ELECTROPHYSIOLOGY

Antiarrhythmic drugs: from mechanisms to clinical practice

Dan M Roden
Vanderbilt University School of Medicine,
Nashville, Tennessee, USA

Correspondence to:
Dan M Roden MD,
Director, Division of Clinical Pharmacology,
Vanderbilt University School of Medicine,
532C Medical Research Building-I, Nashville, TN 37232-6602, USA
email: Dan.Roden@MCMail.Vanderbilt.edu

All drugs currently marketed for the treatment of arrhythmias were developed in the absence of knowledge of the specific molecules the drugs target to achieve their therapeutic and adverse effects. Nevertheless, combining the characterisation of drug effects in vitro and in whole animal models with medicinal chemistry approaches to modify existing molecules has led to new compounds with related pharmacologic actions derived from older drugs (for example, procainamide begat flecainide). It has thus been natural to group drugs with common mechanisms of action. This approach can be useful for the clinician to the extent it allows prediction of a patient's response to a given drug. One widely used scheme is that popularised by Vaughan Williams in which drugs are subdivided into four broad "classes".[1] The Vaughan Williams classification has been criticised because many drugs fall into multiple classes (table 1): quinidine both blocks sodium channels and prolongs action potentials (class I + III), while amiodarone blocks sodium channels, exerts antiadrenergic actions, prolongs action potentials and QT intervals by blocking potassium channels, and blocks calcium channels (classes I + II + III + IV, respectively).[2 3] Moreover, both compounds exert other important pharmacologic actions, such as inhibition of specific pathways of drug elimination (both), α blockade with vasodilation (quinidine), and interaction with nuclear thyroid hormone receptors (amiodarone). These actions probably contribute to some of the effects observed during treatment with these compounds.

A virtue of the Vaughan Williams' approach to classification is that drugs of a common "class" frequently exhibit similar toxicities, notably proarrhythmia. This likely reflects the fact, discussed below and elsewhere in this series, that while the mechanisms whereby drugs suppress arrhythmias are incompletely defined and likely highly variable from patient to patient, the mechanisms underlying proarrhythmia are better understood and less variable among patients. Thus, for example, sodium channel blocking drugs with slow onset and offset kinetics of block (the "class Ic" (and to a lesser extent "Ia") effect, seen with flecainide) are likely to produce conduction slowing at normal rates and the stereotypical set of toxicities, described below (proarrhythmia: sodium channel block). As our understanding of the molecular basis of these and other proarrhythmia syndromes (and indeed arrhythmias in general) evolves, it seems likely that drugs exerting antiarrhythmic effects yet lacking the potential to cause serious toxicity may be developed.

The "Sicilian Gambit" proposed an alternate approach to classifying antiarrhythmic drug actions.[2] In this scheme, the arrhythmia mechanism assumes primacy, and antiarrhythmic drugs (or other treatments) are then classified by the way in which they interact with arrhythmogenic triggers or substrates to suppress arrhythmias. A near trivial example is macroreentry based on the presence of a bypass tract. Understanding this mechanism then allows the clinician to select drugs that target the portion of the circuit at which pharmacologic interruption is most likely (the AV node) or target the circuit by ablation of the accessory pathway. The identification of such a "vulnerable parameter" in an arrhythmia mechanism should, in theory, allow development of entirely new approaches to treatment.

