CARDIAC ARRHYTHMIAS
Disturbances of cardiac rhythm are frequently encountered both in the operating theatre and in the intensive care unit. The anaesthetist should be aware of the factors involved in the prevention of such arrhythmias, be able to diagnose the type of rhythm abnormality, discover its aetiology and initiate the appropriate primary treatment. Arrhythmias may affect myocardial performance to different extents, depending on the nature of rhythm, the presence of cardiac disease and the patient's general condition. Fortunately, the majority of rhythm disturbances can be explained in terms of autonomic nervous system imbalance and are of little clinical significance, seldom requiring the administration of antiarrhythmic drugs.

Cardiac arrhythmias may occur in the following conditions:

Pre-existing disease
Patients with coronary atheroma and subsequent ischaemic heart disease (Katz and Bigger, 1970; Perlothe and Hultgren, 1975), hypertension (Prys-Roberts, Meloche and Foëx, 1971), rheumatic and congenital heart disease (Buckley and Jackson, 1961) are most likely to have some disturbance of rhythm during anaesthesia. Endocrine disorders such as thyrotoxicosis and phaeochromocytoma are well recognized as causing cardiovascular irregularities (Bird et al., 1969; Bingham, Elliott and Lyons, 1972; Stechling, 1974). The management of tetanus in the intensive care unit is often complicated by serious cardiac arrhythmias (Kerr et al., 1968).

Disturbances of normal physiology
In anaesthetic practice cardiac arrhythmias are most frequently associated with adverse changes of ventilation, notably hypoxia and hypercarbia (Price, 1960). The resulting respiratory acidosis stimulates the vasomotor areas in the brain stem, resulting in increasing sympathetic outflow and release of catecholamines. Another frequent source of excess sympathetic activity is surgical stimulation under light anaesthesia. It has long been known that arrhythmias may be initiated reflexly by sympathetic or parasympathetic activity. Disturbances in acid-base balance, both metabolic alkalosis (Lawson, Butler and Ray, 1973) and metabolic acidosis—the latter whether secondary to generalized hypoxia or regional hypoxia, such as coronary atheroma—are associated with abnormalities in cardiac rhythm. Extremes of temperature, both hypothermia (Lloyd and Mitchell, 1974) and malignant hyperpyrexia (Britt, 1972), are associated with an increased frequency of arrhythmias. Variation in the intracellular or extracellular concentrations of certain electrolytes may result in cardiac irregularities; hypokalaemia and hyperkalaemia in particular give rise to problems in patients on digitalis and in renal failure (Lowenstein, 1973; Vaughan and Lunn, 1973; Curry et al., 1976; Steiness and Olesen, 1976). The response to altered concentrations of sodium and calcium have been reviewed by Katz and Bigger (1970).

Pharmacological causes
Anaesthetic agents. The effect of anaesthetic agents on cardiac electromechanical activity has been reviewed recently (Pratila and Pratilas, 1978). Almost all anaesthetic agents depress the myocardium and the resulting hypotension may lead to rhythm changes. However, the intrinsic ability of anaesthetic agents to produce arrhythmias varies markedly. No volatile anaesthetic drugs currently available for clinical use produce cardiac arrhythmias when given in anaesthetic concentrations. However, certain agents such as cyclopropane (Lurie et al., 1958; Price et al., 1958) and trichloroethylene (Barnes and Ives, 1944) have been known to cause increased cardiac irritability.
when excessive concentrations are required. The presence of hypercarbia in spontaneously breathing patients anaesthetized with cyclopropane or halothane is a common cause of arrhythmias (Johnstone, 1950; Black et al., 1959). The surgical use of adrenaline infiltration to produce a dry operating field was soon recognized as a hazardous clinical procedure in association with certain volatile anaesthetics (Katz and Katz, 1966). Trichloroethylene, cyclopropane and halothane were particularly susceptible to this interaction. Other halogenated agents such as enfurane, methoxyflurane and fluoroxyne have a wider margin of safety in this situation (Katz and Bigger, 1970; Lippman and Reisner, 1974; Reisner and Lippman, 1975).

**Muscle relaxants.** Suxamethonium, especially on repeated administration, causes bradycardia and cardiac arrhythmias in adults and particularly in children (Leigh et al., 1957; Lupprian and Churchill-Davidson, 1960). The frequency of bradycardia and asystole may be reduced by pre-treatment with a non-depolarizing muscle relaxant (Mathias and Evans-Prosser, 1970) or an anticholinergic agent, although the use of atropine itself has been associated with tachydyssrhythmias (Massumi et al., 1972). Major problems arise with the use of suxamethonium in patients with burns, trauma, uraemia and neuromuscular disorders. The rapid increase in serum potassium contributes to a large extent to the cardiovascular hazards (Tolmie, Joyce and Mitchell, 1967; Bali and Dundee, 1975; Ohmura, Wong and Shaw, 1976).

