Review Article

Is there an ideal antiarrhythmic drug? A review – with particular reference to class I antiarrhythmic agents

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Introduction

The number of antiarrhythmic drugs has grown dramatically over the last 15 years, because of the need for effective and safe agents to prevent or control cardiac arrhythmias.

In the clinical situation, logical choice of a particular antiarrhythmic drug depends not only on a demonstration of its effectiveness against various sorts of arrhythmias, but also on a knowledge of its pharmacokinetics, haemodynamics and adverse effects.

Myocardial action potential

Since the mode of action of antiarrhythmic drugs continues to be interpreted according to their effects on the myocardial action potential, the characteristics of the latter must be briefly discussed.

When the membrane potential of the cardiac cell is reduced from the resting potential (around -90 mV) to the threshold potential (-60 to -70 mV), a rapid upstroke of the action potential follows, phase 0 (Figure 1). This is mainly mediated by a fast inward sodium current (except sinoatrial and atrioventricular nodes), whilst the slow inward calcium current contributes to the later part of it. The fast sodium current not only reduces the membrane potential but also reverses it to about $+30$ mV (positive overshoot). The rapid inward sodium current is quickly inactivated and rapid repolarization starts, phase 1, which is believed to result in part from the inactivation of sodium conductance and partially related to the activation of a chloride ion inward current. This is followed by the plateau, phase 2, the major determinant of which is the slow current. This current is carried mainly by calcium ions; sodium ions, however, can also participate. After the plateau, final repolariza-

Figure 1 Diagram of a myocardial action potential, adapted from Kumana & Hamer, 1979. Purkinje cells: no overshoot and no phase 1; contractile cells: no rising phase 4.

tion, phase 3, is initiated. This phase is due mainly to passive potassium ion leakage from the cell, thus restoring the negative membrane potential. The net cellular ionic exchange during the action potential is corrected by continual activity of the cell membrane energy-dependent sodium/potassium pump.

Phase 4 diastolic depolarization represents the pacemaker activity in Purkinje cells and pacemaker tissue. The slow diastolic depolarization reflects a gradual shift in the balance between background inward and outward current components in the direction of net inward (depolarizing) current.

Classification of antiarrhythmic agents

An understanding of the manner in which drugs are used to treat arrhythmias must be based in part on an

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understanding of their effects on the electrical activity of the normal heart and its constituent cells.

The most widely used classification of antiarrhythmic drugs is that introduced by Vaughan Williams (1970), based on the principle mode of action of these agents on the action potential of the myocardial cell. He classified antiarrhythmic drugs which were available at that time into at least three groups: (1) drugs with direct membrane action, e.g. quinidine and lignocaine; (2) the sympatholytic drugs such as the beta-adrenoceptor antagonists and adrenergic neurone blocking drugs, e.g. propranolol; (3) compounds prolonging the duration of the myocardial action potential, such as amiodarone. At that time, a fourth group was suggested which included centrally acting drugs such as phenytoin, but this was controversial. This classification was subsequently modified to include the slow channel antagonist, verapamil, as a class IV agent (Singh & Vaughan Williams, 1972). Later, subclassification of class I agents into a and b was introduced by Singh & Hauswirth (1974); class Ia comprising quinidine and quinidine-like drugs, and class Ib consisting of lignocaine and phenytoin. Opie (1980) applied minor changes to that classification by introducing the subgroup Ic to include aprindine and propranolol (which, in addition to its beta-adrenoceptor blocking action, also has membrane stabilizing activity). Harrison *et al.* (1981) also divided class I into three groups a, b and c, depending upon their effects on action potential duration.

A fifth class of antiarrhythmic action involving impedance of chloride ion transmembrane flux has been suggested by Millar & Vaughan Williams (1981), with alinidine as a member of this group. Table I shows the classification of antiarrhythmic drugs (adapted from Camm & Ward, 1981).

Class I antiarrhythmic action (membrane stabilizing)

Szekeres & Vaughan Williams (1962) demonstrated that a number of antiarrhythmic compounds had similar effects on the myocardial action potential by interference with the mechanism of depolarization. All agents classified under this category (Table I) restrict the fast sodium inward current responsible for the upstroke of the myocardial action potential. They also have a similar, so called 'local anaesthetic' activity on nerve. This is due to the similarity between the sodium depolarizing current in the nerve and myocardial cell, but since the concentration of drug needed to block nerve conduction is 10–200 times greater than that required to treat arrhythmias, it is unlikely to occur during antiarrhythmic therapy (Vaughan Williams, 1980). Although several agents of this group depress myocardial contractility, there is not an invariable association between restriction of fast inward current and negative inotropism. For instance, papaverine is a class I agent that has a positive inotropic action (Vaughan Williams & Szekeres, 1961).

