Specific drugs for specific ventricular arrhythmias: an evaluation of current therapy and the role of propafenone

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Drug management of ventricular arrhythmias follows few scientific principles. Specific therapy for specific arrhythmias must be a goal for the future. Already a few important arrhythmia subtypes demanding specific therapy have been identified. As new drugs become available, they may offer particular effects against identifiable clinical arrhythmias.

Introduction

Drug treatment of ventricular arrhythmias is largely empirical. Improved knowledge of arrhythmia mechanisms and the availability of a wide range of antiarrhythmic medications has not yet brought about a specific basis for ventricular arrhythmia treatment. Future prospects for identifying and developing specific antiarrhythmic drugs against specific ventricular arrhythmias are bleak. Most ventricular arrhythmias involve several electrophysiological mechanisms and most antiarrhythmic drugs possess complex and wide-ranging electrophysiological effects.

Perhaps more realistic than the concept of a specific drug for a specific ventricular arrhythmia is to identify the antiarrhythmic drug with the best cost-benefit ratio for clinically recognizable ventricular arrhythmias.

Types of ventricular arrhythmias

Ventricular arrhythmias may be classified by their electrocardiographic characteristics: isolated ventricular ectopic beats; ventricular ectopic beat pairs; non-sustained ventricular tachycardia; sustained monomorphic ventricular tachycardia; polymorphic ventricular tachycardia; ventricular flutter; ventricular fibrillation and torsade de pointes. However to discuss drug therapy, the description of arrhythmia should include information about the underlying pathology. As an example, the fundamental electrophysiology of ventricular fibrillation is probably similar whether the arrhythmia arises in the acute phase of myocardial infarction or as a complication of hypertrophic cardiomyopathy, but prevention of its occurrence by antiarrhythmic therapy is critically influenced by the underlying aetiology.

Discussion of relative efficacy suggests review of comparative testing of antiarrhythmic drugs. Few such studies have been performed and most have involved small numbers of highly selected patients. Whilst some information is available on ventricular ectopic beat suppression there is almost no comparative work on more dangerous arrhythmias, such as ventricular tachycardia and ventricular fibrillation, perhaps reflecting the difficulties of randomized drug assignment in patients with these arrhythmias and the individual needs of patients afflicted by these arrhythmias.

Specific ventricular arrhythmias and their antiarrhythmic management

VENTRICULAR FIBRILLATION COMPLICATING ACUTE PHASE MYOCARDIAL INFARCTION

Since the earliest days of coronary care unit management of myocardial infarction it has been recognized that complicating ventricular fibrillation (VF) was not a homogenous event. Primary and secondary forms, differentiated by the absence or presence of shock and/or heart failure have markedly different prognoses, time-frames of occurrence and probably require different therapeutic approaches. By definition, the poor
haemodynamic status of patients with secondary VF all but precludes the administration of most conventional class Ia and class Ic drugs.

The electrophysiology of coronary artery occlusion and natural or induced reperfusion is complex, and several ‘types’ of VF can be distinguished. All have the same final electrocardiographic pattern and all VF probably has the same basic electrophysiology. The immediate treatment (DC cardioversion) is the same for all forms of VF. The differences relate to the underlying pathophysiology of the arrhythmia and are sufficient to demand different prophylactic strategies.

Acute occlusional VF

This subtype of VF occurs within the first few minutes of coronary artery occlusion. Mechanistically it probably bears a close relationship to the phase Ia arrhythmias of the Harris dog model of experimental infarction. Clinical evidence suggests that this arrhythmia is not prevented by lignocaine but it is possible that β-adrenergic-blocking drugs do offer prophylaxis; this being the mechanism of reduced sudden death in survivors of acute infarction chronically treated with β-blockers.

Acute phase post-occlusional VF

This form of VF is seen in coronary care units. It occurs approximately 30 min–6 h after coronary artery occlusion. Clinical evidence indicates that lignocaine offers protection from the arrhythmia albeit at the cost of an increased incidence of asystole.

