



Supplement

Antiarrhythmic Drugs : Present and Future

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Abstract

The treatment of cardiac arrhythmias has undergone a sea change with the advent of catheter ablative procedures (radiofrequency ablation) and use of implantable cardioverter defibrillator (ICD). The antiarrhythmic drugs at times are used to prevent device related arrhythmia rather than being used for primary treatment of arrhythmias.

Antiarrhythmic drugs are grouped according to their drug action as proposed by Vaughan William or by their action on ion channels. Currently amiodarone is the most commonly used drug followed by sotalol, class II, class IV and other class III drugs. It is now well known that amiodarone has several non-cardiac toxic effects particularly on long term therapy. Efforts are on to develop newer drugs which have efficacy of amiodarone without complex pharmacokinetics and toxicity. Newer drugs like azimilide with class III action are also being developed. ©

Antiarrhythmic drugs are often classified according to their electrophysiologic effects. The classification proposed by Vaughan Williams is a classification of drug actions that should be antiarrhythmic, not a classification of drugs (Table 1).¹ An alternate classification based on action of drugs on ion pumps is also included (Table 1). The benefits and risks of antiarrhythmic therapy should be considered in every case before initiating the therapy. The potential benefits include decrease in arrhythmia related symptoms (difficult to demonstrate) and reduction in mortality (very little evidence for most drugs). The cardiovascular risks include increased mortality during long term therapy, heart failure, bradyarrhythmias or heart block and new proarrhythmia (torsade de pointes) or worsened arrhythmias. Non cardiovascular toxic effects can occur due to many agents. A brief description of available antiarrhythmic drugs is given below.¹ Table 2 summaries dosage schedules.

LIDOCAINE (Xylocaine)

Lidocaine is often the drug of choice for the acute suppression of symptomatic ventricular arrhythmias in patients with myocardial infarction (MI). It is effective in decreasing the incidence of primary ventricular fibrillation (VF) but does not reduce total mortality rates. The side effects usually pertain to central nervous system (CNS) and include tinnitus, seizures, drowsiness, dysarthria, confusion, hallucinations, dysesthesia and even coma. Lidocaine should be avoided unless a temporary pacemaker is available in patients with infra-nodal conduction defects.

MEXILETINE (Mexitil)

Mexiletine is used in the treatment of ventricular arrhythmias and has, on occasion, been effective in treating arrhythmias that were refractory to other agents. Success rates vary between 6 and 60 percent. Mexiletine therapy should be initiated with a low dosage, which is increased at 2- to 3-day intervals until efficacy or intolerable side effects, such as tremor or other CNS symptoms, develop.

PROCAINAMIDE (Pronestyl – SR, Procan – SR)

Procainamide, like quinidine, is effective against both supraventricular and ventricular arrhythmias. Although the two drugs have similar electrophysiologic effects, they are clinically different, and one agent may be effective for a patient when the other is not. Procainamide is useful in acute management of patients with reentrant supraventricular tachycardia (SVT) and atrial fibrillation (AF) and flutter associated with Wolff-Parkinson-White syndrome (WPW).

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DISOPYRAMIDE (Norpace)

Disopyramide is effective against a broad range of supraventricular and ventricular arrhythmias. Although its antiarrhythmic profile is similar to that of quinidine and procainamide it is better suited for long term therapy. Its negative inotropic and anticholinergic actions limit its usefulness. The predominant side effects include new or worsened congestive heart failure, urinary retention, constipation, dry mouth, and esophageal reflux.

QUINIDINE (Quinagulate, Quinadex)

Quinidine has been used successfully for a variety of supraventricular and ventricular arrhythmias, including conversion of AF or flutter, SVT, ventricular extra-systoles, VT and VF. Marked prolongation of the QT interval, syncope, torsade de pointes type of proarrhythmia and sudden death have been reported even with low or usual dosage.

PROPAFENONE (Rythmol)

Propafenone was marketed in Germany in 1977. It is similar to other antiarrhythmic agents in overall efficacy and tolerance by patients. It has a role in the treatment of many types of arrhythmias, including supraventricular arrhythmias.