The main electrophysiological property of this group of antiarrhythmic compounds is reduction of

Table I Classification of antiarrhythmic agents (adapted from Camm & Ward, 1981)

<i>Class I</i> <i>Membrane stabilizing*</i>	<i>Class II</i> <i>Sympatholytic</i>	<i>Class III</i> <i>Prolonging action potential duration</i>	<i>Class IV</i> <i>Slow channel antagonists</i>	<i>Class V</i> <i>Chloride channels antagonists</i>
Ia: Disopyramide Procainamide Quinidine	Beta-adrenoceptor blocking agents Bretylium Guanethidine Bethanidine	Amiodarone Bretylium Bethanidine Clofilium Meobentin N-acetyl procainamide Sotalol	Diltiazem Tiapamil Verapamil	Alinidine
Ib: Ethmozin Lignocaine Mexiletine Phenytoin Tocainide				
Ic: Ajmaline Aprindine Encainide Flecainide Lorcainide Propafenone				
Others (unclassified): Antazoline Carbamazepine Prajmalium				

*There is no general agreement yet on classifying class I agents into these three subgroups

Table II Summary of properties of class I antiarrhythmic drugs

<i>Drug</i>	<i>Dosage</i>	<i>Therapeutic plasma concentration</i>	<i>Levels associated with toxicity</i>	<i>Elimination half-life</i>	<i>Bio-availability</i>	<i>Protein binding</i>	<i>Metabolism and excretion</i>
Ajmaline	i.v.: 2 mg/kg	i.v.: 1–3 µg/ml	15 µg/ml	i.v.: 15 min			
Aprindine	orally: 50–150 mg/day	1–2 µg/ml	> 2 µg/ml	13–50 h	80%	85–95%	primarily hepatic, 2% excreted unchanged in urine
Disopyramide	orally: 100–200 mg every 6–8 h i.v.: 2 mg/kg	2–5 µg/ml	7 µg/ml	5–7 h	80–90%	35–95%	40–60% excreted unchanged in urine
Encainide	i.v.: 0.5–1 mg/kg over 15 min orally: 25–100 mg every 6–8 h	10–150 ng/ml		3.4 h	7–80%		mainly hepatic
Ethmozin	orally: 200–750 mg/d	250–1300 ng/ml		4–10 h	High		
Flecainide	i.v.: 1–2 mg/kg orally: 200 mg twice daily	200–800 ng/ml		7–22 h	95%	48%	25% excreted unchanged in urine
Lignocaine	i.v.: bolus 1–2 mg/kg + infusion 1–4 mg/min	1.4–6 µg/ml	9 µg/ml	1.8 h	30%	40–80%	primarily hepatic, < 5% excreted unchanged in urine
Lorcinide	orally: 200–300 mg/day i.v.: 1–2 mg/kg over 10 min., may be repeated every 8–12 h	150–400 ng/ml		5–8 h	variable, may approach 100%	85%	primarily hepatic, < 2% excreted unchanged in urine
Mexiletine	i.v.: 150–250 mg over 5 min + infusion orally: 200–300 mg every 8 h	0.5–2.0 µg/ml	3 µg/ml	12–16 h	90%	75%	primarily hepatic, < 10% excreted unchanged in urine
Phenytoin	orally: loading dose 1000 mg over 24 h, maintenance 300–400 mg/day i.v.: 25–50 mg/min to 100 mg repeated every 5 min up to 1000 mg	10–20 µg/ml	< 20 µg/ml	8–60 h	98%	88–96%	primarily hepatic, < 5% excreted unchanged in urine
Prajalium	orally: 20 mg every 6 h	43–145 ng/ml		7.3 h			
Procainamide	i.v.: 100 mg over 2 min then 20 mg/min (total 1 g) orally: 250–500 mg every 3–6 h	4–10 µg/ml	> 16 µg/ml	2.5–4.7 h	75–90%	15%	40–60% renally excreted
Quinidine	orally: 1.2–2 g/day maximum 4 g/day in divided doses	2.3–5 µg/ml	> 6 µg/ml	6–8 h	80–90%	80–90%	primarily hepatic 20% excreted unchanged in urine
Tocainide	orally: 400–600 mg every 8 h i.v.: 750 mg over 15 min	6–10 µg/ml	marginally higher > 11 µg/ml	12–15 h	approaching 100%	50%	30–50% excreted unchanged in urine

Table III Adverse effects, contra-indications and precautions of class I antiarrhythmic agents

