Topics in Therapeutics

Edited by R.G. Shanks

Topics in Therapeutics 3

Edited by R. G. Shanks, M.D.

G. K. Hall & Co.
Medical Publications Division
Boston, Massachusetts

G. K. Hall & Co.
Medical Publications Division
70 Lincoln Street
Boston, Massachusetts 02111

79 80 81 / 4 3 2 1

LC 79-5139
ISBN 0-8161-2181-8

TOPICS IN
THERAPEUTICS

Editor's Foreword

Advances in the drug treatment of disease occur for many different reasons. Appreciation of the nature and course of a disease and improvement in the understanding of a disease mechanism and of the nature of complications may provide a basis for advances in treatment with existing drugs. Alternatively, the development of novel or improved drugs and their introduction into clinical medicine may lead to an advance in treatment, not only of the specific disease for which they were introduced, but through astute observation, of other conditions. Prophylactic use of drugs for prevention of the complications of some degenerative diseases may in future herald new aspects of treatment. Recent studies indicate that patients may not take drugs as they have been prescribed. This aspect of therapeutics may have been neglected in the past. Several aspects of these subjects are described in this book to illustrate some current topics in therapeutics.

Contributors

L J Beilin MD, FRCP	Clinical Reader & Hon. Consultant Physician, Dept of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford
A M Breckenridge MD, MSc, FRCP	Professor of Clinical Pharmacology, University of Liverpool
D A Chamberlain MD, FRCP	Consultant Physician, Royal Sussex County Hospital, Brighton
J Crooks MD, FRCP FRCP(Ed), FRCP (Glas)	Professor of Therapeutics, University of Dundee
S H Curry BPharm, PhD, MPS	Reader in Pharmacology, The London Hospital Medical College, London
C T Dollery MB, FRCP	Professor of Clinical Pharmacology, Royal Postgraduate Medical School, London
J W Dundee MD, PhD, FFARCS, MRCP	Professor of Anaesthetics, Queen's University, Belfast
M Hamilton MD, FRCP	Consultant Physician, Chelmsford and Essex Hospital
D Jack PhD, FPS, FRIC	Allen & Hanbury's Research Ltd, Ware
D G Julian MD, FRCP	Professor of Cardiology, University of Newcastle-upon-Tyne
J Koch-Weser MD	Director, Centre de Recherche Merrell International, Strasbourg
D R Laurence MD, FRCP	Professor Pharmacology and Therapeutics, University College Hospital Medical School, London
A R Lorimer MD, FRCP	Consultant Cardiologist, Royal Infirmary, Glasgow

D G McDevitt MD, MRCP	Reader in Clinical Pharmacology, Queen's University, Belfast and Consultant Physician, Belfast City Hospital
M D Milne MD, FRCP	Professor of Medicine, Westminster Hospital Medical School, London
A G Mowat MB, ChB, FRCP	Consultant Rheumatologist, Nuffield Orthopaedic Centre, Oxford
B F Robinson MD, FRCP	Reader in Cardiovascular Medicine, St George's Hospital Medical School, London
J H Shelley BSc, MB ChB	Director of Clinical Investigation, CH Boehringer Sohn, Ingelheim am Rhein, West Germany
A J Smith MA, DM, FRCP	Consultant Physician, United Sheffield Hospitals
M Thomas MA, MD, MRCP	Consultant Cardiologist, Midhurst Medical Research Institute, Sussex
P Turner MD, BSc, FRCP	Professor of Clinical Pharmacology, St Bartholomew's Hospital, London
Margaret Turner-Warwick PhD, FRCP	Professor of Medicine (Thoracic) Cardiothoracic Institute, Brompton Hospital, London

Contents

Clinical Management of Arrhythmias in Acute Myocardial Infarction

MICHAEL THOMAS

Cardiac arrhythmias are the most important therapeutically reversible complications of acute myocardial infarction. The electrocardiographic varieties are legion – and the drugs and other measures used in treatment equally confusing to many. This dissertation is intended to portray simple principles of management for therapeutic success under practical conditions. Treatment essentially involves action but it is also necessary to avoid adding to the patient's natural problems by inappropriate intervention. A working knowledge of the main arrhythmias is assumed. Principles of therapy depend very much on the clinical circumstances. Patients managed in fully equipped, continuously supervised special care units only require professional expertise for best therapeutic results. Patients becoming ill in the home, in the street or at work provide very different early problems as do those who are electively looked after at home by their family doctor. A first requirement for any medical attention is a diagnosis. Whatever the circumstances of the illness the heart rhythm should be determined at the first opportunity. In the event of the patient becoming unwell through an arrhythmia, and especially should the heart stop, specific intervention must be based on a knowledge of the heart rhythm. Evidently this may be had on a continuous basis in a special care unit but only on a sporadic basis, if at all, if the patient is cared for at home. The theme of patient care suggested hereafter applies, of course, to the monitored, continuously supervised patient.