Reperfusional VF

Although much feared and an important feature of experimental infarction, VF associated with myocardial reperfusion is uncommon in man. As it probably represents the electrical reactivation of jeopardized myocardial cells, reperfusional VF may betoken a good prognosis (once appropriately corrected) and it is uncertain whether prophylactic measures are desirable.

Late VF

Late VF (≥ 48 h postinfarction) is well recognized but has received little attention. Undoubtedly some episodes of late VF represent infarction or ischaemia de novo, but other episodes correlate with the extent and location of the original infarction. Myocardial infarction complicated by bundle branch block and axis shift is particularly associated with a high risk of late VF. No effective antiarrhythmic prophylaxis has yet been identified. Recognition that the risk of late VF in these patients appears to last only 6 weeks from the initial event is the basis of recommendation that hospitalization for the risk period may be the best management strategy.

Secondary VF

VF in the presence of shock and/or cardiac failure carries an ominous immediate and late prognosis. Despite this, remarkably little research has been conducted on secondary VF prophylaxis, and at present no antiarrhythmic drug regimen is of proven value. It is possible that widespread use of thrombolytic therapy in acute infarction may in time limit infarct size as to reduce the incidence of this complication.

Sustained Monomorphic Post-Infarction Ventricular Tachycardia (VT)

This arrhythmia depends upon a certain architecture of myocardial damage with subsequent healing to establish a permanent re-entrant pathway. A left ventricular aneurysm is a common but not universally associated finding. Optimal medical management entails invasive electrophysiological identification of antiarrhythmic drugs which will prevent VT induction. Continuous long-term oral therapy with the identified therapy has been associated with an improved prognosis. The class Ic agents and amiodarone (despite the problem of electrophysiology testing) are the drugs most often found to be effective for this arrhythmia, but overall drug efficacy rates are low and antiarrhythmic surgery has emerged as an important alternative management strategy.

Sudden Death and Ventricular Arrhythmias Associated with the Long QT Syndrome

Despite the lack of a randomized study, registral evidence strongly suggests that conventional antiarrhythmic therapy is ineffective in reducing mortality and controlling the arrhythmic complications of the congenital long QT syndrome. β-adrenoreceptor-blocking drugs and/or left stellate ganglionectionomy have emerged as the most useful interventions. No particular β-blocking drug of superior efficacy has been identified.
SUDDEN DEATH AND VENTRICULAR ARRHYTHMIAS IN HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is associated with a wide spectrum of symptoms and in some patients carries a significant risk of death. Sudden death may be a consequence of mechanical problems such as outflow tract obstruction but probably most events are arrhythmic. Sudden death is associated with a history of syncope (especially when the first event occurs at an early age), a family history of precocious death and the dynamic electrocardiographic exposure of ventricular arrhythmias. In the subset of patients most at risk, evidence suggests that amiodarone can reduce mortality.

VENTRICULAR ARRHYTHMIAS IN MITRAL VALVE PROLAPSE

Despite much research, mitral valve prolapse remains ill understood. The condition is associated with ventricular arrhythmias and there is a small but important risk of sudden death; high-risk subjects might be identified by electrocardiographic abnormalities. No systematic comparisons of antiarrhythmic management have been reported but anecdotal evidence suggests that β-adrenoceptor-blocking agents offer greater efficacy than other classes of antiarrhythmic drugs.

HIS BUNDLE VENTRICULAR TACHYCARDIA

This rare form of ventricular tachycardia is usually not of ischaemic (overt coronary artery disease) aetiology. Several paediatric cases have been reported. Although no scientifically controlled comparative studies have been performed, evidence from published cases suggests that β-adrenoreceptor-blocking agents offer greater efficacy than other classes of antiarrhythmic drugs.