Table 1 Antiarrhythmic drugs exert a multiplicity of electrophysiologic actions

	Na^+ channel block (I*)		K^+ channel block (III)				
	At all rates	*Predominantly at fast rates*	I_{Kr}	*Other K^+ channels*	*Ca^{2+} channel block (IV)*	*β-blockade (II)*	*Other clinically important autonomic or electrophysiologic actions (all ✓✓)*
Adenosine					✓?		$I_{K\text{-}ACh}$ activation
Amiodarone	✓✓		✓	✓	✓✓		Reduction of β receptor number (non-competitive β blockade), also a "class II" effect
β Blockers						✓✓	
Bretylium			✓?	✓?			Inhibition of norepinephrine (noradrenaline) reuptake
Calcium channel blockers (verapamil, diltiazem)			✓		✓✓		
Digitalis							Na^+-K^+ ATPase inhibition; vagotonic actions anticholinergic effects
Disopyramide	✓✓		✓	✓?			
Dofetilide			✓✓				
Flecainide	✓✓		✓	✓			
Ibutilide			✓✓				Na^+ channel activation (also →↑QT)
Lidocaine		✓✓					
Mexiletine		✓✓					
Moricizine	✓✓						
Procainamide	✓✓		✓	✓?			Ganglionic blockade
Propafenone	✓✓		✓	✓		✓	
Quinidine	✓✓		✓✓	✓			α blockade; vagolytic
Sotalol			✓✓	✓		✓✓	
Tocainide		✓✓					

✓✓ clinically important drug action.
✓ reported drug action that may contribute to clinical effects.
*Roman numerals refer to the Vaughan Williams classification.

Table 2 Important side effects of antiarrhythmic drugs

	Mortality post-MI	*Exacerbation of sustained VT*	*Atrial flutter with 1:1 AV conduction*	*Torsades de pointes*	*Brady-arrrhythmia*	*Exacerbation of heart failure*	*Other clinically important adverse effects*
Adenosine					✓ (transient)		
Amiodarone	↓			Rare	✓		Pulmonary fibrosis Photosensitivity Corneal microdeposits Cirrhosis Neuropathy Hypotension (IV)
β Blockers	↓↓				✓✓	✓ (acute)	Bronchospasm Altered response to hypoglycaemia
Bretylium							Hypotension
Calcium channel blockers (verapamil, diltiazem)	↔				✓	✓	Constipation (verapamil)
Digitalis	↔				✓		Arrhythmias Altered mentation, vision Nausea
Disopyramide				✓		✓	Constipation Urinary retention Glaucoma Dry mouth
Dofetilide	↔			✓			
Flecainide	↑↑	✓	✓			✓	
Ibutilide				✓			
Lidocaine							Altered mentation Seizures
Mexiletine	↑						Nausea Tremor
Moricizine	↑↑						
Procainamide	↑			✓			Drug induced lupus (arthritis, rash, occasional pericarditis) Nausea Hypotension (IV) Marrow aplasia
Propafenone			✓		Occasional	✓	Bronchospasm (especially in PMs)
Quinidine	↑	✓	✓	✓	✓		Diarrhea Nausea
Sotalol	↔			✓		✓	Bronchospasm
Tocainide							Nausea Marrow aplasia

PM, poor metabolisers. IV, intravenous.

For example, it is increasingly recognised that altered intracellular calcium homeostasis may play an important role in arrhythmias in settings such as heart failure. Drugs targeting the molecular events that make altered intracellular calcium homeostasis arrhythmogenic might therefore attack the "vulnerable parameter" in this situation.

Differential drug effects in atrial flutter versus atrial fibrillation was an interesting (and it turns out incorrect) prediction of the initial publication of the Sicilian Gambit. It was postulated that atrial fibrillation should respond particularly well to drugs that prolong atrial refractoriness, while atrial flutter would respond especially well to drugs that slow conduction. In fact, clinical studies have demonstrated that the exact opposite occurs. Drugs with predominant QT prolonging effects (dofetilide, ibutilide) are more effective in atrial flutter than in atrial fibrillation, whereas drugs with predominant sodium channel blocking effects (flecainide) are more effective in fibrillation than flutter. It seems likely that QT prolonging agents are especially effective because they prolong refractoriness in an especially vulnerable portion of the circuit to terminate flutter (or that they affect the boundaries of the circuit). Thus, this interesting exception to the initial prediction of the Sicilian Gambit merely serves to reinforce the underlying concept, that a full understanding of arrhythmia mechanisms is desirable to use available treatments rationally and to develop new ones.