FLECAINIDE (Tambocor)

Flecainide is very effective in suppressing a variety of ventricular and supraventricular tachycardias. The finding of increased mortality rates when flecainide is given to patients with coronary artery disease (CAD) has led to restricted usage; however, there has been no evidence to indicate that this increase in mortality rate is seen when flecainide is given to treat supraventricular arrhythmias in patients without CAD.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers, verapamil and diltiazem are useful as antiarrhythmic agent in the management of SVT, where they are administered to slow the ventricular rate in patients with atrial fibrillation or flutter and to treat and prevent AV nodal reentrant tachycardia. Intravenous diltiazem is useful for the temporary control of rapid ventricular rate during AF and flutter.

BRETYLIUM (Bretylol)

Bretylium is effective for acute therapy of VT and VF. The usual intravenous dosage for bretylium is 5 mg/kg given at a rate dependent upon the clinical setting.

SOTALOL (Betapace)

Sotalol is unlike other beta-adrenergic antagonists in that it

Table 1 : Classification of drug actions as proposed by vaughan williams

Class I	: Membrane active drugs
IA	: Quinidine, Procainamide, Disopyramide, Moricizine
IB	: Lidocaine, Mexiletine, Tocainide, Phenytoin
IC	: Flecainide and propafenone
Class II	: Beta adrenergic antagonism Propranolol, Esmolol, Acebutolol, Timolol and Metoprolol
Class III	: Prolong duration of action potential and refractoriness Amiodarone, Sotalol, Bretylium, Ibutilide, dofetilide, N – acetyl procainamide (NAPA).
Class IV	: Calcium channel antagonists Verapamil and Diltiazem
Unclassified in this system Digoxin, Adenosine	

ALTERNATE CLASSIFICATION OF ANTIARRHYTHMIC DRUG ACTIONS :

Class I — Sodium channel blockers	Class II — Beta blockers	Class III — Potassium channel blockers	Class IV - Calcium channel blockers
Disopyramide (Norpace)	Acebutolol (Sectral)	Amiodarone (Cordarone, Pacerone)	Diltiazem (Cardizem, Tiazac)
Flecainide (Tambacor)	Atenolol (Tenormin)	Azimilide (Stedcor)	Verapamil (Calan, Covera, Isoptin)
Lidocaine (Xylocaine)	Betaxolol (Kerlone)	Bepidil	
Mexiletine (Mexitel)	Bisoprolol (Zebeta)	Dofetilide (Tikosyn)	
Moricizine (Ethmozine)	Carvedilol (Coreg)	Ibutilide (Corvert)	
Procainamide (Procan, Procanabid, Pronestyl)	Esmolol	Sotalol (Betapace)	
Propafenone (Rythmol)	Metoprolol (Toprol, Lopressor)	Tedisamil	
Quinidine (Various)	Nadolol (Corgard)		
Tocainide (Tonocard)	Propranolol (Inderal)		
	Sotalol (Betapace)		
	Timolol (Blocadren)		
Miscellaneous			
Adenosine (Adenocard)			
Digoxin (Lanoxin)			

Table 2 : Dosage and plasma concentration ranges for antiarrhythmic agents

Agent	Usual initial dosage	Modification of dosage in disease	Dosage range	Maximum Single Dose	Therapeutic Range, µg/mL
Quinidine (sulfate)	200 mg q 6 h	None	800-2400 mg / day	600	0.7 – 5.5
Procainamide (sustained release)	500 mg q 6 h	↓ CHF ↓ RI	2000-6000 mg / day	1500	4 – 8
Disopyramide	100 mg q 6 h	↓ CHF ↓ HI ↓ CHF	300-1200 mg / day	300	2 – 5
Lidocaine	—	↓ CHF ↓ HI	1-4 mg/ min IV	—	1.5 – 5
Tocainide	400 mg q 8 h	↓ HI ↓ RI	1200-2400 mg/ day	800	4 – 10
Mexiletine	200 mg q 8 h	↓ CHF ↓ HI?	600 – 1200 mg/ day	400	0.7 – 2
Flecainide	50-100 mg q 12 h	↓ CHF ↓ RI ↓ HI ?	200- 400 mg / day	200	
Propafenone	150 mg q 8 h	SEE TEXT	300 – 900 mg/ day	300	
Amiodarone (load)	600-1400 mg/ day	NONE	200 – 600 mg / day	600	
Bretylium	—	↓ RI	1-4 mg / min IV	—	
Ibutilide	1 mg, repeat after 10 min	—	0.01 mg / kg – 1 mg X 2	1 mg	
Dofetilide	500 mcg bid	↓ RI	125 – 1000 mcg / d	500 mcg	