HEART FAILURE AND VENTRICULAR ARRHYTHMIAS

Sudden death and arrhythmias complicating heart failure are currently the subject of much investigation, particularly since evidence links ventricular arrhythmias in heart failure with an adverse prognosis. Several small studies have determined that treatment of ventricular ectopic beats and VT with class I antiarrhythmic agents does not improve prognosis. By contrast, ACE inhibitor therapy does reduce ventricular ectopic beats and it was hoped that sudden death rates might similarly be altered. The Consensus study has shown beyond reasonable doubt that ACE inhibitor therapy can reduce mortality although mechanical death rather than sudden electrical death was modified. Clearly, in heart failure patients there are serious restrictions on antiarrhythmic drug use; class Ic drugs and disopyramide are relatively if not absolutely contraindicated. The role of amiodarone in controlling serious arrhythmias and in improving prognosis is under investigation as is the new partial β-agonist, xamoterol.

Torsade de pointes

Torsade de pointes is a cardiovascular manifestation of drug toxicity. Optimal management is to stop all drugs potentially responsible, to correct electrolyte imbalance and to consider atrial pacing in order to stabilize cardiac electrophysiology. Only very rarely should antiarrhythmic drug administration be considered, particularly since all antiarrhythmic drugs are capable of arrhythmogenesis. Of the antiarrhythmic agents, such as mexiletine, advocated for control of torsade de pointes there are almost as many reports attesting a role for these same agents in causing the arrhythmia.

CATECHOL-INDUCED ARRHYTHMIAS

Catechol-related VT occurs in children, and is refractory to conventional antiarrhythmic agents but can be prevented by β-adrenoceptor-blocking drugs. Catecholamine-related VT in adults may also respond to β-adrenoceptor-blocking drugs but in many patients the arrhythmia occurs through a mechanism of exercise-induced myocardial ischaemia in the presence of underlying coronary artery disease.

VENTRICULAR ECTOPIC BEATS POSTINFARCTION

The rationale for treating ventricular ectopic beats in survivors of acute myocardial infarction is not established. Although ventricular ectopic beats are of adverse prognostic significance, currently there is no evidence that their partial or even complete suppression will result in an improved prognosis. The CAPS study was a pilot study for a more major investigation to re-examine the clinical benefit of ventricular ectopic beat suppression. It demonstrated that encainide and flecainide, and to a less extent moricizine, were more effective for ventricular ectopic beat suppression than was imipramine. Whether this comparative efficacy has any bearing on protection
Mortality after myocardial infarction can be reduced by the use of \(\beta\)-adrenoreceptor-blocking drugs\(^{61}\). These agents are not particularly potent in their suppression of ventricular ectopic beats and it has been considered that they might possess anti-VF properties which are not directly related to ventricular ectopic beat suppression. However, in subgroup analysis of a larger study it was observed that those infarct survivors who gained prognostic benefit from \(\beta\)-blockers were those in whom ventricular ectopic beats were suppressed\(^{1401}\).

Antiarrhythmic drugs — situations of particular usefulness

\(\beta\)-ADRENORECEPTOR-BLOCKING DRUGS

\(\beta\)-blocking drugs have many uses in the treatment of cardiovascular disease. Often they are not considered as true antiarrhythmic agents. Yet their benefits in mortality reduction in the long QT syndrome\(^{20}\) and in infarct survivors\(^{81}\) suggests that they may possess important effects against VF. They also have important applications in the control of catecholamine-dependent VT\(^{37}\).

CLASS Ic AGENTS

Propafenone, flecainide, lorcainide, encainide and indecanide are some of the most powerful antiarrhythmic agents and are capable both of remarkable suppression of ventricular ectopic beats and of impressive success rates in the control of ventricular tachyarrhythmias. Demonstrating comparative superiority of one vs the others would involve very large studies and, in practice, recommendations regarding their use has depended more upon tolerability and adverse effect profiles than upon arrhythmia-suppression rates\(^{30}\). Propafenone\(^{41-44}\), lorcainide, encainide and indecanide have complex pharmacokinetics but, in practice, they appear as effective and as reliable as the pharmacokinetically simpler drug, flecainide.

