of class III effect may thus be expected to carry a lower risk of torsades de pointes proarrhythmia. Precordial QT dispersion has been studied as a marker of torsades de pointes.[82,83] Amiodarone produced less QT dispersion than other agents with a class III mechanism of action (sotalol and sematilide), or class Ia action. It was hypothesised that homogeneous prolongation of ventricular repolarisation times, as reflected by homogeneous regional QT interval prolongation, may partly explain the relative lack of proarrhythmia with amiodarone compared with the other agents studied.

4. Conclusion

In general, the efficacy of an antiarrhythmic agent cannot be reliably predicted based on its known cellular or physiological mechanism(s) of action, because of the numerous and complex modulating factors which may interact at various levels to influence the final clinical outcome. Certain surrogate measures, obtained during electrophysiological studies, such as refractory periods or tachycardia cycle length, may be useful in predicting antiarrhythmic efficacy. In contrast, however, the risk and type of proarrhythmia can be predicted with reasonable accuracy from an agent's mechanism of action. This may ultimately be the most practical use of the current classification systems applied to antiarrhythmic agents.

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