**Digoxin** can cause increased cardiac irritability, especially when toxic concentrations are attained. This effect is accentuated by hypokalaemia (Steiness and Olesen, 1976).

**Surgical situations**

The majority of surgically induced arrhythmias are reflex responses to sympathetic or parasympathetic stimulation. The oculocardiac reflex has been reported to occur with pressure on the eyeball or traction on the extraocular muscles (Berler, 1963; Alexander, 1975). The high frequency of cardiac irregularities during oral and dental surgery is well recognized (Miller et al., 1970; Alexander, 1971; Plowman, Thomas and Thurlow, 1974; Thomas, Kyriakou and Thurlow, 1978). Intracranial neurosurgical manipulation may cause changes in heart rate or rhythm, particularly and of greatest significance in posterior-fossa surgery, as a result of pressure or traction on the brain stem and cranial nerves (Michenfelder, Gronert and Rehder, 1969). Traction on intra-abdominal and pelvic viscera has been reported as causing cardiac arrhythmia (Folkow et al., 1962). In surgery within the thorax (Wylie and Bowman, 1964) handling and stimulation of the pericardium, heart and aorta may produce transient irregularities of rhythm, often with a subsequent decrease in cardiac output. Instrumentation and manipulation of the larynx and trachea may result in cardiac arrhythmias which are of major interest to anaesthetists (King et al., 1951; Denlinger, Ellison and Ominskey, 1974).

Disturbances of cardiac rhythm may also be encountered in patients with invasive monitoring devices such as pulmonary artery balloon flotation catheters (Buchbinder and Ganz, 1976) and in patients with a pacemaker.

While most of these arrhythmias are controlled by removal of the exciting cause, those which do not respond will require pharmacological intervention. It is thus important before commencing anti-arrhythmic therapy to have an understanding of the electrophysiology of myocardial muscle and the conducting tissues, and the disturbances which are responsible for, or contributing to, cardiac arrhythmias (Lappas, Powell and Daggett, 1977).

**CLASSIFICATION OF ANTI-ARRHYTHMIC DRUGS**

Vaughan Williams has suggested that anti-arrhythmic drugs may possess one or more main classes of action (Vaughan Williams, 1970, 1974, 1975). The first consists of a direct membrane action reducing the entry of inward depolarizing current. This effect has been called "membrane-stabilizing", "quinidine-like" and "non-specific" and can be detected as an increase in electrical threshold, slowing of conduction velocity or a reduction of the maximum frequency at which cardiac muscle will follow an electrical stimulus. High concentrations of drug are generally required to produce effects. The most sensitive test to show this effect is to demonstrate, by micro-electrode recording, a reduction in the maximum rate of depolarization in the absence of any effect on resting potential or prolongation of the action potential. Drugs with these effects (Class I action) on cardiac muscle also produce local anaesthesia in nerve, although greater concentrations are required for this effect.

Lignocaine and mexiletine have been shown to shorten the duration of the action potential. The relevance of this effect to the Class I anti-arrhythmic...
action of these drugs is unknown. Disopyramide and quinidine increase action potential duration slightly.

Drugs with Class I anti-arrhythmic action include lignocaine, quinidine, procainamide, phenytoin, mexiletine and disopyramide. Some of these drugs have additional properties and uses. Lignocaine is used as a local anaesthetic; phenytoin has anticonvulsant properties and is used for the treatment of epilepsy. Quinidine and disopyramide have atropine-like effects.

Some beta-adrenoceptor blocking drugs have Class I effects in addition to their action in blocking beta adrenoceptors. Drugs with this action are propranolol, oxprenolol, alprenolol, pindolol, metoprolol and acebutolol (Shanks, 1976). Practolol, sotalol, timolol and atenolol are devoid of Class I activity (table I). The reasons for the presence or absence of Class I activity in different beta-blocking drugs are unknown (Shanks, 1976). There has been controversy over the contribution of this Class I action to the therapeutic effects of beta-blocking drugs. The current view would appear to be that it does not contribute to the beneficial effects of these drugs, including the treatment of cardiac arrhythmias, because no difference has been shown between the effects of different beta-blocking drugs. Likewise, Class I actions do not appear to contribute to the adverse effects of beta-blocking drugs. These views have been confirmed by studies which have shown that the concentration of a beta-blocking drug required for Class I actions (in an isolated tissue bath) is much greater than is required to produce beta-adrenoceptor blockade and a therapeutic effect in man (Shanks, 1976).

