Antiarrhythmic drugs

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The number of antiarrhythmic drugs available in Canada is increasing. To provide optimum treatment of cardiac arrhythmias, the physician must appreciate the narrow toxic-to-therapeutic ratio and be familiar with the clinical pharmacology of currently available antiarrhythmic drugs. The use of conventional and newer antiarrhythmic drugs will be discussed in this summary.

Classification of antiarrhythmic drugs (Table)
Vaughan Williams[1] proposed a four-level classification system which was modified recently by Harrison[2] to include newer drugs. Although this classification is based upon cellular electrophysiologic findings, it is useful clinically, particularly when treating patients with combined therapy. Class I agents have membrane – stabilizing or local anaesthetic effects and act primarily by blocking fast sodium channels. Examples of Class I drugs include quinidine, procainamide, disopyramide, lidocaine, tocainide and investigational drugs like flecainide. Class I drugs are subclassified as Ia, Ib, Ic on the basis of effects on intracardiac conduction.

TABLE Classification of antiarrhythmic drugs

Class			*Drugs*
I	Local anaesthetics		
	Ia	↓ phase 0 ↑ repolarization ↓ conduction ↓ automaticity	Quinidine Procainamide Disopyramide
	Ib	↓ repolarization ↓ automaticity	Lidocaine Mexiletine Tocainide
	Ic	↓ ↓ phase 0 ↓ ↓ conduction	Flecainide Encainide
II	Beta-blockers	Inhibit sympathetic activity	Propranolol
III		Prolongation of the action potential	Amiodarone Bretylium
IV	Calcium antagonists	Block the slow inward current	Verapamil

Class II drugs are beta-blocking agents such as propranolol. Class III drugs mainly prolong the duration of the action potential; examples are amiodarone and bretylium. Class IV drugs are calcium antagonists such as verapamil and diltiazem.

Quinidine, procainamide, disopyramide
Quinidine is the oldest antiarrhythmic drug and remains widely used. Quinidine is a Class Ia agent. It decreases automaticity and Vmax, slows conduction and increases refractory periods of the atrium, His-Purkinje system and ventricle. In the AV node these effects are countered by its anti-cholinergic properties. Quinidine is also a vasodilator and has mild inotropic effects. The drug is mostly metabolized by the liver with an elimination half-life of five to ten hours. It is an effective antiarrhythmic agent for the prevention of atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular premature beats and ventricular tachycardia. Quinidine is also used to terminate atrial fibrillation and is effective in approximately 20 per cent of patients. It is less effective in terminating atrial flutter and may in some instances increase the ventricular rate (by converting a 2:1 to a 1:1 atrioventricular response) because of drug-induced slowing of atrial rate and its vagolytic effect in the AV node. Treatment is usually started at 200 mg q 6 hours orally, with a range of doses of 800 to 2400 mg/day. Slow release preparations are available that can be given twice daily. Plasma levels for antiarrhythmic effects are 2 to 5 $\mu g \cdot ml^{-1}$. The most frequent side effect is diarrhoea (20 to 30 per cent of patients) and the most serious is syncope or sudden death (one to two per cent of patients) usually associated with marked QT prolongation and ventricular tachycardia (torsades de pointes). Quinidine increases plasma digoxin concentrations and for this reason digoxin dosage should be reduced by 50 per cent in patients receiving quinidine.

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Procainamide possesses most of quinidine's electrophysiologic properties. It has less vagolytic activity and causes less QT prolongation. It has minimal negative inotropic effect. Procainamide is metabolized by the liver into N-acetyl procainamide (NAPA) which is excreted by the kidneys. The parent compound appears to have greater electrophysiologic effects than NAPA. Procainamide is useful for the same spectrum of arrhythmias described for quinidine. It is used to treat both supraventricular and ventricular arrhythmias. Procainamide may be given by the intravenous route to obtain rapid antiarrhythmic effects. A loading dose of 1000 mg can be given intravenously over a 20 min period (50 $mg \cdot min^{-1}$) following by a maintenance infusion rate of 2 to 8 $mg \cdot min^{-1}$. We have found this regimen to be useful to convert atrial fibrillation of recent onset and sustained ventricular tachycardia. The usual range of oral dosages are 2000 mg to 6000 mg/day. The elimination half-life of procainamide is short (three to five hours) and oral administration requires four-hour dosing intervals. Sustained-release preparations are now available allowing six-hour dosing intervals. Drug-induced lupus erythematous may develop in patients receiving prolonged therapy especially in those who are slow acetylators and is a major limiting factor for its long-term use. The therapeutic plasma level is 4 to 12 $\mu g \cdot ml^{-1}$.

Disopyramide is a synthetic agent which has similar electrophysiologic effects to those of quinidine and procainamide. However, disopyramide has significant negative inotropic effects and more potent vagolytic effects. Disopyramide is used to treat supraventricular and ventricular arrhythmias and is similar to quinidine or procainamide in efficacy. The elimination half-life is eight to nine hours and about half an oral dose is excreted unchanged by the kidney. Oral dosages range from 400 to 800 mg/day. The most frequent side effects are dry mouth, constipation, urinary retention and blurred vision. Because of its negative inotropic effects, disopyramide should be avoided in patients with left ventricular dysfunction. The therapeutic plasma level is 2 to 5 $\mu g \cdot ml^{-1}$.

