Cardiac arrhythmias: theory and practice

Effective treatment of the fast, irregular pulse with digitalis was established by Withering 200 years ago,1 and Wenckebach's observations on quinine led to the introduction of quinidine in 1918.2 Other antiarhythmic drugs did not emerge until around 1950, but since then many new drugs have been discovered and the choice is now bewildering. The development of systems of classification has lent some order to the apparent chaos, but do such systems help the clinician to choose the most appropriate drugs for the individual patient?

Vaughan Williams has grouped antiarhythmic drugs into four classes on the basis of their effects in vitro on the cardiac action potentials of normal cells.3 Class I drugs inhibit the fast inward sodium current and thus slow the maximum rate of depolarisation. They are further divided into three subgroups on the basis of their effects on the total action potential duration: class 1A drugs (for example, quinidine, procainamide, disopyramide) lengthen the action potential duration; class 1B drugs (for example, lignocaine, mexiletine, tocainide) shorten it; and class 1C drugs (for example, flecaïnide, encaïnide, lorcaïnide) have little effect. There are other important differences among the three subgroups. For example, the Q-T, interval tends to be prolonged by drugs of classes 1A and, to a less extent, 1C but not those of class 1B, and the drugs of class 1A have a greater negative inotropic effect than the drugs of the other subgroups.

Class II drugs, which include the β blockers and bretylium, diminish the effects of catecholamines. Class III drugs (for example, amiodarone and the β blocker sotalol) mimic the effects of hypothyroidism on the action potential, prolonging the action potential duration without altering the rate of depolarisation. The class IV drugs verapamil and diltiazem inhibit the slow inward calcium current.

This brief account is, however, an oversimplification of the pharmacological actions of these drugs, some of which have properties of more than one class, and all of which have other properties. Indeed, the classification is better seen as one of different classes of action of antiarhythmic drugs rather than of different classes of drugs. Furthermore, the various actions defined by this classification are not clearly related to the effectiveness of a drug in treating a particular arrhythmia in an individual patient. For example, the clinician cannot assume that because quinidine has proved effective procaïnide will also prove effective in the same patient.

Other classifications based on the effects of antiarrhythmic drugs on the electrophysiological properties of intact myocardial tissues such as the atiroventricular node and the His Purkinje fibres are of more help to the experimental cardiologist, but they ignore other effects of these drugs and still do not greatly help the practising physician.4 A more clinically useful method categorises drugs according to the cardiac tissues which each affects, as shown in the table.

Classification of antiarrhythmic drugs by site of action

<table>
<thead>
<tr>
<th>SITE OF ACTION</th>
<th>CLASS I DRUGS</th>
<th>CLASS II DRUGS</th>
<th>CLASS III DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINOATRIAL NODE</td>
<td>β Blockers</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Class IV drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VENTRICLES</td>
<td>Class I drugs</td>
<td></td>
<td>Class III drugs</td>
</tr>
<tr>
<td>ACCESSORY PATHWAYS</td>
<td>Class Ia drugs</td>
<td></td>
<td>Class II drugs</td>
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</tbody>
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This categorisation has at least the merit that it reminds the clinician of the drugs which may be effective in treating an arrhythmia arising from a particular part of the heart. It does not, however, help him to choose one drug rather than another from within each category.

How, then, having decided that treatment is necessary and that some form of non-drug treatment (for example, cardioversion, a pacemaker, or surgery) would not be more appropriate, does the clinician choose the best option? In most cases the choice is still either empirical (often according to fashion) or at best dictated by the need to avoid an adverse drug effect or interaction; sometimes the nature of the patient's disease may help. Two examples show the operation of these factors.

Firstly, in most cases of established fast atrial fibrillation digitalis is still the treatment of choice on the basis of long experience. In some circumstances, however, other drugs may be preferred. Digitalis would be contraindicated in the treatment of atrial fibrillation due to accessory pathways
since it delays conduction through the normal tissues only; in such a case amiodarone would be appropriate. In atrial fibrillation associated with hyperthyroidism digitalis may be ineffective and a β blocker preferred. And with little evidence that digitalis is of value in preventing attacks of paroxysmal atrial fibrillation quinidine would be first choice.