Pharmacology

A contemporary view is that all drugs exert their desirable and undesirable effects by interacting with specific molecular targets.[2 3] A common set of targets for antiarrhythmic drugs are ion channels, the pore forming protein structures that underlie ionic currents flowing during the action potential. Specificity of drug action is achieved by drugs that target only a single population of ion channels. The virtue of this approach is that side effects (caused by interaction with other targets) are rare. Unfortunately, as discussed below, targeting individual cardiac ion channels may result in significant proarrhythmia. Amiodarone is an example of a drug with multiple ion channel and other target molecules, and it seems likely that the low incidence of proarrhythmia during amiodarone treatment reflects the fact that "antidotes" to specific proarrhythmia syndromes are built into the drug's mechanism of action. On the other hand, extracardiac side effects are particularly common during amiodarone treatment, again reflecting this multiplicity of pharmacologic targets. A detailed discussion of all the pharmacologic actions of all available antiarrhythmics is beyond the scope of this review. Nevertheless, it is useful to consider widely used drugs with respect to pharmacologic actions that assume special

Table 3 Clinically important pharmacokinetic characteristics of antiarrhythmic drugs

	Elimination half life							*Major route(s) of metabolism*			
	sec	*< 60 min*	*2–12 hr*	*> 12 hr*	*IV use*	*Bio-availability < 100%*	*Active metabolite(s)*	*CYP3A4*	*CYP2D6*	*Renal excretion*	*Other*
Adenosine	✓				✓						Cellular adenosine reuptake
Amiodarone				✓	✓	✓	✓	✓			
β Blockers		✓	✓		✓	✓	some				
Bretylium			✓		✓					✓	
Calcium channel blockers (verapamil, diltiazem)			✓		✓	✓	✓	✓			
Digoxin				✓	✓	✓					P-glycoprotein
Disopyramide			✓		✓ (not US)		✓	✓			
Dofetilide			✓					(minor)		✓	
Flecainide				✓	✓ (not US)				✓	✓	
Ibutilide			✓		✓						
Lidocaine		✓			✓	✓	✓	✓			
Mexiletine			✓				✓	✓			
Moricizine			✓				✓				
Procainamide			✓		✓		✓				N-acetylation
Propafenone			✓		✓ (not US)		✓		✓		
Quinidine			✓		✓ (rarely used)		✓	✓			
Sotalol			✓		✓ (not US)					✓	
Tocainide			✓							✓	

relevance in clinical management. These include proarrhythmia syndromes discussed below and other important adverse effects presented in table 2 as well as pharmacokinetic properties presented in table 3.

Proarrhythmia: torsades de pointes

Torsades de pointes is estimated to occur in 1–8% of patients exposed to QT prolonging antiarrhythmics: sotalol, quinidine, dofetilide, and ibutilide fall into this category. While this reaction is generally viewed as "unpredictable", certain risk factors can be identified: female sex, underlying heart disease (particularly congestive heart failure or cardiac hypertrophy), hypokalaemia, and hypomagnesaemia. In patients receiving these drugs for atrial fibrillation (the majority in contemporary practice), the reaction is quite uncommon when the underlying rhythm is actually atrial fibrillation but tends to occur shortly after conversion to sinus rhythm; ibutilide may be an exception.[4] The clinical parallels between torsades de pointes in drug associated cases and in the congenital long QT syndromes has suggested the possibility that some patients displaying apparently "idiopathic" responses to drugs may in fact harbour subclinical congenital long QT syndrome mutations. With the identification of the disease genes in the congenital form of the syndrome has come the possibility of testing this idea, an area of very active research.[5]

Most drugs that cause torsades de pointes have as a major pharmacologic action block of a specific repolarising potassium current, I_{Kr}. Thus, patients are thought to develop drug induced torsades de pointes either because the channels underlying I_{Kr} are unusually sensitive to drug block (which is now recognised with hypokalaemia and with some mutations) or because they harbour subclinical mutations in other repolarising channels. In the latter case, baseline QT intervals can be normal because of a robust I_{Kr}, but block of the current produces exaggerated QT prolongation.