Lidocaine, mexiletine, tocainide

Lidocaine is the most frequently used intravenous antiarrhythmic agent because of its rapid onset of action and its efficacy against ventricular arrhythmias, primarily with acute myocardial infarction. Mexiletine and tocainide are congeners of lidocaine that are suitable for oral use. Unlike quinidine, this group (Class Ib) of drugs shortens the action potential duration with little effect on conduction. The major electrophysiologic effect is depression of spontaneous phase 4 depolarization. Mexiletine and tocainide are probably less potent than other available oral drugs but may provide effective therapy of ventricular arrhythmias particularly those associated with acute myocardial infarction or cardiac surgery. Mexiletine and tocainide may be more effective when used in combination with a Class Ia agent or a beta-blocker. Lidocaine has a relatively wide toxic-to-therapeutic ratio, at high concentrations it can cause seizures. Mexiletine and tocainide have a high incidence of dose-related side effects (tremor, dizziness, visual blurring, nausea) but serious toxicity is rare. Lidocaine and mexiletine are eliminated metabolically by the liver (90 per cent), tocainide is excreted 40 per cent unchanged in the urine and 60 per cent metabolized by the liver. The half-life is 9–12 hours for mexiletine and 11–15 hours for tocainide. Lidocaine is administered with a loading dose of 1 to 2 $mg \cdot kg^{-1}$ followed by a 1 to 4 $mg \cdot min^{-1}$ infusion. The elimination half-life of lidocaine is one to two hours in normal subjects and can be over ten hours in patients with acute myocardial infarction and heart failure. In order to avoid toxic concentrations, the dose of lidocaine should be decreased and frequently reassessed in elderly patients and in patients with congestive heart failure or hepatic dysfunction. The therapeutic oral dose range of mexiletine is 400 to 1200 mg/day and 1200 mg to 2400 mg/day for tocainide.

Flecainide – encainide

Flecainide and encainide are Class Ic antiarrhythmic drugs presently undergoing clinical testing in the United States and Canada. They are primarily used for ventricular arrhythmias. Both drugs are extremely potent and available data suggest that they are usually well tolerated. However, worsening of arrhythmias has been reported to occur in some patients treated with encainide or flecainide.

Beta-blockers

As antiarrythmic agents, beta-blockers are frequently used to control the ventricular rate in atrial

fibrillation, and for catecholamine (phaeochromocytoma, anaesthesia with halothane) or ischaemia-related arrhythmias. They are also used in combination with Class Ia agents to control recurrent supraventricular tachycardia. More recently, several trials have demonstrated a reduction in sudden death following myocardial infarction in patients treated with beta-blockers. This reduction in mortality may be related to an anti-ischaemic effect and/or a direct antiarrhythmic effect.

Amiodarone, bretylium

Amiodarone and bretylium are Class III agents. Amiodarone is a benzofuran derivative that greatly prolongs the action potential duration and the atrio-ventricular refractory periods. It is probably the most effective antiarrhythmic agent for both supraventricular and ventricular arrhythmias. However, its use is associated with a variety of adverse effects some of which can be fatal. Side effects include corneal micro-deposits, hypothyroidism, hyperthyroidism, blue skin discoloration, bradyarrhythmias and pulmonary interstitial fibrosis. Amiodarone has a very long elimination half-life (3 to 15 weeks). The drug is not yet commercially available. In Canada, amiodarone is currently reserved for malignant or severely incapaciting arrhythmias refractory to conventional drugs.

Bretylium is a sympathetic ganglion blocking agent. The drug is used intravenously for the treatment of malignant ventricular arrhythmias usually in the setting of acute myocardial infarction. The elimination half-life is five to ten hours. The major side effect of bretylium is postural hypotension that may persist for several hours or days after the drug has been discontinued. Initial release of catecholamines may cause transient sinus tachycardia, hypertension and acceleration of arrhythmias. Bretylium is given with a loading dose of 5 $mg \cdot kg^{-1}$ over 10–15 minutes followed by a maintenance infusion at a rate of 0.5–3.0 $mg \cdot min^{-1}$. Bretylium can be effective in treating recurrent ventricular tachyarrhythmias refractory to lidocaine and other conventional drugs.

Calcium antagonists

Verapamil is the prototype of this class of drugs. The sinus node and the AV node are particularly sensitive to verapamil because these tissues are dependent on slow channel activity. Intravenous verapamil is the drug of choice for terminating supraventricular tachycardia and may be useful to slow the ventricular response in atrial fibrillation or flutter. Verapamil may accelerate the ventricular rate in patients with atrial fibrillation and preexcitation (Wolff-Parkinson-White). The drug should not be used in that situation. The drug must be used with caution in patients with myocardial dysfunction or sinus node disease. The intravenous dose is 5 mg infused over one to two minutes, a second injection of 5 mg may be given 15 minutes later. Oral verapamil (80 to 120 mg, three or four times a day) may be effective for the prevention of supraventricular tachycardia.

In summary, no ideal antiarrhythmic agent is currently available. Nevertheless, the appearance of several new drugs now makes it easier for the clinician to individualize and to optimize the treatment of arrhythmias. A more detailed discussion of this topic can be found in recent reviews.[3,4]

References

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