<i>Drug</i>	<i>Cardiac adverse effects</i>	<i>Non-cardiac adverse effects</i>	<i>Contra-indications and precautions</i>
Ajmaline	–Intraventricular conduction delay –AV block –Accelerate arrhythmias	–Hepatotoxicity –Agranulocytosis –Neurological: eye twitching, convulsions, respiratory depression	
Aprindine	–Prolonged conduction times, increased PR and QRS duration	–Neurological: tremor, dizziness, vertigo, ataxia, visual disturbances –Psychosis –Hepatotoxicity –Agranulocytosis	
Disopyramide	–Cardiac decompensation –Hypotension –Prolonged cardiac conduction –Complete AV block –Atypical ventricular tachycardia (Torsade de pointes) –Suppression of sinus node function	–Nausea and vomiting –Vagolysis –Skin rash –Psychosis, jaundice, hypoglycaemia –Agranulocytosis	–Significant left ventricular dysfunction –Second and third degree AV block
Encainide	–Worsening of conduction system disease –Prolonged H-V interval and QRS complex –Worsening of ventricular arrhythmias	–Dizziness, ataxia, tremor –Diplopia –Nausea –Metallic taste –Leg cramps	
Ethmozin	Limited information	–i.v.: dizziness, vertigo, headache –p.o.: nausea, epigastric distress pruritis, headache	
Flecainide	–Proarrhythmias –Haemodynamic impairment –Chest pain	–Neurological: dizziness, visual impairment, headache, tremor, paraesthesia –Gastrointestinal: nausea, constipation, diarrhoea, abdominal pain –Asthenia, fatigue	–Conduction system disease –Depressed left ventricular function
Lignocaine	Rare –Cardiac depression –Heart block –Sino-atrial block	Common –CNS: dizziness, tinnitus, visual disturbances, somnolence to convulsions	–Half the dose in poor liver blood flow (low cardiac output, beta blockers) or liver disease –Sick-sinus syndrome
Lorcainide	–Prolongation of PR interval and QRS duration –Worsening conduction disturbances –Hypotension	–Insomnia with sweating and nightmares –Dizziness –Dry mouth –Flatulence –Vivid dreams	–Severe conduction system disease –Severely depressed left ventricular function –Dosage adjustment may be needed in patients with severe hepatic dysfunction
Mexiletine	–Prolonged conduction –Bradycardia –Hypotension –Cardiac depression	–CNS: tremor to convulsions –GI: nausea and vomiting –Dermatological: photosensitive dermatitis	–Severe left ventricular failure –Hypotension –Bradycardia –Sick-sinus syndrome –Concomitant therapy with other class I drugs
Phenytoin	–i.v.: increased or decreased ventricular response rates, decreased contractility, vasodilatation, hypotension	–Neurological: nystagmus to coma –Gingival hyperplasia –Megaloblastic anaemia –Lymphoma-like syndrome –Rash –Hirsutism	–Complete heart block –Caution in liver insufficiency
Procainamide	–Worsening of arrhythmias –Worsening of conduction system disease –Hypotension	–Lupus erythematosus-like syndrome –Agranulocytosis –GI upset –Drug fever –Rash –Eosinophilia	–Shock –Severe heart failure –Heart block –Severe renal failure

Table III Continued

Drug	Cardiac adverse effects	Non-cardiac adverse effects	Contra-indications and precautions
Quinidine	-Syncope and sudden death -Worsening of ventricular arrhythmias (Torsade de pointes) -Worsening of conduction system disease and bradycardia -Facilitation of AV conduction Rare: worsening of congestive heart failure	-GI disturbance -Cinchonism -Fever -Dementia -Haemolytic anaemia -Thrombocytopenia and agranulocytosis -Hypersensitivity reaction -Neurological: tremor to convulsion -GI: nausea, vomiting -Skin rash, hepatitis	-Pre-existing long QT interval, or in combination with any drug causes long QT -Digitalis-induced arrhythmia
Tocainide			

the maximum rate of depolarization (MRD) in the myocardial cell. Other effects of this group, which vary somewhat from one drug to another, comprise an increase in the threshold of excitability, a reduction of conduction velocity and prolongation of the effective refractory period (ERP). These changes are associated with inhibition of the spontaneous diastolic depolarization in automatic fibres, without a significant change in resting membrane potential (Singh *et al.*, 1981a; Keefe *et al.*, 1981).

At the present time class I antiarrhythmic compounds are subdivided into three subgroups (Harrison *et al.*, 1981; Keefe *et al.*, 1981; Hillis & Whiting, 1983; Table I). Class Ia: drugs that block fast inward sodium current (phase 0) during the depolarization of the cardiac cell membrane. Drugs of this type prolong the action potential duration. Class Ib: agents that decrease phase 0 of the action potential and shorten its

duration. Class Ic: compounds that slow phase 0, but have little or no effect on the duration of action potential.