CHF = Congestive cardiac failure; HI = Hepatic insufficiency; RI = Renal insufficiency

prolongs the action potential, producing a dose-related increase in refractoriness of cardiac tissues. This unique combination of properties makes sotalol effective in a variety of supraventricular and ventricular arrhythmias. It has been found to be effective in patients with sustained VT evaluated by programmed ventricular stimulation. A major concern is occurrence of torsades de pointes.

AMIODARONE (Cordarone)

At present, amiodarone is widely used in a wide range of VT, SVT, for conversion and slowing of rate in AF, AV nodal reentrant tachycardia, and tachycardias associated with the WPW syndrome.

Without a loading-dose regimen, amiodarone requires several weeks to months before producing its antiarrhythmic action. Large intravenous dosages or oral loading dosages can hasten the onset of therapeutic effects. From small prospective studies, loading dosages have varied from 600 to 1400 mg / day for 2 to 21 days. Recent large clinical trials have utilized a lower loading dose, of 600 to 800 mg daily for 14 days. Because of relatively rapid redistribution out of myocardial tissue, the dosage should be tapered over a period of several weeks. The usual maintenance dose varies from 200 to 600 mg / day, and because of the severe nature of adverse reactions, the lowest effective dosage should be prescribed.

There are several side effects which can occur. The most serious being lethal interstitial pneumonitis. Hyper- or hypothyroidism occurs in 4 percent of patients treated chronically. Accumulation of corneal microdeposits is almost uniform during long-term therapy and can progress to the point of interfering with vision. A proper monitoring of lung function, thyroid function and eye examination is strongly recommended in patients who are on chronic therapy.

IBUTILIDE (Corvert)

Ibutilide was given FDA approval for the rapid conversion of recent-onset AF or flutter in 1995. Ibutilide is available only for intravenous administration.

DOFETILIDE (Tikosyn)

Dofetilide was approved and marketed in 2000 for oral therapy of AF and flutter. In controlled trials of 1000 patients, 30% of patients with AF given a dosage of 500 µg bid converted to sinus rhythm, compared to 6% in the control treated with sotalol and 1% of given placebo. Prevention of recurrence was demonstrated, with 62 to 71 % remaining in sinus rhythm after 6 months, compared to 59% for sotalol and 26 to 37% for placebo. The Danish Investigators of Arrhythmia and Mortality on Dofetilide, or DIAMOND trial¹ in 1518 patients with reduced ejection fraction and symptoms of heart failure showed the drug to be safe with reduced incidence of hospitalization for heart failure.

ADENOSINE (Adenocard)

Adenosine is very effective for the acute conversion of paroxysmal SVT due to reentry involving the AV node. Sixty percent of patients respond at a dose of 6 mg, and an additional 32 percent respond when given a higher dose, of 12 mg. Because of the fleeting and relatively selective action of adenosine on the AV node, some have suggested that it be used as a diagnostic tool in patients with narrow and wide – complex tachycardia.

MANAGEMENT OF ARRHYTHMIAS

Atrial fibrillation (AF)

Treating AF, first of all, requires identifying and, when possible, correcting underlying cardiac or noncardiac disorders. If the arrhythmia persists, attempts should be made to terminate it by pharmacologic or electrical means. Quinidine and other class IA drugs, such as procainamide and disopyramide, and more recently class IC drugs (flecainide and propafenone) and class III drugs (amiodarone and sotalol) have all been used. Depending on factors such as the age of the patient, the duration of the arrhythmia, the left atrial size, and the severity of any underlying cardiac or noncardiac disorders, antiarrhythmic-drug therapy is successful in converting AF to sinus rhythm in 35 to 75 percent of patients. Recently, Ibutilide and Dofetilide have also been utilized for conversion of AF and control of ventricular rate in AF. It is not clear which drug is most effective, because different antiarrhythmic drugs have rarely been compared in the same patient.