Probably all patients with acute myocardial infarction have arrhythmias of some sort. Usually they are of little physiological or prognostic significance; some are lethal. The tempo of clinical response to a cardiac arrhythmia depends on a variety of considerations, and while each rhythm has its electrical peculiarities, the functional consequences of arrhythmias depend on two main issues:

1 Is blood flow to vital organs maintained adequately? – and
2 What are the risks and natural history of the particular rhythm?

The choice of treatment depends in part on the speed with which these two

considerations are changing. As to blood flow – it is evident that life depends on an adequate blood flow. If flow requirements are not met, brain, heart, liver and kidneys may suffer irreversibly. In general terms it is not important whether flow is provided by low heart rate/high stroke volume combination or by high rate/low stroke volume but in extremes of ranges there are limiting factors especially in the presence of heart muscle, valve, and pericardial disease. The natural history of the particular rhythm determines therapeutic action. Many rhythms revert spontaneously to sinus rhythm and while no harm is likely to come to the supervised patient, it is legitimate to await events. Some rhythms carry individual risks if allowed to go on for prolonged periods. Rapid, unstable atrial fibrillation and systemic emboli is one example. Some rhythms have a natural propensity to deteriorate into life threatening forms; for instance ventricular tachycardia precipitating ventricular fibrillation. Thus general attitudes to arrhythmias are modified by specific considerations. Before extending discussion of treatment along these lines, one overwhelmingly important fact has to be appreciated. Ventricular fibrillation inevitably leads to death unless urgently reverted by DC shock. Most arrhythmias with fatal outcome kill via ventricular fibrillation. It follows that to deal with this (1) the condition must be diagnosed immediately, and (2) DC shock has to be given immediately. Thus in the controversy of home versus special care unit treatment it must be remembered that VF at home means death whereas VF in a special care unit should be survived.

Returning to general principles of therapy in the continuously supervised patient, prophylaxis is better than treatment; and it is in ventricular arrhythmias, the most important killers, that prophylaxis has been most extensively explored. Individual patients with recurrent arrhythmias associated repeatedly with cardiac arrest – such as ventricular tachycardia, will often rather obviously benefit from drug prophylaxis which prevents the 'triggering' arrhythmia. Recurrent cardiac arrest may thus be shown to be prevented in certain individuals by prophylaxis against the precipitant arrhythmia. The more general situation is not so clear. Specific prophylactic measures include blanket prescription of anti-arrhythmic drugs such as lignocaine (and relatives) and β-blocking drugs. While lignocaine is certainly effective in most cases of ventricular ectopic beats and runs of ventricular tachycardia, it has not been easy to prove that primary ventricular fibrillation will be prevented. Part of the analytical problem relates to the low frequency of cardiac arrest in later hours of the acute illness. Early reports were rather negative but later comments are more positive in support of lignocaine prophylaxis. The opposite was the case with propranolol. At first optimism followed apparent life saving, but later results were non supportive. It is quite a different story later on in convalescence – later than 1–2 weeks after the acute illness – when practolol has been shown to dramatically improve the prognosis for life after anterior myocardial infarction. This finding may well point the way to the most significant medical impact on the natural history of acute myocardial infarction. Before disregarding routine prophylactic therapy

in the acute illness we should again note two points. Individual patients with recurrent arrhythmias associated with cardiac arrest undoubtedly benefit from preventing the initiating arrhythmia. Second, in trials designed to test the prophylactic value of drugs in the acute illness, all other reasonable treatment was given – and it could well be that in circumstances in which all other reasonable treatment may not be given, for example at home, then prophylactic benefit may be seen. There are non specific considerations in prophylaxis. A quiet, unexciting environment seems to reduce the frequency of arrhythmias, whereas changes and upsets, such as moving to another ward in hospital, sometimes precipitate cardiac instability.