Propafenone\(^{42}\) does have special properties that set it apart from the other class Ic agents. Experimental work has documented a small but important \(\beta\)-adrenoreceptor-blocking action\(^{45}\). As yet there is little evidence in man that this additional antiarrhythmic effect is of clinical relevance but anecdotal evidence is supportive\(^{37,46}\). On theoretical grounds, there would be much to commend a drug that offered in a single compound, the advantages of class Ic and class II actions. Current clinical studies confirm propafenone's important class Ic actions with impressive suppression rates for ventricular ectopic beats\(^{47-51}\) and VT\(^{52-54}\) associated with a wide range of cardiovascular pathology.

CLASS Ib AGENTS

Mexiletine, tocainide and lignocaine offer a narrow, precise electrophysiological action with an extremely low incidence of cardiovascular adverse effects. In particular, in normal doses, they cause little or no depression of left ventricular performance. Their usefulness is limited by a relatively high rate of non-cardiovascular adverse effects predominantly of the gastrointestinal and central nervous systems. Lignocaine has a special and perhaps specific role in the prophylaxis of primary VF (acute phase postocclusion VF) complicating acute myocardial infarction\(^{11}\). Mexiletine and tocainide are of substantial value in treating symptomatic ventricular arrhythmias in patients with impaired left ventricular function and these agents may have an important future, used as combination therapy with other antiarrhythmic compounds\(^{35}\).

CLASS Ia AGENTS

Procainamide, quinidine and disopyramide have a long tradition of use as antiarrhythmic agents and are effective against a wide variety of ventricular arrhythmias. Yet there are no ventricular arrhythmias for which they might be considered 'specific'. Their use has been limited by important and sometimes serious unwanted effects (procainamide — ANF conversion; quinidine — syncope, arrhythmogenesis; disopyramide — left ventricular depression), but used wisely, taking care to minimize dosing, they are an important part of the therapeutic armamentarium against ventricular arrhythmias.

CLASS III AGENTS

Amiodarone probably is the most important agent for VF prevention and it can control a remarkable proportion of otherwise drug-refractory life-threatening ventricular tachyarrhythmias\(^{56}\). Serious non-cardiac adverse effects limit its use although most are reversible on stopping therapy and many can be avoided by prescribing only the smallest dose necessary for arrhythmia control. Amiodarone's remarkable efficacy is associated with little or no depression of left ventricular
performance thus earning it a particular role in the treatment of ventricular tachyarrhythmias complicating heart failure\[31\]. Whether this represents a 'specific' indication or not depends upon definition, but certainly few other drugs can match its performance in this situation. Amiodarone also improves prognosis for the high-risk subset of patients with hypertrophic cardiomyopathy\[22\]. Were it not for fears of toxicity, amiodarone undoubtedly would have been tested in many other clinical situations, for example the prophylaxis of secondary VF.

**CLASS IV AGENTS**

Despite the importance of calcium to the electrophysiology of ischaemic myocardium, no studies to date have indicated a 'specific' role for calcium antagonist drugs in the management of ventricular tachyarrhythmias.

**DIGOXIN**

Digoxin therapy has little to offer in the management of ventricular tachyarrhythmias.

**BRETYLIUM**

Bretylium is an unusual drug with important antisympathetic properties. It has been used as a 'last resort' in the management of serious and otherwise medically intractable ventricular arrhythmias but its usage may deserve reappraisal. It has achieved chemical defibrillation of VF\[57\] but this result is the exception rather than the rule.

**Conclusions**

Detailed and accurate descriptions of arrhythmias and the availability of antiarrhythmic drugs with either precise or unique electrophysiological effects would be necessary if specificity in arrhythmia treatment were to be achieved. Experience to date suggests that such developments are unlikely. Arrhythmias can be identified only crudely and most involve multiple electrophysiological mechanisms. Antiarrhythmic drugs offer imprecise and, at times, unpredictable electrophysiological effects. \(\beta\)-adrenoreceptor-blocking drugs and the class Ib agents have precise, relatively restricted, electrophysiological actions and it is not surprising that they may have nearly 'specific' roles. Propafenone appears unique in possessing two of the most powerful antiarrhythmic actions, \(\beta\)-adrenoreceptor blockade and a Vaughan Williams Class Ic action, but the clinical situations in which these effects may best be deployed are yet to be identified.

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