Secondly, in ventricular arrhythmias the choice is from a larger range of drugs of broadly similar efficacy. In acute ventricular tachyarrhythmias lignocaine is still widely preferred as first choice, with intravenous amiodarone being given if lignocaine fails. Refractory arrhythmias may require other drug treatment: it would make sense, in the absence of other guidance, to substitute a drug of class Ia (for example, procainamide) and then one of class Ic (for example, flecainide). For chronic ventricular arrhythmias a drug of class Ia would be first choice. Amiodarone, while highly effective and fashionable, has long term adverse effects which are frequent and may be serious, and its future use seems likely to be only short term, except in selected cases where the benefit is thought to outweigh the long term risks. Of other established drugs, such as mexiletine, none has any clear cut advantages, and it is too soon to say whether tocainide and the class Ic drugs such as flecainide will prove to be any better.

The precise choice of drug in cases such as these may be further influenced by contraindications (anticipated adverse effects or interactions)—for example, disopyramide and quinidine (because of their anticholinergic actions) in patients with glaucoma or prostatism; drugs of class Ia in patients with cardiac failure or heart block (which they will tend to exacerbate); and combinations of drugs which prolong the Q-T interval (drugs of class Ia and amiodarone, because of the risk of ventricular tachyarrhythmias, particularly torsade de points). Further guidance may be given by the technique of inducing a patient’s arrhythmia (for example, by rapid pacing or by delivering precisely timed stimuli during the cardiac cycle) and then observing its response to selected drugs. The responsiveness to class I drugs in these controlled circumstances has been claimed to be a good predictor of the subsequent responsiveness during long term treatment for both ventricular and supraventricular tachyarrhythmias, and in some series this method has predicted effective treatment in over 70% of patients, though in the case of amiodarone its value is controversial. There are, however, disadvantages: the technique requires special skill and is not universally available; only a few drugs can be studied at a time; the induced arrhythmia may not prove to be the same as that requiring treatment; and the induction of arrhythmias may be hazardous (in one series just over half of patients required DC cardioversion to terminate the induced arrhythmia, though none died). Finally, the successful long term suppression of arrhythmias will depend on the achievement of similar plasma concentrations to those effective during the short term study. Because of these problems this technique is likely to be used only in selected patients in skilled centres.

Despite large advances in our understanding of the pathogenesis of cardiac arrhythmias and of the pharmacological effects of antiarrhythmic drugs drug treatment of cardiac arrhythmias remains, if not entirely unsatisfactory, far short of ideal. In most studies a single drug has been given, often to patients thought (though not always proved) to be resistant to other treatment, and has been shown to be effective in a variable proportion of cases. In fewer instances controlled comparisons have been made of two drugs, and even then it has been difficult to determine any features (relating to the patient or his disease) which would lead to a rational preference of one drug to another. Until such information is available we shall continue to depend mostly on empiricism and the avoidance of adverse effects and interactions.

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Containing the use of diagnostic tests

In the past 25 years requests received in diagnostic departments have risen by about 10% a year while inpatient admissions and outpatient attendances have increased by less than 2% yearly. Much of this inflation is due not to the introduction of new tests but to a greater demand for well-established procedures. In the Public Health Laboratory Service, for example, 1.5 million urine specimens were received for culture in 1979 compared with only 0.5 million 11 years earlier. Reporting on the substantial increase in the use of diagnostic services during the 1960s, Ashley et al commented that “demand cannot continue indefinitely at the present rate,” but more than a decade later demand is still increasing, with diagnostic departments now accounting for over 9% of the costs of acute hospital services.

Are the current levels of testing justified? We are not sure. Making diagnoses is at the nub of clinical practice, but research on diagnostic tests has concentrated more on issues such as the precision of results obtained in the laboratory and the comparative accuracy of one test against another than on determining which patients benefit from which tests. Results of the few studies which have evaluated the use of diagnostic tests in the NHS suggest that unnecessary investigation is commonplace. After a series of multicentre studies of radiological procedures the Royal College of Radiologists has...