Consider now the established arrhythmia. Each arrhythmia has characteristic haemodynamic consequences according to the particular disorganisation of cardiac co-ordination. In myocardial infarction the superadded consequences of ventricular failure impose their own stamp on the effects of an arrhythmia and in many instances ventricular failure determines the severity and urgency of the clinical situation. Myocardial infarction and overt ventricular failure result in a range of reduced stroke volume at rest and a limitation of the increase in stroke volume which normally is available on demand. In the worse degrees of heart failure, stroke volume may actually fall when an increased load is placed on the heart. Thus in the diseased heart variations in heart rate, due to arrhythmias, may not be followed by the usual changes in stroke volume. Low heart rate is not compensated by stroke volume increase. Bradycardia in acute myocardial infarction may reduce cardiac output far more than in the normal heart. Likewise, increasing heart rate from a low level (e.g. by atropine or pacing) may be critically important in maintaining the circulation. Tachycardia poses a different problem. Tachycardia in the presence of coronary disease is especially limiting in terms of diastolic coronary blood flow. The heart may become even more ischaemic and overall heart failure result. With increased ischaemia, angina pectoris may accompany further heart failure with rapid clinical deterioration in some patients. The extreme situation is seen in ventricular tachycardia at ventricular rates of more than 200/min when arterial pressure and flow may fall so low as to mimic cardiac arrest.

It follows from the above remarks that an electrocardiographically identical arrhythmia can have widely differing consequences for individual patients. When and how to intervene depends on an appreciation of many factors and a good feel for this can only be gained from practical experience in judging the risks of the arrhythmia versus the risks of treatment. As a guideline to the clinical management of the main types of arrhythmias the following comments are offered.

Cardiac instability is most marked in the first minutes and hour of the acute illness. Deaths are most common at this stage and a precise knowledge of the mechanisms preceding death is not available. The sudden death syndrome merges with early acute myocardial infarction. The heart has a propensity to slow down

and the ventricles to fibrillate. At this early stage the two main risks – sinus or other bradycardia and unannounced ventricular fibrillation – need to be anticipated by having atropine to hand and to be equipped for immediate diagnosis of ventricular fibrillation and the delivery of DC shock.

Ventricular fibrillation (VF) is associated with total loss of the pumping action of the heart. Failure to deal with VF effectively renders all other acute arrhythmic therapy a hypocrisy. Speed is essential and if the heart fibrillates under supervision the first measure should be DC shock. If shock fails to restore an effective beat then general measures including external cardiac massage, ventilation and I/V bicarbonate should be given before drugs and renewed attempts.

Ventricular tachycardia (VT) often precedes and precipitates ventricular fibrillation. Although the circulation situation during VT is always significantly better than in ventricular fibrillation, clinical 'collapse' resembling complete mechanical arrest may occur at ventricular rates of 200/min and over. Some cardiac output is maintained and intravenous lignocaine 1–2 mg/kg should be given while preparing for DC shock. In patients resistant to lignocaine and/or shocks, later choice drugs such as diphenylhydantoin, β-blocking agents and quinidine may be used. In less urgent circulation failure such drugs may be given at spaced time intervals without DC shock, but it should be borne in mind that accumulation of such agents in the patient may lead to progressive reduction in arterial pressure independent of the effects of the arrhythmia. In resistant cases intravenous infusion of potassium may be helpful – but here too, close supervision is necessary. A useful sequence is to shock after each pharmacological intervention as soon as it is apparent that the drug itself has not succeeded. When later choice drugs are used, heart block syndromes after DC shock should be anticipated and facilities for cardiac pacing put on standby.

Supraventricular rhythms are especially common. Varieties of supraventricular tachycardia (SVT) with different degrees of atrioventricular block and atrial fibrillation are important in terms of delicate clinical handling. Usually they are self limiting and provided the circulation is adequate, intervention may often be deferred with safety. In the case of atrial fibrillation, particularly with alternating sinus rhythm, heparin intravenously is to be commended to help prevent intra-atrial clot and emboli. In some patients, supraventricular arrhythmias are haemodynamically serious and circulation failure and a shock state have to be anticipated. Such deterioration takes place when the stroke volume is markedly reduced by the infarction and when the ventricular rate compromises diastolic coronary flow with resultant general heart failure.