Tables II, III and IV represent a summary of some pharmacokinetic properties, adverse effects, contra-indications/precautions and effectiveness of some class I antiarrhythmic drugs.

Class II antiarrhythmic action (sympatholytic)

It is well known that stress and anxiety (where catecholamines are increased) may precipitate cardiac arrhythmias. Therefore, drugs which antagonize the effects of catecholamines on the heart would be expected to be effective antiarrhythmic agents in certain situations. Sympatholytic drugs may act either directly by competition at the receptor site (beta-adrenoceptor antagonists) or interference with the

Table IV Spectrum of activity of some class I antiarrhythmic compounds against various cardiac arrhythmias

Drugs	Atrial				Ventricular				Dig. ind.		Anomalous pathway		
	PC	TACH	FLUT	FIB	PC/AI	PC/CH	TACH	FIB	SVA	VA	AV	TACH	A FLUT/FIB
Ajmaline							+						
Aprindine	+	+			+	+	+	+	+	+	+		+
Disopyramide	+	+	+	+	+	+	+	+				+	+
Encainide	+	+				+	+						
Ethmozin	+					+							
Flecainide	+	+		+		+	+					+	+
Lignocaine					+	+	+	+		+			+
Lorainide	+	+				+	+	+				+	+
Mexiletine		+			+	+	+	+		+		+	
Phenytoin					+				+	+			
Procainamide	+	+	+	+	+	+	+	+				+	+
Propafenone*	+	+				+	+					+	+
Quinidine	+	+	+	+	+	+	+	+				+	+
Tocainide					+	+	+						

(+) indicates success in treating arrhythmia; however, absence of (+) does not mean total ineffectiveness (compiled from references used in this article, * Keller *et al.*, 1978; Rudolph *et al.*, 1979), PC: premature contractions, TACH: tachycardia, FLUT: flutter, FIB: fibrillation, AI: acute ischaemia, CH: chronic, Dig. ind.: digitalis induced, SVA: supraventricular arrhythmias, VA: ventricular arrhythmia, AV: atrioventricular, A: atrial.

release of noradrenaline from sympathetic nerves (bretylium, guanethidine) (Vaughan Williams, 1980). Initially there was controversy concerning the mode of action of beta-adrenoceptor blocking agents and the possible contribution of their local anaesthetic properties to the control of cardiac arrhythmias. It has been shown, however, that the dextro-isomer of propranolol (D), which is far less active as a beta-adrenoceptor blocking drug than the laevo-isomer (L), but possesses a comparable local anaesthetic potency, is much less effective than the laevo-isomer as an antiarrhythmic compound (Dohadwalla *et al.*, 1969). Coltart *et al.* (1971) found that the plasma concentrations of racemic propranolol (DL), associated with suppression of chronic ventricular premature contractions, occur over the same range as those producing beta-adrenoceptor blocking action. They also found that high concentrations of dextropropranolol failed to control ventricular premature contractions in patients who had previously responded to lower concentrations of racemic propranolol. It was apparent, therefore, that this class of compounds exert antiarrhythmic activity, at therapeutic concentrations, through sympatholytic action rather than through local anaesthetic activity.

Class III antiarrhythmic action (prolonging action potential duration- APD)

The rationale for this class of antiarrhythmic action stems from the observations that atrial arrhythmias are commonly associated with thyrotoxicosis and that hypothyroidism is rarely associated with arrhythmias (Singh *et al.*, 1981a). Furthermore, thyrotoxicosis in rabbits shortens APD while hypothyroidism prolongs it (Freedberg *et al.*, 1970). Chronic administration of the antianginal agent, amiodarone, produces a situation similar to hypothyroidism, i.e. prolongation of atrial and ventricular APD due mainly to prolongation of the repolarization phase (Singh & Vaughan Williams, 1970). Consequently, amiodarone has been found to be an effective antiarrhythmic drug, and has been used for a variety of supraventricular and ventricular arrhythmias and arrhythmias associated with the Wolf-Parkinson-White (WPW) syndrome with remarkable success (Van Schepdael & Solvay, 1970; Rosenbaum *et al.*, 1976; Wellens *et al.*, 1976). Its use, however, is limited by adverse effects such as those reported by McGovern *et al.* (1983).

Bretylium is another member of this class, which prolongs APD in addition to its sympatholytic action.