The second class of anti-arrhythmic action consists of antagonism of cardiac sympathetic drive by presynaptic prevention of transmitter release (bretylium and reserpine), by post-synaptic receptor blockade (beta-blocking drugs) or by a central action. The most widely investigated and clinically used group of drugs having this effect are the beta-adrenoceptor blocking drugs. Initial studies indicated that pronethalol and prpanolol were effective in animals in abolishing or preventing arrhythmias produced by catecholamines (Sekiya and Vaughan Williams, 1963; Howe and Shanks, 1966). When it was shown that these drugs had also Class I activity, the exact mechanism of the anti-arrhythmic action was unclear. Propranolol exists in laevo- and dextro-isomers, the generally used form consisting of equal parts of both isomers. While the L-isomer has about 100 times the beta-blocking activity of the D-isomer, both have equal Class I activity (Howe and Shanks, 1966; Dohadwalla, Freedberg and Vaughan Williams, 1969). The L-isomer has a much greater effect than the D-isomer in abolishing catecholamine-induced arrhythmia (Barrett and Cullum, 1968). In addition, beta-blocking drugs such as sotalol and practolol, which are devoid of Class I activity, are effective in abolishing sympathetically-induced arrhythmia (Dunlop and Shanks, 1968). Thus beta-adrenoceptor-blocking drugs have a specific anti-arrhythmic effect in animals, resulting from blockade of beta-adrenoceptors.

The third class of anti-arrhythmic drugs comprises those which prolong the duration of the action potential. Such an effect occurs after the administration of the anti-anginal drug, amiodarone, which has little or no effect on automaticity (Singh and Vaughan Williams, 1970; Rosenbaum et al., 1976). A similar effect has been shown by the prolonged administration of beta-blocking drugs to rabbits (Raine and Vaughan Williams, 1978) and man (Raine and Pickering, 1977).

Class IV anti-arrhythmic effect results from interference with the slow inward sodium current (Vaughan Williams, 1974). Verapamil is an example of a drug in this category.

EFFECTS OF DRUGS ON EXPERIMENTAL ARRHYTHMIA

In recent years extensive studies have been carried out on the effects of drugs on cardiac arrhythmias in experimental animals. These studies have been used for the development of new anti-arrhythmic drugs, for investigation of the mode of action of such drugs and as a possible predictor of the effects of a drug in patients. Several different types of arrhythmias have been used and full descriptions of these can be found elsewhere (Allen et al., 1972; Allen et al., 1977).

Ouabain-induced ventricular tachycardia

Observations are made in dogs anaesthetized by pentobarbitone and artificially respired with room air. With the electrocardiogram and arterial pressure being recorded, the drugs are given i.v. Ventricular tachycardia is produced by the i.v. injection of ouabain, a rapidly-acting digitalis glycoside, starting with 40 µg kg⁻¹, 30 min later 20 µg kg⁻¹ and then 10 µg kg⁻¹ every 15 min until the tachycardia is produced. Observations have shown that this ventricular tachycardia will persist for at least 150 min. Ten minutes after the tachycardia is produced, the test drug is administered by continuous
i.v. infusion until sinus rhythm returns or no response has occurred after infusion for 100 min. Drugs with Class I actions are effective in abolishing ouabain-induced arrhythmias (Dunlop and Shanks, 1968; Allen, Shanks and Zaidi, 1971; Allen et al., 1977). Thus lignocaine, mexiletine and propranolol are effective, but practolol is not. The relevance of this type of acute digitalis-induced ventricular tachycardia to the arrhythmias produced by digitalis toxicity in man is not known.

**Halothane–adrenaline arrhythmias**

Observations are made in dogs anaesthetized with pentobarbitone and artificially respired with room air and 1.0% halothane. Fifteen minutes later adrenaline $0.2 \, \mu g \, kg^{-1}$ is injected i.v. The dose of adrenaline is progressively increased until a dose of adrenaline is obtained which produces a burst of self-terminating ventricular tachycardia or multifocal ventricular ectopic beats lasting about 20–30 s. After the test dose of adrenaline which produces an arrhythmia has been established, the test compound is injected i.v. Five minutes later the adrenaline challenge is repeated using the same dose. Increasing doses of the test compound are given to determine the minimum dose that prevents the adrenaline challenge from producing any ectopic beats. Beta-adrenergic-blocking drugs are most effective in preventing arrhythmias of this type (Allen and Shanks, 1974). Although drugs with Class I actions are effective, considerably larger doses (10–20 times) are required than for beta-adrenoceptor-blocking drugs (Allen, Shanks and Zaidi, 1971).