Treatment of supraventricular rhythms depends on the patient's tolerance of the arrhythmia. If deterioration requires action, the rate of effect of treatment must be evaluated against the rate of deterioration of the patient. If the diagnosis from the elctrocardiogram is not clear, precise information may be obtained from an intracardiac electrode placed (transvenously) in the right atrium. This is attached to the 'V' head of a fully isolated electrocardiograph – when the

recording clearly shows the position of the P waves with respect to R waves. This technique is often not conveniently available and treatment has to be initiated without the fullest knowledge of the rhythm. In this case, a useful procedure is to slow the heart with very slow I/V injection of practolol (still available in I/V form) while monitoring the heart continuously. The injection should be made over 10–15 minutes, pausing whenever the heart is seen to slow. Up to 15–20 mg may be given in patients of average size. Slowing of the heart has two main benefits. First, the slower rate may allow precise ECG diagnosis, and second, the 20–40 beats difference may be disproportionately beneficial in circulation terms, so giving more time for analysis and other therapy. Of course the rhythm may be particularly controlled – as in some patients who prove to have atrial fibrillation and in whom the heart rate may be reduced almost by half. This rhythm may then be further controlled by digitalis or converted by DC shock. DC shock has advantages as primary treatment if the overall clinical situation is deteriorating and the rhythm is not certainly diagnosed. If there is any chance of the rhythm being ventricular in origin then of course digitalis should not be used and DC shock following I/V lignocaine 100 mg is to be preferred. DC shock is sometimes hazardous in the presence of therapeutic levels of digitalis glycoside and early DC shock should also be used in patients whose rate of general deterioration may become serious before digitalis has controlled an atrial arrhythmia. If DC shock in the presence of digitalis is unavoidable, it should be preceded by lignocaine 100 mg I/V. The first shocks should be of low energy – e.g. 10 WS and facilities for cardiac pacing should be at hand. Occasionally atrial arrhythmias provide real problems in treatment and a variety of drugs must be tried – such as verapamil, quinidine, β-blockade, etc. Care should be taken especially if an accumulation of such agents begins to lower the systemic pressure. Rather than risk this, some rhythms may be captured by rapid cardiac pacing at a higher frequency than the arrhythmia; gradually reducing rate may then break the rhythm. Normally pacemakers do not have sufficiently high frequency for this exercise and modifications are necessary.

The last major group of arrhythmias is the bradycardias. Bradycardia occurs in many electrocardiographic guises but especially as supraventricular bradycardia. A syndrome involving slowing of the heart, hypotension, nausea, vomiting and a sense of impending dissolution frequently accompanies the earliest changes in acute ischaemia and infarction. Ventricular fibrillation can follow an interpolated 'escape' ectopic beat and this may well be the mechanism of 'sudden death'. Slowing of the heart occurs mainly in relation to diaphragmatic and septal infarction but also in anterior lesions. Sinus or other bradycardia may also accompany recurrent angina at rest and here too the risk of ventricular fibrillation is high. The clinical management of the bradycardia obviously depends on the circumstances and the extent to which the patient's circulation is compromised. In emergency situations, deterioration of the patient's circulation may be offset merely by raising the patient's legs to about 45° from horizontal. This

'autotransfuses' several pints of blood into the chest and appears to counter the heart slowing reflex. Acceleration of the heart by atropine I/V in incremental doses of 0.3 mg up to approximately 1.5 mg is often specifically effective. On the other hand bradycardia due to second degree (e.g. 2:1) heart block is often best treated by isoprenaline 0.05 mg slowly I/V.

Slowing of the heart may be related to atrioventricular node and related rhythms originating in the main bundle conducting systems. These rhythms tend to be idiosyncratic and the drug sensitivity is difficult to predict. If the patient's overall state will allow, close observation but no action is often the best policy. The most predictable way of handling A/V nodal bradycardia of circulatory significance is by electrical pacing. With the system 'on demand' the drug sensitivity of the rhythm can then be determined with more confidence. This is especially true when a nodal rhythm is varying in electrical characteristics in association with bundle conduction faults. Such rhythms are notoriously unpredictable and electrical pacing provides welcome security. Complete heart block deserves individual attention. Here again the severity of the circulation illness varies widely for any given heart rate. The worse the mechanical heart function and the lower the stroke volume, the more severe the circulation problem. If the heart rate and stroke volume combination gives adequate cardiac output (say, over 3 litres/min in an average size patient) the concern is prediction of the immediate future. In fully supervised circumstances, where pacing may be instituted at short notice, it is sometimes acceptable to merely observe in the expectation of the rhythm reverting to a sinus origin – heart rate can be kept up by isoprenaline infused by pump. For the most part, and certainly where close supervision is in doubt, electrical pacing is the definitive treatment. As a general rule there should be no hesitation in pacing patients with complete heart block. A cautionary comment is in order. Such patients sometimes have very irritable ventricles and some experience of right heart catheterisation is desirable.