Class IV antiarrhythmic action (slow channel antagonism)

Cardiac arrhythmias, due to both re-entry and enhanced automaticity, can be initiated by a slow inward current, mediated mainly by calcium ions. With the

depression of the fast inward current, a marked reduction in conduction velocity may occur, associated with the emergence of the slow current. In addition, action potentials of pacemaker cells may also arise entirely on the basis of the slow current (Singh *et al.*, 1981a). Since not only calcium but also sodium ions can traverse slow inward current channels, the term 'calcium antagonist' is not altogether appropriate (Vaughan Williams, 1980) for the description of drugs such as verapamil.

Verapamil, introduced first as an antianginal drug, does not possess any of the three previously mentioned classes of antiarrhythmic actions. It has been demonstrated that verapamil depresses myocardial contractility and flattens the plateau of the atrial and ventricular action potential (Singh & Vaughan Williams, 1972). It is considered to be a useful antiarrhythmic agent against most types of supraventricular tachycardia, including those associated with WPW syndrome (Krikler & Spurrell, 1974), and is also effective in reducing the ventricular response in patients with atrial flutter or fibrillation (Aronow *et al.*, 1979). Its negative inotropic action can summate with that of other drugs given at the same time, such as beta-adrenoceptor antagonists (Keefe *et al.*, 1981; Schwartz *et al.*, 1981). Although this has mainly involved intravenous administration, reports have recently been published about possible interactions between oral verapamil and atenolol (Hutchison *et al.*, 1984) or metoprolol (Eisenberg & Oakley, 1984) associated with transient episodes of complete heart block or Wenckebach atrioventricular block, respectively.

Characteristics of the ideal antiarrhythmic drug

An ideal antiarrhythmic compound should fulfil the following criteria: (1) effectiveness against a specific group of arrhythmias; (2) absence of adverse effects, both cardiac and non-cardiac; (3) no clinically significant adverse interactions (pharmacokinetic and pharmacodynamic) with other drugs especially those commonly used in patients with cardiac problems; (4) ability to be administered orally as well as intravenously. Orally administered drugs should have little or no first-pass metabolism; (5) no clinically significant polymorphic metabolism between subjects; (6) reasonably long half-life to allow less frequent dosing; (7) relatively little between and within patient variability in pharmacokinetic parameters; (8) good correlation between its effectiveness and its plasma concentrations.

Despite the rapidly increasing number of different antiarrhythmic agents with different modes of action, none appears to possess all the ideal properties. This is evident from the following discussion concerning the

above mentioned factors with special reference to class I antiarrhythmic compounds:

Effectiveness against a specific group of arrhythmias

An ideal antiarrhythmic drug should be effective against a certain well-defined group of arrhythmias. This is, however, not the case with the drugs at present available. Arrhythmias resistant to an antiarrhythmic drug(s) (even when accepted therapeutic plasma concentrations are achieved) are not uncommon. For example, although lorcinide was effective in treating some ventricular arrhythmias resistant to other medications such as ajmaline, disopyramide, flecainide and procainamide (Meinertz *et al.*, 1980; Somani, 1981), it was not successful in treating all patients.

The possession of additional autonomic activity may exert an unpredictable influence on arrhythmias. For example, disopyramide's anticholinergic activity may facilitate atrioventricular (AV) nodal conduction and increase the ventricular response in cases of atrial flutter or fibrillation (Singh *et al.*, 1981b) depending on the degrees of vagal activity in the patient concerned.

The control of each patient's arrhythmia is still subject to trial and error, and past experience and clinical judgement are important.

Absence of adverse effects

Over the last two decades antiarrhythmic-induced arrhythmias have become widely recognized. Quinidine syncope may occur as a result of paroxysmal ventricular flutter or fibrillation (Selzer & Wray, 1964). Disopyramide, a wide spectrum antiarrhythmic drug effective against various forms of atrial and ventricular arrhythmias (Sloman *et al.*, 1977; Vismara *et al.*, 1977; De Baker *et al.*, 1981; Tonkin *et al.*, 1982), can cause serious adverse effects such as atypical ventricular tachycardia 'torsade de pointes' associated with prolongation of QTc [QT interval corrected for heart rate] (Chia, 1980; Roccioni *et al.*, 1983). Moreover, its myocardial depressant effect may be severe enough to precipitate cardiogenic shock (Story *et al.*, 1979).

Mexiletine is effective in treating ventricular arrhythmias (Campbell *et al.*, 1973; Talbot *et al.*, 1973). It has, however, some cardiac adverse effects (Table III); for example, Cocco and colleagues (1980) reported that it induced atypical ventricular arrhythmia not associated with QTc prolongation.