The management of torsades de pointes includes recognition, withdrawal of any offending agents, empiric administration of magnesium regardless of serum magnesium, correction of serum potassium to 4.5–5 mEq/l, and manoeuvres to increase heart rate (isoprenaline (isoproterenol) or pacing) if necessary. Long term management of patients with QT prolongation on a congenital or even acquired basis usually relies on β blockers, although in some cases pacemakers or implantable cardioverter defibrillators (ICDs) are advocated.

Proarrhythmia: sodium channel block

The first drugs used to suppress cardiac arrhythmias were quinidine, procainamide, and lidocaine, which share the common property of sodium channel block. Modifications in these chemical structures led to compounds with more potent sodium channel blocking capability. Indeed agents with this property (flecainide, propafenone) are very effective in suppressing isolated ectopic beats and are among the drugs of choice for treatment of re-entrant supraventricular tachycardia in patients with no underlying structural heart disease. However, extensive clinical studies with these agents, and drugs that are no longer available but that exerted very similar pharmacologic properties, have identified a number of serious liabilities of sodium channel block.

First, in patients with a history of sustained ventricular tachycardia related to a remote myocardial infarction, exacerbation of ventricular tachycardia is common. Such exacerbation presents as a pronounced increase in frequency of episodes, which are often slower than pre-drug, but less organised and more difficult to cardiovert. Treatment of this arrhythmia by additional sodium channel block is undesirable; β blockers or sodium infusion have been found effective in anecdotes. Deaths have been reported. The mechanism of ventricular tacchyarrhythmia (VT) in these cases is thought to relate to slow conduction in border zone tissue, and the conduction slowing caused by sodium channel blockers tends to further exacerbate the clinical arrhythmia.

Second, the rate of atrial flutter, a macroreentrant arrhythmia occurring in the right atrium, is usually slowed by sodium channel block. When this occurs, the patient who pre-drug had atrial flutter at 300/min and 2:1 atrioventricular (AV) transmission with narrow complexes at 150/min may present with wide complex tachycardia at 200/min, representing a slowing of atrial flutter to 200/minute and 1:1 AV transmission. QRS widening often accompanies this fast rate since sodium channel block is enhanced at fast rates.[6] The management of this entity requires recognition, withdrawal of offending agents, and AV nodal blocking drugs. This reaction can occur not only in patients being treated with flecainide, propafenone, or quinidine for atrial flutter (where, as described above, sodium channel blockers may not be especially effective) but also in patients whose presenting arrhythmia is atrial fibrillation and is "converted" by drug to atrial flutter. Many experts would not prescribe these drugs to patients with atrial fibrillation or flutter without co-administering an AV nodal blocking drug.

Third, sodium channel block increases threshold for pacing and defibrillation.

Fourth, the use of the sodium channel blockers flecainide or encainide to suppress ventricular extrasystoles in patients convalescing from myocardial infarction was found in the cardiac arrhythmia suppression trial (CAST) to increase mortality.[7] While the mechanism underlying this effect is not known, a synergistic action of sodium channel block and recurrent transient myocardial ischemia to provoke ventricular tachycardia or ventricular fibrillation is strongly suspected from clinical and animal model studies. The clinical implication of CAST for contemporary antiarrhythmic treatment and antiarrhythmic drug development cannot be underestimated. As a result of this landmark trial:

- non-sustained ventricular arrhythmias are generally not treated (or treated with antiadrenergic agents);
- we recognise increasingly that the risk of adverse reactions to antiarrhythmic drugs is driven by an interaction between the drug and an abnormal electrophysiologic substrate;
- drug development moved away from drugs with prominent sodium channel blocking properties to drugs with more prominent effects to prolong action potentials[8];
- and non-pharmacologic therapy has emerged as a major mode of treatment.[9]
- Most importantly, CAST demonstrated the power of the controlled clinical trial to evaluate treatments for any disease and the dangers of relying on surrogate end points (such as extrasystoles) to guide drug therapy.