Supraventricular Tachycardia (SVT)

Catheter ablative techniques have revolutionized the management of patients with SVT. These techniques are treatment of choice for all symptomatic patients with tachycardia mediated by accessory pathways or with atrial flutter and for most patients with symptomatic AV nodal reentrant tachycardia. In those patients where ablation techniques can not be applied due to financial or other reasons, the long term drug treatment remains important and is summarized in Table 3.²

Prevention of Ventricular Tachycardia (VT)

In the past decade ICDs have become firmly established as the first line therapy for survivors of unstable ventricular arrhythmias.³ The ICDs are also being increasingly used for primary prevention in high risk patients. The evidence for using ICDs for secondary prevention of VT comes from three large studies called as AVID, CIDS and CASH. These studies showed a 20-30 % reduction in all cause mortality with ICD implantation.⁴

Table 3 : Long-term antiarrhythmic-drug therapy for supraventricular tachycardia

Tachycardia	First Choice	Second Choice	Third Choice
AV nodal reentrant and AV reentrant (concealed by pass tract)	Calcium-channel blockers, beta-blockers, digoxin	Flecainide, propafenone*†, Quinidine, procainamide, disopyramide‡	Amiodarone
WPW syndrome	Flecainide, propafenone* Quinidine, procainamide, disopyramide‡	Beta-blockers, calcium-channel blocker†	Amiodarone, Sotalol
Sinus-node reentrant	Calcium-channel blockers, beta-blockers, digoxin	Flecainide, propafenone*†, Quinidine, procainamide, disopyramide‡	—
Unifocal atrial Reentrant	Flecainide, propafenone* Quinidine, procainamide, disopyramide‡	Amiodarone, sotalol	—
Automatic	Beta-blockers, calcium channel blockers, digoxin	Flecainide, moricizine†	Amiodarone
Multifocal atrial	Magnesium and potassium supplements	Metoprolol, verapamil†	—

*For patients with no associated heart disease; †To be used in combination with a first-choice drug; ‡For patients with associated heart disease; AV = Atrioventricular, WPW = Wolff-Parkinson-White

Despite their inferiority with respect to total mortality when compared with ICDs, antiarrhythmic drugs are moderately effective at suppressing both inducible and spontaneous VT.⁴ Oral amiodarone appears to be the most effective drug, 50-60 % efficacy in preventing VT recurrences. Class III drugs also have some efficacy in suppressing VT. In a recent randomized study, both oral d, l-sotalol (160 mg bid) and dofetilide (500 mg bid) suppressed the inducibility of VT in about 35% of patients. Either of these drugs is a reasonable option in patients where amiodarone is to be avoided. Class IA drugs have largely fallen out of favor because of side effects, the risk of pro-arrhythmia, and the availability of better options. Nonetheless, procainamide and quinidine are associated with a roughly 30% success in suppressing inducible VT and may play a role in preventing device therapies in selected patients. Finally, lidocaine and mexiletine can be safely used in combination with other medications (e.g. class III drugs or amiodarone) for suppression of VT in difficult cases.

INVESTIGATIONAL DRUGS

Analogs of amiodarone, such as ATI-2001, dronedarone, and SR-33589 are being developed. Dronedarone has a very well characterized pharmacokinetic and pharmacodynamic profile and has a reasonable safety profile at doses lower than 2000 mg per day. More data is needed from this new drug.

Azimilide is an antiarrhythmic drug with potassium-channel-blocking properties that prolongs the cardiac action potential and refractory periods. In a recent study azimilide was found to be effective

in patients with symptomatic tachyarrhythmias and ICDs therapies. Other drugs, such as ambasilide, are also in clinical development, and chromanol 293B is in preclinical testing.

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