Encainide has been shown to be successful in suppressing ventricular premature contractions (Roden *et al.*, 1980; Winkle *et al.*, 1981b). On the other hand, Winkle *et al.* (1981a) have reported ventricular arrhythmias associated with its use which they sugges-

ted may be related to slow intraventricular conduction rather than repolarization changes. Ventricular tachycardia from a similar mechanism was reported in association with flecainide treatment (Muhiddin *et al.*, 1982). Nathan *et al.* (1984) reported 6 further cases of cardiac arrhythmias associated with flecainide therapy. In addition, aggravation of ventricular arrhythmias has been reported with several other class I antiarrhythmic drugs including aprindine, disopyramide, mexiletine, procainamide, quinidine and tocainide (Velebit *et al.*, 1982).

Aprindine which has been shown to be effective against supraventricular and ventricular tachyarrhythmias (Kesteloot *et al.*, 1973; Danilo, 1979; Zipes *et al.*, 1980), may produce sinus node dysfunction and prolongation of QTc (Southworth & Ruffy, 1982).

The worst complication of antiarrhythmic drugs is fatal ventricular tachycardia and fibrillation which has been reported, for example, with ajmaline administration (Wellens *et al.*, 1980).

Among the serious non-cardiac adverse effects of antiarrhythmic agents is the agranulocytosis induced by aprindine (Van Leeuwen & Mayboom, 1976). Systemic lupus erythematosus is a serious complication of procainamide therapy (Dubois, 1969) which precludes its long-term use (Korowsky *et al.*, 1973). In addition, the high incidence of adverse effects, such as perspiration and insomnia, associated with lorcinide administration, ranging between 60–100% (Meinertz *et al.*, 1980; Meinertz *et al.*, 1981), is regarded as a major problem in its use. Winkley *et al.* (1980) have noted some adverse effects in approximately two thirds of patients treated with tocainide; the most common of which were tremor and nausea. Blurring of vision, dizziness and oral paraesthesia were the most frequent non-cardiac adverse effects of flecainide (Anderson *et al.*, 1981; Hodges *et al.*, 1982; Hellesstrand *et al.*, 1982; Muhiddin, 1983).

In the light of these potentially serious adverse effects accompanying antiarrhythmic drug administration, a high therapeutic ratio is necessary to ensure the relative safety of a drug.

Absence of adverse drug interactions

When two or more drugs are administered simultaneously to patients, they may exert their effects independently or may interact. Adverse interactions could be serious or even life threatening. Drug interactions can be either pharmacokinetic or pharmacodynamic.

Pharmacokinetic interactions These occur when one drug alters the plasma concentration of another due to interactions of the following type: (i) those affecting drug absorption; (ii) those due to changes in distribution of drugs; (iii) those affecting drug metabolism and (iv) those affecting renal excretion of the drugs.

Interactions affecting drug absorption Either the rate of absorption or the amount of drug absorbed can be altered by drug interactions. Herzog and co-workers (1982) have shown delayed absorption of mexiletine after pretreatment with antacid (the major component of which was aluminium hydroxide). This was reflected in a delay in attaining the peak plasma concentration which was explained by a possible prolongation of gastric emptying time caused by aluminium hydroxide. However, the availability of mexiletine was not significantly affected.

Interactions due to changes in distribution of drugs The interaction between quinidine and digoxin has received much attention. Combined quinidine and digoxin therapy leads to an increase in the serum digoxin concentrations. This is thought to be due to the displacement of digoxin from its tissue binding sites by quinidine (Chapron *et al.*, 1979; Hager *et al.*, 1979). Another explanation, however, is reduced renal clearance of digoxin (Doering, 1979; Hager *et al.*, 1979), which is speculated to be due to inhibition of renal secretion of digoxin by quinidine rather than reduction in glomerular filtration (Hager *et al.*, 1979). Furthermore, it has been shown recently that quinidine increases the rate and extent of digoxin absorption (Pedersen *et al.*, 1983).

Fraser and colleagues (1980) concluded that total serum phenytoin concentration during concurrent administration of salicylates and phenytoin must be carefully interpreted because of salicylate displacement of phenytoin from its plasma protein binding sites.

Interactions affecting drug metabolism Many drugs are inactivated by metabolism in the liver. One drug can increase or decrease the rate of metabolism of the other by induction or inhibition of the hepatic microsomal enzyme system and thereby alter its plasma concentration and effect. Data *et al.* (1976) found a reduction in the elimination half-life of quinidine by co-administration of phenobarbitone and phenytoin which are enzyme inducers. Furthermore, in an attempt to control recurrent ventricular arrhythmias, Urbano (1983) demonstrated a decrease in plasma quinidine concentrations when phenytoin was added; however, the quinidine concentration returned to its pre-phenytoin level when the phenytoin dosage was halved.