Effect of drugs on long term arrhythmia mortality

A number of other studies have also supported a detrimental effect of sodium channel blockers in the post-myocardial infarction population. Early trials with disopyramide and mexiletine both showed trends to increased mortality. In CAST-II, moricizine was found to increase mortality notably in the two weeks following the institution of treatment, although the effect long term was less striking than with flecainide and encainide. A meta-analysis[10] and a non-randomised post-hoc analysis[11] suggested that quinidine or procainamide treatment in patients with atrial fibrillation was associated with a higher mortality than among patients not receiving these agents. The role of antiarrhythmic drugs to maintain sinus rhythm versus AV nodal blocking drugs or other treatment to control rate in atrial fibrillation is being studied in AFFIRM, whose results should be available in the next 2–3 years.

One consequence of CAST was a general consensus, on the part of clinical investigators and regulatory authorities, that licensing new antiarrhythmic drugs might well require demonstration that those drugs did not increase mortality. Two large mortality trials have been conducted with "pure" I_{Kr} blocking compounds: SWORD tested the dextro-rotary (non-β blocking) isomer of sotalol, and DIAMOND tested dofetilide. In SWORD, d-sotalol increased mortality,[12] whereas in DIAMOND, dofetilide produced no effect on mortality.[13] These differences likely arose from differences in trial design, and in particular efforts to minimise the possibility of torsades de pointes during long term treatment in DIAMOND. Amiodarone has been tested in a CAST-like population and been found to exert a modest effect to decrease mortality,[14] an effect that may be potentiated by co-administration of β blockers.[15] Despite numerous attempts, calcium channel blockers have not been shown to exert a major effect to reduce mortality following myocardial infarction. ALIVE is testing a new potassium channel blocking agent (azimilide). At this point, the mainstay of drug treatment to reduce mortality following myocardial infarction remains therapies directed at maintaining a normal cardiovascular "substrate", such as β blockers, angiotensin converting enzyme (ACE) inhibitors, HMG-CoA reductase inhibitors (statins), and aspirin.

Drug interactions

Because antiarrhythmic drugs often have narrow margins between the doses or plasma concentrations required to achieve a desired therapeutic effect and those associated with toxicity, drug interactions tend to be especially prominent. This difficulty is exacerbated by the fact that most patients receiving antiarrhythmic drugs receive other treatments as well. Conceptually, drug interactions arise from two distinct mechanisms, pharmacokinetic and pharmacodynamic. Pharmacokinetic drug interactions arise when one drug modifies the absorption, distribution, metabolism, or elimination of a second. Pharmacodynamic interactions arise because of interactions that blunt or exaggerate pharmacologic effects without altering plasma drug concentrations.

The greatest likelihood of important pharmacokinetic drug interactions arises when a drug is eliminated by a single pathway and a

Table 4 A molecular view of drug metabolism

	CYP3A4	*CYP2D6*	*CYP2C9*	*P-glycoprotein*
• Substrates	Amiodarone Quinidine Many HMG CoA reductase inhibitors (statins) Terfenadine, astemizole Cisapride Many calcium channel blockers Lidocaine, mexiletine Cyclosporine Many HIV protease inhibitors Sildenafil	Propafenone Flecainide Codeine Timolol Metoprolol Popranolol	Warfarin	Digoxin Many antineoplastic agents
• Inhibitors	Amiodarone Verapamil Cyclosporine, erythromycin, clarithromycin Ketaconazole, itraconazole Mibefradil, other calcium channel blockers Ritonavir	Quinidine Propafenone TCAs Fluoxetine	Amiodarone	Quinidine Amiodarone Verapamil Cyclosporine Erythromycin Ketaconazole Itraconazole
• Inducers	Rifampin Phenytoin Phenobarbital			

TCAs, tricyclic antidepressants.

second drug is administered that modifies the activity of that pathway. Identification of specific genes whose expression results in the enzymes or transport systems mediating drug disposition has led to the realisation that, in some patients, mutations in these genes can result in abnormal drug disposition even in the absence of interacting drugs. Thus, the field of drug interactions and of genetically determined drug disposition are closely linked. The clinical consequences of modulating a drug disposition pathway depend on the pharmacologic effects produced by altered parent drug concentrations and/or altered concentrations of active metabolites whose generation depends on the pathway targeted. These general principles are best understood by considering specific examples (table 4).