**Arrhythmia after coronary artery ligation**

Observations are made in dogs anaesthetized with methohexitone and respired with room air and halothane. The heart is exposed through an incision in the fourth or fifth left intercostal space and the left anterior descending coronary artery dissected free 2 cm below the tip of the left atrial appendage and ligated in two stages as described by Harris (1950). The chest is then closed in layers and the dog allowed to recover. Further observations are made 18–44 h after ligation of the coronary artery when the animal is conscious and the electrocardiogram recorded. At this time all dogs have developed a severe ventricular arrhythmia consisting of multifocal ventricular tachycardia interspersed with normal sinus beats. Drugs are administered by continuous i.v. infusion or by a series of increasing doses until the arrhythmia is abolished or adverse effects occur.

Drugs with Class I actions, for example lignocaine, phenytoin, mexiletine and propranolol, are effective in abolishing this arrhythmia whereas drugs such as practolol, which has no Class I effect, are ineffective (Allen, Shanks and Zaidi, 1971; Allen et al., 1972; Allen and Shanks, 1974).

**Threshold current for ventricular fibrillation**

Allen and his colleagues have recently described methods for studying the effects of anti-arrhythmic drugs on the threshold current for ventricular fibrillation in anaesthetized dogs (Allen et al., 1977). Observations are made in the normal myocardium and in an area of ischaemic myocardium. Lignocaine and mexiletine, drugs with Class I actions, increase the threshold current for ventricular fibrillation in both situations. Measurement of the plasma concentrations of the drugs at the time when there was a doubling of the current required to produce ventricular fibrillation showed that the plasma concentrations are similar to those required in man for a therapeutic effect (Allen et al., 1977).

These studies in experimental arrhythmia show that the drugs with Class I actions are effective in abolishing or preventing the arrhythmias produced by ouabain and coronary artery ligation. These drugs are also effective in the same dose range in preventing the arrhythmia produced by adrenaline. Presumably this effect also results from their Class I actions. In contrast, much smaller doses of beta-adrenoceptor-blocking drugs, irrespective of the possession of Class I activity, are effective in preventing adrenaline-induced arrhythmias. It would appear that, in clinical practice, drugs such as lignocaine abolish cardiac arrhythmias through their Class I actions and beta-blocking drugs through their Class II effects. The actions of drugs with Class III and IV actions have not been investigated in a similar way in experimental arrhythmias, and the results correlated with their effects in patients.

**ASSESSMENT OF THE EFFICACY OF ANTI-ARRHYTHMIC DRUGS IN MAN**

In recent years increasing use has been made of drugs for the prevention and control of cardiac arrhythmia especially those occurring after acute myocardial infarction. During this time several new drugs including mexiletine, disopyramide and the beta-adrenoceptor-blocking drugs have become available for the treatment of cardiac arrhythmia.
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Formerly the effects of a drug on cardiac arrhythmias were assessed by observation of the electrocardiogram before and for a few minutes after drug administration. Continuous recording of the electrocardiogram in patients with frequent and complex premature ventricular contractions (PVC) has shown that large variations in the total number of PVC can occur from one half-hour to the next (Winkle, 1978). In some patients the spontaneous variations in ventricular ectopic rate was such that, if a single dose of an anti-arrhythmic drug had been given at the end of the test period, it might have been concluded that the spontaneous effect had been caused by the drug. Similar variations occur on longer periods of observation. These results indicate that, in assessing the effect of a drug on cardiac arrhythmias, sufficient care must be used to ensure that changes in an arrhythmia are in fact drug-induced. The introduction of facilities for the continuous recording of the electrocardiogram over periods of 24 h and computer analysis has greatly facilitated the study of anti-arrhythmic drug effects (Murray, Campbell and Julian, 1978). In particular, computer analysis has enabled the processing of a greater amount of data and has been a marked improvement on continuous observer monitoring of the electrocardiographic records replayed and displayed at a fast speed. The introduction of continuous ambulatory monitoring systems has also greatly facilitated studies in patients both in hospital and while ambulatory.