Intravenous lignocaine is rapidly metabolized in the liver and its metabolism can be affected by liver microsomal enzyme activity which is enhanced by barbiturates and reduced by chloramphenicol (Opie, 1980). Feely *et al.* (1982) found that the clearance of lignocaine, a drug whose systemic elimination is highly dependent on liver blood flow, is reduced by 25% after cimetidine pretreatment.

Moreover, phenytoin dosage may require to be increased if an enzyme inducer, such as phenobarbitone is administered at the same time (Burns *et al.*, 1965), while dicoumarol has the reverse effect on phenytoin dosage (Hansen *et al.*, 1966).

Interactions affecting renal excretion of the drugs As far as antiarrhythmic drugs are concerned, renal excretion of some agents is urinary pH dependent as it determines the degree of drug ionization and thereby renal tubular reabsorption. Quinidine, for example, may interact with antacids which alkalinize the urine and thus increase the reabsorbed fraction of the drug leading to a possible intoxication (Stockley, 1981). As mentioned earlier, quinidine may increase serum digoxin concentration, possibly due to inhibition of renal tubular secretion of digoxin (Hager *et al.*, 1979).

Pharmacodynamic interactions These are interactions between drugs which have similar or antagonistic pharmacological effects or adverse effects. It has been reported that collapse may occur after oral disopyramide in patients receiving beta-adrenoceptor blocking agents (Manolas *et al.*, 1979). Other deleterious effects, such as widening of intraventricular conduction or ventricular asystole, may also result when disopyramide is administered with other class I antiarrhythmic drugs (Ellrodt & Singh, 1980).

Oral and intravenous ineffectiveness

An ideal agent would be effective on oral and intravenous administration. Intravenous administration alone is restrictive, because of potential tissue damage, discomfort to the patient and the inconvenience of the need of trained personnel to give the drug. This is in addition to the higher potential risk of cardiovascular adverse effects that may be precipitated by intravenous injection. An orally effective antiarrhythmic drug is more convenient for administration, can be repeated during the day, and has a lesser chance of inducing serious cardiovascular adverse effects. However, the pharmacokinetic properties of a compound are the determinants of the availability of that compound in an oral form, i.e. good absorption and minimal first-pass effect. Since lignocaine has unfavourable first-pass degradation in the liver (Stenson *et al.*, 1971), it cannot be given orally. This restricts its use to patients in coronary and intensive care units to treat ventricular arrhythmias (Southwarth *et al.*, 1950) and to attempt to prevent them (Lie *et al.*, 1974).

Lorcinide also undergoes first-pass hepatic extraction. This process, however, is saturable during multiple dosage regimes (Jahnchen *et al.*, 1979; Ronfeld, 1981).

No clinically significant genetically-determined polymorphic metabolism between subjects

Each individual is unique in his metabolic performance including drug metabolism. The genetic effects which underlie the wide variation in drug half-lives are predominantly due to differences in the hepatic metabolism of the drug. Among antiarrhythmic drugs, the metabolism of encainide, phenytoin and procainamide are examples of this polymorphism.

Encainide metabolism is polymorphic (Woosley *et al.*, 1981, 1982). About 90–95% of patients treated with oral encainide have high first-pass hepatic extraction, while the remaining proportion have delayed elimination with longer half-life of parent drug and no significant concentrations of metabolites present.

Phenytoin metabolism may also be affected by genetically determined parahydroxylation. Some patients may exhibit defects in parahydroxylation while others may be rapid parahydroxylators (Kutt *et al.*, 1964, 1966).

Procainamide undergoes *N*-acetylation in the liver by the enzyme *N*-acetyl transferase. The degree of activity of this enzyme shows bimodal distribution and categorizes individuals into slow and fast acetylators (Chapman, 1977). It appears also, that slow acetylators develop antinuclear antibodies more rapidly than rapid acetylators (Woosley *et al.*, 1978).

Reasonably long elimination half-life

Long elimination half-life is another favourable criterion of an ideal agent, since it makes frequent drug dosing unnecessary and also ensures that the night period will be covered adequately. The short half-life of ajmaline (in addition to a high propensity to produce atrioventricular block) makes its use restricted (Schwartz *et al.*, 1981). The short half-life of lignocaine necessitates a continuous intravenous infusion following a bolus dose to achieve a smooth therapeutic blood concentration in controlling arrhythmias. Procainamide has a short half-life (2.5–4.7 h) and this necessitates 3–6 hourly dosing, although the development of a slow release procainamide preparation has allowed for a less frequent (8 hourly) dosing (Karlsson, 1973; Shaw *et al.*, 1975). The relatively long elimination half-life of flecainide of 7–22 (mean 14) h makes possible its oral administration 2–3 times a day (Conard *et al.*, 1979).