CYP3A4

More drugs are metabolised by this enzyme than by any other. *CYP3A4* is expressed not only in the liver, but also in the intestine and other sites, such as kidney. Presystemic drug metabolism by *CYP3A4* in the intestine and the liver is one common mechanism whereby some drugs have a very limited systemic availability. The activity of *CYP3A4* varies widely among individuals, although there is no genetically determined polymorphism yet described. As shown in table 4, many widely used cardioactive agents are substrates for *CYP3A4* and inhibition or induction of *CYP3A4* activity can lead to important drug interactions.

Perhaps the most spectacular example of a *CYP3A4* mediated drug interaction was that between terfenadine and the *CYP3A4* inhibitors erythromycin or ketaconazole.[16] Terfenadine is a very potent I_{Kr} blocker in vitro but is ordinarily almost completely (> 98%) metabolised by *CYP3A4* before entry into the systemic circulation. With co-administration of *CYP3A4* inhibitors, this presystemic metabolism is inhibited, terfenadine plasma concentrations rise > 100 fold, and torsades de pointes can ensue. A similar mechanism also explains torsades de pointes during treatment with astemizole and cisapride, and has led to withdrawal or limitations of the drugs' use. *CYP3A4* metabolism is induced by co-administration of drugs such as rifampin, phenytoin, and phenobarbital. In this circumstance, concentrations of *CYP3A4* substrates may fall, with attendant loss of pharmacologic effect. This has been well documented with quinidine and mexiletine.

CYP2D6

This enzyme is expressed in the liver and is responsible for biotransformation of many β blockers (timolol, metoprolol, propranolol), propafenone, and codeine. *CYP2D6* "poor metabolisers" are deficient in *CPY2D6* activity, on a genetic basis; 7% of whites and African Americans (but very few Asians) are poor metabolisers. Quinidine and a number of antidepressants (both tricyclics and selective serotonin reuptake inhibitors such as fluoxetine) are potent *CYP2D6* inhibitors. When these inhibitors are given to patients receiving β blockers or propafenone (which has weak β blocking activity), or such substrate drugs are administered to patients who are poor metabolisers, exaggerated β blockade occurs. Indeed, clinical data strongly support the idea that absence of *CYP2D6* activity increases the likelihood of side effects during propafenone treatment.[17] On the other hand, absence of *CYP2D6* activity in a patient receiving codeine results in failure of biotransformation to a more active metabolite (morphine). Thus, in this situation, inhibition of drug metabolism actually leads to a ("paradoxical") decrease in pharmacologic effect.

P-glycoprotein

Movement of drugs across cell membranes is increasingly recognised as a process dependent on normal expression and function of specific "transport" molecules. The most widely studied of these is P-glycoprotein, expressed on the luminal aspect of enterocytes, on the biliary canalicular aspect of hepatocytes, and the capillaries of the blood–brain barrier. Many widely used drugs are P-glycoprotein substrates, although the functional consequences of P-glycoprotein inhibition are small because