For many years standardized dosage regimes were used for the administration of anti-arrhythmic drugs. With the introduction of methods and facilities for the measurement of plasma concentrations of these drugs, it was seen that the same dose produced wide variations in steady-state plasma concentrations between patients. Koch-Weser and Klein (1971) showed in patients receiving procainamide 3 g day$^{-1}$ that the plasma concentrations ranged from less than 2 $\mu$g ml$^{-1}$ to greater than 11 $\mu$g ml$^{-1}$. They also established that the therapeutic plasma concentration of procainamide was between 4 and 8 $\mu$g ml$^{-1}$. Thus some patients had a sub-therapeutic plasma concentration while others had a concentration which was associated with an increase in adverse effects. As a result of such studies, dosage regimes could be implemented to fit each patient more accurately and if an inadequate response or adverse effects were occurring, a determination of plasma concentration could be carried out and if necessary the dose altered.

A similar situation may occur with lignocaine where measurement of the plasma concentration after the i.v. administration of the conventional dose regime of a bolus of 100 mg followed by constant i.v. infusion at 2 mg min$^{-1}$ showed inadequate plasma concentrations during the first hour of therapy (Campbell et al., 1978a). As a result of such studies, new dosage regimes have been described for lignocaine (Aps et al., 1976).

Appreciation of the importance of measuring plasma drug concentrations has been utilized in the development of dosage regimes for new drugs. This is of particular importance for i.v. administration where a therapeutic plasma concentration should be provided at an early stage of treatment and maintained throughout treatment. Such principles were used in the development of mexiletine, as a method of measurement of the plasma concentration was available at an early stage of clinical investigation, and as a result the therapeutic plasma concentration and adequate dosage regimes were quickly defined (Shanks, 1978).

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Lignocaine

Lignocaine has been a most valuable drug for the treatment of ventricular arrhythmias, although it is only effective on parenteral administration. Lignocaine was initially introduced and used as a local anaesthetic agent until Southworth and colleagues (1950) successfully reversed ventricular tachycardia and ventricular fibrillation during cardiac catheterization by the administration of lignocaine. Lignocaine has Class I anti-arrhythmic actions and is a potent local anaesthetic. It is effective against a wide range of ventricular arrhythmias, but is generally ineffective in suppressing atrial arrhythmias (Harrison, Sprouse and Morrow, 1963). The therapeutic plasma concentration of lignocaine is 2.0–5.0 $\mu$g ml$^{-1}$ (Koch-Weser, 1972). Approximately 70% of the lignocaine entering the liver is metabolized on a single pass through the liver (Stenson, Constantin and Harrison, 1971). Thus lignocaine clearance is critically dependent on liver blood flow. Less than 3% of a dose of lignocaine appears in the urine. Lignocaine disposition has been described by a linear, two-compartment open model. In normal subjects the half-life of the distribution phase is 8 min and of the elimination phase 108 min (Boyes et al., 1971).

The pharmacokinetics of lignocaine may be altered by disease states. In patients with cardiac failure long-term infusions may produce 50% greater...
plasma concentrations. Thus in such patients the dose of lignocaine may require a reduction to reduce the occurrence of adverse effects. In patients with chronic liver disease, the clearance of lignocaine may be reduced, and the rate of administration may need to be reduced to prevent adverse effects (Harrison, Meffin and Winkle, 1977).

Lignocaine is generally given by i.v. injection, but has been given by i.m. injection in general practice to cover the period of transportation from home to hospital. Studies have shown that lignocaine 100 mg given i.v. and 300 mg by i.m. injection into the deltoid muscle in patients with acute myocardial infarction, maintained blood concentrations in the therapeutic range for at least 2 h (Barber et al., 1977).

In patients without cardiac failure, the widely used regime for the administration of lignocaine is an i.v. bolus injection of 100 mg followed by a constant i.v. infusion of 2 mg min\(^{-1}\). A steady-state plasma concentration of between 2 and 4 \(\mu g\) ml\(^{-1}\) is generally obtained within 2–3 h. Recurrence of arrhythmia is treated by the i.v. injection of 25–50 mg bolus. Recently it has been shown that with this regime the plasma concentration is small (<2.0 \(\mu g\) ml\(^{-1}\)) about 45–60 min after this drug administration is commenced (Aps et al., 1976; Campbell et al., 1978a). These authors have recently suggested that this trough could be prevented by the administration of a larger dose of lignocaine during the first part of the infusion. Aps and his colleagues (1976) have recommended that the bolus injection is followed by an infusion rate of 4 mg min\(^{-1}\) for 30 min, 2 mg min\(^{-1}\) for 2 h and then 1 mg min\(^{-1}\) throughout the remainder of the infusion. Campbell and his colleagues (1978a) have recommended an initial bolus of 75 mg followed by an infusion of 10 mg min\(^{-1}\) for 20 min followed by 1.5 mg min\(^{-1}\).