Relatively little between and within patient variability in plasma pharmacokinetic parameters

Ideally, plasma concentrations of an antiarrhythmic drug should reveal only slight between and within patient variability, but this seems difficult to obtain. For instance, there is a wide variation between in-

dividuals in their plasma concentrations of flecainide (Duff *et al.*, 1981; Hodges *et al.*, 1982), lignocaine (Zito *et al.*, 1977), mexiletine (Johnston *et al.*, 1979), procainamide (Koch-Weser & Klein, 1971) and quinidine (Follath *et al.*, 1981). This is due, in fact, to variability in the extent of drug absorption, distribution, metabolism and excretion.

The extent of absorption of orally administered drug depends upon several factors such as the pH of the gastrointestinal tract at the site of absorption since it governs the degree of ionization. Weak basic drugs such as quinidine are expected to be absorbed mainly from the small intestine where the pH at the absorption site is alkaline, while weak acids such as phenytoin may be less favourably absorbed.

The extent of protein binding of an antiarrhythmic drug and consequently its total plasma concentration can be dependent on the plasma concentration of the protein(s) to which it binds. For example, Edwards *et al.* (1982) have shown that alpha-1 acid glycoprotein concentration is closely correlated with lignocaine protein binding in both normal subjects and patients. They suggested that this observation could be applicable to other basic drugs which bind to the same protein such as disopyramide and quinidine. Subsequently, David and colleagues (1983) have demonstrated an increase in the protein binding of disopyramide after myocardial infarction and this increase was dependent on the alpha-1 acid glycoprotein concentration.

Metabolism of a drug may be highly variable and it is usually the major source of between patient variation regarding both plasma concentration and response. Each individual has a metabolic capacity determined by various factors; genetic, environmental, physiological and sometimes pathological. Plasma concentrations of phenytoin, for instance, a drug which is mainly metabolized in the liver, show considerable variation between patients (Richens, 1979).

Elliot *et al.* (1959) found that urinary pH varies widely in a normal population and it follows a circadian rhythm. Urinary excretion of some antiarrhythmic drugs such as lignocaine and mexiletine is pH-dependent; the amount excreted is higher when the urine is acidic than when it is alkaline (Kiddie & Kaye, 1974, 1976). This also applies to flecainide, the urinary excretion of which under acidic conditions is greater than under alkaline conditions (Muhiddin *et al.*, 1984). Therefore, plasma concentrations of these compounds may vary between and within individuals. Johnston and associates (1979) demonstrated a wide variability between individuals in respect of their plasma mexiletine concentration which was found to be directly correlated with urinary pH; within subject variability was also reported. Furthermore, dietary habits would be of importance since they influence urinary pH which tends to be alkaline with a vegetarian diet.

In acute myocardial infarction, any circulatory collapse would be expected to produce metabolic acidosis and subsequent treatment with sodium bicarbonate would increase urinary pH, and as a result urinary excretion of drugs such as flecainide and mexiletine could be hindered and thereby increase the risk of toxicity. On the other hand, from a clinical toxicological point of view, attempts to acidify urine could be considered as a therapeutic measure in patients with toxic serum concentrations of such drugs.

Good correlation between therapeutic effect of a drug and its plasma concentrations

Accurate measurement of plasma concentrations of an antiarrhythmic drug and good correlation between these concentrations and its pharmacological effects would be a valuable criterion of an ideal agent since it would allow safe drug dosage adjustment. It has been reported that the antiarrhythmic activity of mexiletine (Pottage *et al.*, 1978), prajmalium (Trompler *et al.*,

1983) and quinidine (Singh *et al.*, 1981a) is well correlated with their plasma concentrations. On the other hand, this is not applicable to procainamide (Dreifus, 1981).

Ideally the parent compound should be the only active form of a drug, and it should be metabolized into inactive, non-toxic and easily excretable metabolites which do not interfere with the analysis of the parent agent. This is not the case, however, with disopyramide, encainide, lignocaine, procainamide and quinidine, which have pharmacologically active metabolites (Follath *et al.*, 1981; Roden *et al.*, 1980).

Conclusion

Although there are many effective antiarrhythmic agents, in clinical use in the light of the ideal characteristics discussed in this article they all fall short of these criteria. Research for an ideal antiarrhythmic drug must, therefore, continue.

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