Such brief outline of management in the multitude of arrhythmias which may be encountered in acute myocardial infarction is necessarily incomplete. Therapeutic success does not lie in an encyclopaedic detailed knowledge however, but rather in developing an appreciation of informed decisive therapy together with caution in delicate situations.

The Prevention of Arrhythmias in Coronary Disease

D G JULIAN

Nearly all disturbances of rhythm and conduction can be controlled by currently available pharmacological and electrical methods of treatment. Unfortunately, many of the most serious arrhythmias occur in circumstances where they are not or could not be detected before they lead to a fatal outcome. Although other arrhythmias and heart block are dangerous this chapter considers only the prophylaxis of ventricular fibrillation because of its frequency as a cause of death.

Ventricular Arrhythmias under Coronary Care

For many years attention has been focused on the detection of certain ventricular ectopic arrhythmias in acute myocardial infarction in the belief that the correction of such arrhythmias would prevent ventricular tachycardia and fibrillation. This approach largely followed the lead of Lown et al (1967) who claimed that ventricular fibrillation was not unheralded and that failure to prevent it was due to inadequate observation and treatment. It has been assumed that certain types of ventricular arrhythmia, notably frequent ventricular tachycardia, were often followed by ventricular fibrillation and that ventricular fibrillation was usually preceded by such arrhythmias. More recently, however, data has accumulated to indicate that primary ventricular fibrillation is not preceded by a warning arrhythmia in 25-50% of cases (Lawrie, 1969; Dhurandhar et al, 1971; Bennett and Pentecost, 1972; Wyman and Hammersmith, 1974; Lie et al, 1974a). Unheralded primary ventricular fibrillation is particularly common soon after the onset of symptoms.

Even if ventricular fibrillation is sometimes not preceded by ventricular arrhythmias, are they good predictors when they do occur? Earlier reports (Woods and Barnes, 1960; Julian et al, 1964) suggested a good correlation

between the types of arrhythmia which Lown cited and subsequent ventricular fibrillation, but such studies were made without continuous monitoring. Moss et al (1972) in studying 60 patients with an acute myocardial infarction admitted to a Pre-Hospital Satellite Industrial Coronary Care Unit noted that closely coupled ventricular premature beats were reliable pre-hospital predictions of serious ventricular arrhythmias but that frequent ventricular beats were not particularly associated with subsequent ventricular arrhythmia. On the other hand, complete absence of ventricular premature beats was a significant indicator of rhythm stability during the next 24 hours. Mogenson (1970) showed that frequent ectopic beats, particularly of the R on T type, were associated with subsequent ventricular tachycardia but, perhaps because ventricular fibrillation was uncommon in his series, he was unable to show any association with this arrhythmia.

Lie et al (1974a) however, concluded that ventricular arrhythmias were not predictive of ventricular fibrillation and that this arrhythmia was no more likely to develop in those that had them than those that did not. However, in subsequent observations this view has been modified (Lie et al, 1975), and these workers now consider that certain ventricular arrhythmias, notably coupling, seen early do carry an enhanced risk of ventricular fibrillation.

This matter is not yet resolved; it is clearly of great importance that it should be as so much effort is devoted to the detection of ventricular arrhythmias. However, one may, in any case, question whether this effort is well directed as several observations have shown contemporary monitoring methods to be inefficient. Thus, Mogenson (1970) reported that many of the arrhythmias which he could detect from continuous ECG write-outs were not observed or treated by the nurses. Romhilt et al (1973) showed, by analysis with an offline computer, that there was a low rate of arrhythmia detection by nurses. We (Vetter and Julian, 1975) undertook a similar study in which patients in adjacent rooms were studied by conventional means in one and an on-line arrhythmia computer in the other. ECG signals from both rooms were fed to continuous tape recorders. These tapes were subsequently analysed and the true incidence of arrhythmias was established by a further analysis by another computer, by visual inspection of the oscilloscopic replay and by writing-out suspected abnormalities. Records were kept of the number of arrhythmias which occurred, of the alarms which were signalled in the coronary care unit, and of the institution of treatment. Several facts emerged:-

1 Nurses were efficient at detecting ventricular fibrillation, frequent ventricular ectopic beats and long runs of ventricular tachycardia, but shorter runs of ventricular tachycardia and closely coupled ventricular ectopic beats were usually missed.

2 These deficiences had important therapeutic implications. Thus, in the computer monitored room, all patients in whom therapy