With therapeutic plasma concentrations (2–5 \(\mu g\) ml\(^{-1}\)) lignocaine exerts no cardiac depressant effect and does not alter heart rate or arterial pressure and has minimal effects on the cardiac conducting system (Harrison, Meffin and Winkle, 1977). Increased plasma concentrations (>9.0 \(\mu g\) ml\(^{-1}\)) may produce adverse effects in the central nervous system including dizziness, tinnitus, respiratory arrest and grand mal seizures.

**Procainamide**

Procainamide possesses Class I anti-arrhythmic actions and is used to treat atrial and ventricular arrhythmias. It is quickly and completely absorbed from the gastrointestinal tract. Approximately 50% of an administered dose is recovered in the urine as unchanged procainamide (Koch-Weser, 1971). The liver metabolizes procainamide to N-acetylprocainamide (NAPA) which has anti-arrhythmic properties and is excreted by the kidneys (Giardina et al., 1976). The rate of acetylation of procainamide to NAPA shows a bimodal distribution with patients being classified as slow and fast acetylators (Reidenberg et al., 1975). The rate of acetylation parallels that of isoniazide, hydralazine and dapsone (Gibson et al., 1975).

The plasma elimination half-life of procainamide is about 3.5 h (Winkle, Glantz and Harrison, 1975). Patients with impaired renal function and low cardiac output may eliminate procainamide more slowly and should receive a smaller dose. The oral administration of the same dose of procainamide may produce great differences in plasma concentrations (Koch-Weser and Klein, 1971). The exact reasons for this variation are not clear, but include individual differences in completeness of absorption, distribution space and elimination rate. These authors have suggested that in most patients a total daily dose of 50 mg/kg of body weight should produce therapeutic plasma concentrations. The usual effective anti-arrhythmic plasma concentration is 4–8 \(\mu g\) ml\(^{-1}\) with toxic effects occurring commonly with concentrations greater than 16 \(\mu g\) ml\(^{-1}\) (Koch-Weser and Klein, 1971).

Procainamide is generally administered orally for the control of cardiac arrhythmias and as it has a rapid rate of elimination should be administered 3-hourly to prevent large swings between peak and trough plasma concentrations. Although such a regime may be used in hospital, it is not practical elsewhere as patients may have difficulty waking in the middle of the night to take a dose. A sustained release preparation of procainamide has now become available and initial studies indicate that with 8-hourly administration of 1.5 g, satisfactory plasma concentrations are maintained (Birkhead et al., 1976).

Minor side-effects produced by procainamide include nausea, vomiting, skin rashes, diarrhoea, mental depression and insomnia. Rapid i.v. injection may produce hypotension and a decrease in cardiac output. Long-term use (greater than 3 months) may produce a lupus-like syndrome with skin rash, fever, arthritis, arthralgia, pleuritic chest pain and pericarditis. Anti-nuclear antibodies develop in at least half of the patients receiving long-term procainamide therapy (Winkle, Glantz and Harrison, 1975). These
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features generally develop after oral administration of procainamide for at least 1 month and probably occur in up to 20% of patients receiving the drug. The syndrome generally disappears slowly after the drug is stopped. Procainamide is now not generally used for periods of treatment exceeding 1 month.

**Diphenylhydantoin (phenytoin)**

Phenytoin has anti-convulsant properties and is widely used as an effective drug in the treatment of epilepsy, but it is also effective in the control of supraventricular tachycardia and many ventricular arrhythmias, especially those associated with digitalis toxicity (Conn, 1965; Stone, Klein and Lown, 1971). Phenytoin has Class I anti-arrhythmic actions.

Phenytoin is largely metabolized in the liver, with 50–75% being excreted in the urine in a conjugated form; less than 5% appears in the urine as unchanged phenytoin. Phenytoin is excreted relatively slowly with a plasma elimination half-life of about 22 h, but because of non-linear kinetics the half-life is longer at high blood concentrations and shorter at small blood concentrations (Arnold and Gerber, 1970). There is a wide range of plasma concentrations for a given dose in patients and it is often desirable to measure the plasma concentration to ensure that it is within the therapeutic range, which is generally considered to be 10–18 μg ml⁻¹ (Bigger, Schmidt and Kutt, 1968). The effect of disease states on the pharmacokinetics is apparently still controversial (Harrison, Meffin and Winkle, 1977).