Table 5 Clinical conditions modifying choice of antiarrhythmic agents

Clinical condition	*Treatments to consider*	*Contraindicated or undesirable treatments*
Arrhythmias		
Torsades de pointes	*Acute*: Magnesium Isoproterenol Pacing Raise serum K+ *Chronic QT prolongation*: β Blockers Pacing	*QT prolonging drugs*: Quinidine Procainamide Disopyramide Sotalol Ibutilide Dofetilide ???Amiodarone
Polymorphic VT with short QT intervals	Anti-ischaemic intervention Intravenous amiodarone	Lidocaine, procainamide (ineffective)
Sustained monomorphic VT	IV procainamide or sotalol	Lidocaine (ineffective)
RV outflow tract VT, fascicular VT	Verapamil β Blocker Adenosine (acutely)	
QT interval prolongation	Flecainide Propafenone Lidocaine Mexiletine ???Amiodarone	Quinidine Orocainamide Disopyramide Sotalol Ibutilide Dofetilide ???Amiodarone
Atrial fibrillation + structural heart disease		Flecainide
Atrial fibrillation with rapid ventricular rate and pre-excitation	IV procainamide cardioversion	Verapamil Adenosine Digitalis
Other concomitant conditions		
Heart failure	Digitalis *Also acceptable:* Amiodarone Dofetilide Quinidine	Diltiazem, verapamil β Blockers if severe Flecainide Disopyramide
Sinus/AV nodal disease		All drugs discussed have the potential to worsen bradyarrhythmias, particularly: Diltiazem, verapamil β Blockers Digitalis Amiodarone
Diffuse conduction system disease		Above + most other antiarrhythmics
Chronic lung disease		Amiodarone
Inflammatory arthritis		Procainamide
Chronic bowel disease		Quinidine (exacerbates diarrhoea) Verapamil, disopyramide (exacerbate constipation)
Asthma		β Blockers Propafenone
Tremor		Lidocaine Mexiletine

This table is not meant to supplant discussions of treatments of choice for various arrhythmia syndromes outlined in other parts of this series. Rather, specific clinical conditions which may dictate an unusual or specific choice of drugs are presented.
IV, intravenous.

most drugs have other pathways for their elimination. Clinically, the most important P-glycoprotein substrate in cardiovascular use is digoxin, which does not undergo extensive metabolism by enzymes such as *CYP3A4* or *CYP2D6*. Rather, its bioavailability is limited by re-excretion by P-glycoprotein into the intestinal lumen, and its elimination is accomplished by excretion by P-glycoprotein and possibly other transporters in liver and kidney. The effect of multiple, structurally unrelated drugs such as quinidine, verapamil, amiodarone, cyclosporine, erythromycin, and itraconazole to increase digoxin concentrations likely has the common mechanism of P-glycoprotein inhibition.[18]

Pharmacodynamic drug interactions

Pharmacodynamic interactions tend to manifest primarily in patients with underlying heart disease. Thus, when β blockers and calcium channel blockers are co-administered, pronounced bradycardia or heart block occurs primarily in patients with underlying conduction system disturbances. Similarly, exacerbation of heart failure is more of a problem when multiple drugs with cardiodepressant actions (including, prominently, antiarrhythmics) are co-administered to patients with underlying heart disease.

Putting it all together: matching the patient, the drug, and the arrhythmia

Decades of clinical investigation and, more recently, whole animal, cellular, molecular, and genetic studies, have now positioned clinicians to more rationally prescribe and monitor treatment with drugs designed to treat cardiac arrhythmias. A number of very important principles can be enunciated based on these data.

Establish a firm diagnosis

The treatment of ventricular tachycardia as aberrantly conducted supraventricular tachycardia not only exposes patients to risk, but delays appropriate therapy. Other diagnostic issues that may impact on choice of treatments include recognition of specific arrhythmias "syndromes", such as torsades de pointes, "idiopathic" ventricular tachycardia arising in the right ventricular outflow tract or the conducting system, polymorphic ventricular tachycardia with a short QT interval arising in a patient with acute ischaemia, and pre-excitation, particularly in a patient with atrial fibrillation (table 5). Each of these syndromes has a specific identified mechanism, and specific treatments that are indicated and contraindicated, based on mechanistic principles.