Phenytoin can be administered i.v. in an emergency, but is generally given orally. The recommended dose for i.v. use is 50–100 mg every 5 min, or until the arrhythmia is controlled, toxicity occurs or 1000 mg has been given (Bigger, Schmidt and Kutt, 1968). The daily maintenance dose for oral administration is 300–400 mg, which can be given once a day.

The rapid i.v. administration of phenytoin may produce hypotension, ventricular fibrillation, asystole, respiratory arrest and death (Harrison, Meffin and Winkle, 1977). These adverse effects probably arise from peripheral vasodilatation and myocardial depression (Mixter, Moran and Austen, 1966). Adverse effects occurring with oral administration of phenytoin include nausea, vertigo, rashes, gingival hyperplasia, megaloblastic anaemia and peripheral neuropathy. The frequency and severity of some of these adverse reactions is related to the plasma concentration of phenytoin.

**Beta-adrenoceptor-blocking drugs**

Beta-adrenoceptor-blocking drugs first became available for the treatment of angina pectoris and cardiac arrhythmias in 1964 and were later shown to be of value in the treatment of hypertension. Propranolol was the first beta-adrenoceptor blocking drug to be widely used and is still the reference drug against which all others are still compared. Several other beta-blocking drugs have become available in recent years, although these are not necessarily available in all countries. Table I lists the beta-block-
been termed intrinsic sympathomimetic activity (ISA) or a partial agonist action. Some, but not all, beta-blocking drugs possess this effect (table I). There is no convincing evidence that this effect contributes to the actions of beta-blocking drugs in man.

Cardioselectivity. Practolol was shown to block selectively beta-adrenoceptors in the heart, while having much less effect on the beta-receptors in the bronchi (Dunlop and Shanks, 1968). Two other beta-blocking drugs, atenolol and metoprolol, have also been shown to be cardioselective (table I). The advantage of these drugs is that they are less likely to produce bronchospasm in patients with asthma. Practolol is no longer available as it produced severe adverse effects on long-term oral administration, which have been designated the oculomucocutaneous syndrome.

Beta-adrenoceptor blocking drugs have been shown to be of value in the treatment of atrial fibrillation by slowing the ventricular rate, supraventricular tachycardia, ventricular ectopic beats and ventricular tachycardia. As several beta-adrenoceptor blocking drugs are available it is not practical to discuss pharmacokinetic details, dosage regimes and adverse reactions in this article.

Many excellent review articles on the actions and uses of beta-adrenoceptor-blocking drugs have been published recently (McDevitt, Shanks and Prichard, 1976; Prichard, McDevitt and Shanks, 1976; Supplement, 1976; Avery, 1977; Braunwald, 1978). These should be consulted for more detailed information about this group of drugs.

Mexiletine

Mexiletine is a new anti-arrhythmic drug introduced in the British Isles in 1976. Animal studies show that it has Class I actions and is effective in abolishing experimental arrhythmias in animals and in increasing the threshold for ventricular fibrillation (Allen et al., 1977; Shanks, 1977, 1978). Mexiletine has no sympathetic blocking actions and does not prolong the duration of the action potential.

The pharmacokinetics of mexiletine in healthy volunteers and patients have been extensively studied (Prescott, Pottage and Clements, 1977; Campbell et al., 1978b, c). These studies have shown that mexiletine is well absorbed on oral administration, giving a high systemic availability. In normal volunteers, an oral dose of 200 mg produces peak plasma concentrations of 0.3–0.5 µg ml\(^{-1}\) within 2–4 h. The absorption of mexiletine is delayed and is apparently less complete in patients with acute myocardial infarction; these changes may be further affected by the prior administration of narcotic analgesics (Prescott, Pottage and Clements, 1977).

After bolus i.v. injection plasma concentrations of mexiletine decrease rapidly as a result of extensive uptake and distribution in the tissues. This decline in the plasma concentration appeared to be the resultant of at least three exponential processes, representing fast and slow distribution phases with a much slower elimination phase. The disposition kinetics of mexiletine are consistent with a three-compartment model: the first “central” compartment probably consists of the blood volume and rapidly equilibrating highly perfused tissues such as myocardium, brain, liver, kidney and lung, while the second and third compartments represent “deep” or “peripheral” tissues such as skin, muscle and fat, which take up the drug more slowly. After distribution the plasma concentration of mexiletine decreases exponentially to give a mean plasma half-life in healthy subjects of 10–11 h with i.v. administration and 9–10 h with oral administration. The mean half-life determined in patients stopping chronic oral therapy was 12–13 h (Prescott, Pottage and Clements, 1977; Campbell et al., 1978b, c).

Mexiletine is eliminated from the body primarily by metabolism, which presumably occurs in the liver. In healthy volunteers a mean of 7.9% of an administered dose of mexiletine was recovered unchanged from the urine in 3 days (Prescott, Pottage and Clements, 1977).

The therapeutic plasma concentration of mexiletine is in the range of 1–2 µg ml\(^{-1}\). Dose regimes for its administration have been described by Prescott and his colleagues (Prescott, Pottage and Clements, 1977). For i.v. use a bolus injection of 150–250 mg should be given over 2–5 min followed by a loading infusion of 250 mg in 30 min, then 250 mg in 2½ h and then 500 mg in 8 h. A maintenance infusion of 500–1000 mg is required each 24 h. This and similar regimes have been shown to maintain the plasma concentration in the therapeutic range during the period of administration. For oral administration the therapeutic plasma concentration can be maintained with 200–300 mg every 6–8 h. A loading dose of 400 mg may be given at the start of oral treatment and in patients with acute myocardial infarction an additional dose of 200 mg may be given at 2 h.

Mexiletine on oral and i.v. administration is effective in suppressing ventricular ectopic beats and
ventricular tachycardia occurring after acute myocardial infarction and with digitalis toxicity, ischaemic heart disease and idiopathically (Campbell et al., 1973; Talbot et al., 1973; Talbot, Julian and Prescott, 1976; Campbell, Pantridge and Adgey, 1978).

In a controlled trial the effects of mexiletine were compared against procainamide and placebo, in patients who had sustained a myocardial infarction and had received lignocaine for ventricular tachycardia or ventricular ectopic beats which were R-on-T, multiform or close-coupled (Campbell et al., 1975). Patients received mexiletine 250 mg 8-hourly, procainamide 500 mg 4-hourly or placebo for 12 days with 24-h e.c.g. monitoring on the 4th and 10th days. Seventy-seven per cent of patients receiving placebo showed serious ventricular rhythm disorders compared with 33% receiving anti-arrhythmic therapy. No major adverse effects occurred in the mexiletine-treated group. In another double-blind study, mexiletine or placebo were given to 165 patients on arrival in a coronary care unit with continuous recording of the electrocardiogram to document arrhythmia. Ventricular tachycardia and R-on-T ventricular ectopic beats were significantly reduced in the mexiletine-treated patients (Campbell et al., 1979).

The i.v. administration of mexiletine may produce small changes in heart rate, cardiac output and arterial pressure, but there was not a marked negative inotropic effect (Banim et al., 1977; Pozenel, 1977). In severely ill patients large i.v. doses of mexiletine may produce bradycardia and hypotension (Talbot et al., 1973). The side-effects which may occur with mexiletine are nausea, tremor, nystagmus, confusions and convulsions (Bell, 1978).

Disopyramide

Disopyramide is a new anti-arrhythmic drug which has been available in the British Isles for about 4 years. It has Class I actions on isolated heart preparations and also has vagolytic actions in animals and man (Mokler and Van Arman, 1962; Sekiya and Vaughan Williams, 1963; Davies, Marrott and Muir, 1979).

Disopyramide is well absorbed after oral administration with almost equal hepatic (metabolic) and renal clearances, although the metabolism is not yet completely understood (Hinderling and Garrett, 1976). After i.v. administration the terminal phase of the elimination phase had a half-life of 4.5 h (Hinderling and Garrett, 1976). The therapeutic plasma concentration is 3–8 µg ml⁻¹. The recommended dose for oral administration is 100 mg 6-hourly. Disopyramide has been shown to be more effective than a placebo in reducing the frequency of ventricular arrhythmias occurring in patients studied with ambulatory arrhythmia monitoring (Vismara, Mason and Amsterdam, 1974).

In a comparison of disopyramide with placebo in patients with acute myocardial infarction admitted to ordinary medical wards (Zainal et al., 1977), the mortality was much less in the disopyramide-treated group than in the placebo group. The comparability of the two groups in this trial has been questioned (Lancet, 1979).

The main side-effects produced by disopyramide result from its anti-cholinergic effects. These are dry mouth, dry eyes and urinary retention. The increase in heart rate which occurs after i.v. administration probably has a similar origin (Davies, Marrott and Muir, 1979). Further experience with this drug, especially on i.v. administration, is desirable.

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ANTI-ARRHYTHMIC DRUGS


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