Anticipate side effects

Unfortunately, the choice of specific agents to be used in common arrhythmia syndromes is often driven more by the clinician's estimate of a likely adverse effect rather than a clear understanding of mechanism or that one drug demonstrates efficacy that is superior to another. Thus, sodium channel blocking agents such as flecainide or propafenone are highly inappropriate to use in treating patients with atrial fibrillation in patients with ischaemic cardiomyopathy, yet are among the drugs of choice in patients with no structural heart disease.[19] Disopyramide is a reasonable option for some patients with atrial fibrillation, but should not be used in patients with glaucoma or prostatism because of the likelihood of precipitating extracardiac adverse effects. Patients with borderline long QT intervals may be at increased risk for torsades de pointes during QT prolonging treatments such as sotalol or dofetilide.

Another variation of this consideration is the presence of chronic non-cardiac disease (table 5). Thus, amiodarone may be relatively contraindicated in a patient with advanced lung disease for two reasons. First, some data suggest such patients may be at increased risk for amiodarone mediated pulmonary toxicity. The second, more important, difficulty with amiodarone from a practical point of view is the likelihood that the patient will present at some point in the future with an exacerbation of dyspnoea, and it will be very difficult, if not impossible, to sort out whether the drug or the underlying disease is responsible. Similarly, drug induced lupus is sufficiently common during long term treatment with procainamide that this drug is especially difficult to use in patients with diseases such as rheumatoid arthritis.

Consider polypharmacy

Many patients for whom antiarrhythmic drug treatment is prescribed are receiving other drugs for cardiac or non-cardiac indications. The prescribing physician should therefore be particularly vigilant when new drugs are added to or removed from a complex regimen in a patient with advanced heart disease, as the likelihood of unanticipated drug actions is high. Drugs that call for special vigilance are those known to be inhibitors of specific metabolic pathways (table 4).

Trial acronyms

AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management
ALIVE: Azimilide post-Infarct Survival Evaluation
CAMIAT: Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CAST: Cardiac Arrhythmia Suppression Trial
DIAMOND: Danish Investigation of Arrhythmia and Mortality on Dofetilide
EMIAT: European Myocardial Infarction Amiodarone Trial
IMPACT: International Mexiletine and Placebo Antiarrhythmic Coronary Trial
SPAF: Stroke Prevention in Atrial Fibrillation
SWORD: Survival With Oral d-sotalol

Approach to evaluation of treatment

General principles of rational drug use apply especially to narrow therapeutic index agents such as antiarrhythmics. The baseline arrhythmia should be qualified (for example, do episodes of atrial fibrillation occur daily or monthly?).[19] Low drug doses that produce efficacy are more desirable than higher ones. Plasma concentration monitoring, ECG evaluation, and interval history should be evaluated during treatment to detect or anticipate potential toxicity. Therapeutic goals should be defined as therapy starts: Get rid of all atrial fibrillation? All symptoms? Should the patient with cardiac arrest survive to get to the hospital, or be discharged from the hospital?[20] Drugs should not be declared ineffective unless those goals are met in a compliant patient receiving doses just below those that produce, or are likely to produce, toxicity.

Finally, patients never "fail" drugs—drugs fail patients.

1. Vaughan Williams EM. Classification of antiarrhythmic action. *Handbook of Experimental Pharmacology* 1989;**89**:45–62.
- *The Vaughan Williams approach to classification, developed in the late 1960s, remains widely used by clinical cardiologists, primarily because of its ability to predict antiarrhythmic drug toxicity.*

2. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991;**84**:1831–51
- *The "Sicilian Gambit" proposed that definition of arrhythmia mechanisms would allow identification of specific "vulnerable parameters" that available or new drugs could target to best suppress arrhythmias.*

3. Priori SG, Barhanin J, Hauer RN, *et al.* Genetic and molecular basis of cardiac arrhythmias; impact on clinical management. Study group on molecular basis of arrhythmias of the working group on arrhythmias of the European Society of Cardiology. *Eur Heart J* 1999;**20**:174–95 (also published in *Circulation* 1999;**99**:518–528, 674–81)
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