differ. In making a single rule valid in all conditions we deny the patient's individuality, even his humanity.

Let me submit for consideration a different ethic. The doctor's first duty, subject to the patient's consent, is to do all he can to maintain health and vigour; to restore health when it has been impaired; to repair incapacities when they are sustained. Second to this comes the duty to relieve or if not relieve then alleviate suffering. If we bear these principles in mind the preservation of life will look after itself in all cases in which it is desirable and desired. Per se it is no part of the doctor's ordinary duties.

If we take the patient's personal needs and wishes as our prime directives we must allow for self-destruction. This is not to decry all the work that is done by suicide prevention services; many suicidal attempts, sometimes called "parasuicides," are cries for help, cries that should be heeded. But about one attempt in seven is fully intended. This is so for the lonely people with multiple physical illnesses or handicaps, who make up the bulk of successful suicides among the elderly. Since the Suicide Act of 1961 killing oneself is not unlawful, and these people are doing only what is within their rights. Barraclough⁴ studied 30 suicides by people over the age of 65; in five of them there was a terminal malignancy or other condition likely to be fatal in two years. Would we really wish that those five had been found in time and rescued to live a little longer with their terminal disease? It is to be hoped that very soon now doctors will come to respect the wishes of the man who has given thought to his duties and obligations and has deliberately decided to end his life on grounds that are obviously valid, at

least for him. We must hope for more than this. There are so many ways of killing oneself disgracefully, as by throwing oneself under a train, or messily or uncomfortably or at great inconvenience. Some day, perhaps, when there is more respect for suicide as a way of death, kindly and comfortable means will be made available.

Conclusion

It is very natural that doctors should feel profound repugnance when the suggestion arises, as they see it, that they should act as "executioners." Yet considerations of humanity no less than common sense lead one to the view that when the process of dying is intolerably long drawn out its abbreviation is a service to the individual patient which only his doctor can perform. This places us all before a very painful dilemma. We shall be able to find our way past it only by the kind of discussion which involves new thinking and much heart-searching. *Non est vivere, sed valere, vita.*

References

- ¹ Leach, G., *The Biocrats*. London, Cape, 1970.
- ² National Society for Autistic Children, *Families at Breaking Point*. London, N.S.A.C., 1971.
- ³ Dawson of Penn, Lord, *House of Lords, Parliamentary Debates*, vol. 103, p. 480. London, H.M.S.O., 1936.
- ⁴ Barraclough, B. M., in *Recent Developments in Psychogeriatrics*, ed. D. W. K. Kay and A. Walk. Ashford, Kent, Headley, 1971.

Scientific Basis of Clinical Practice

Drugs Acting on the Heart

IAN R. GRAY

British Medical Journal, 1971, 4, 736-738

The function of the heart is to maintain a flow of blood through the systemic and pulmonary circulations commensurate with the needs of the tissues, and the return of blood by the venous systems. For the heart to perform perfectly in all circumstances its rhythm and neurological control must be normal, and the conduction of the impulse through the heart muscle intact. The force and amplitude of myocardial contraction must be able to increase appropriately in response to a pressure or volume load, and flow of blood through the coronary vessels must be unimpeded. Symptoms of heart disease occur only when one or more of these vital mechanisms is disturbed: rhythm, conduction, myocardial function, or coronary flow. The drugs which act on the heart may conveniently be considered in relation to these four mechanisms.

Disturbances of Rhythm

The drugs which are used in the management of supra-ventricular and ventricular dysrhythmias fall into three groups—digitalis; quinidine and quinidine-like drugs; and beta-adrenergic blocking drugs.

DIGITALIS

The effect of digitalis on heart-rate and rhythm depends mainly on its action in slowing atrioventricular conduction and prolonging the refractory period of the conducting tissues. It also slows the heart rate through vagal stimulation, but this is probably of little clinical importance. The dysrhythmia most responsive to digitalis is atrial fibrillation, where its effect on atrioventricular conduction slows a rapid ventricular rate. Digitalis is also highly effective in atrial flutter by increasing the degree of atrioventricular block. It is surprising how effective digitalis can be in paroxysmal atrial tachycardia. Some recent studies on the mechanism of this dysrhythmia indicate that an abnormal feedback of the electrochemical impulse from ventricle to atrium may be responsible for this dysrhythmia, and possibly digitalis is effective by interfering with this mechanism.

While digitalis is one of the most valuable and potent drugs used in cardiology, its dangers must not be disregarded. Overdosage with digitals may lead to almost any disturbance of rhythm and conduction—from ventricular extrasystoles, the commonest, to atrial tachycardia with atrioventricular block, said to be the most dangerous. The role of potassium depletion in heightening the vulnerability of the heart to digitalis toxicity is now widely recognized, and every care is necessary when potent diuretics are being used along with digitalis. It is sometimes difficult to judge whether a disturbance of rhythm is due to digitalis intoxication, and whether digitalis should be used in its management. The

Coventry and Warwickshire Hospital, Coventry

IAN R. GRAY, M.D., F.R.C.P., Consultant Cardiologist

newer techniques of digitalis assay should make it easier to assess the level of digitalization, and to detect and manage cases of intoxication.

QUINIDINE

Quinidine and a number of drugs with a similar pharmacological effect are widely used in dysrhythmias. These substances slow conduction and depress myocardial irritability. They are all active in some degree as local anaesthetics, and they all have a toxic effect upon the myocardium. This is through interference with the passage of sodium ions across the cell membrane of the myocardium, a vital stage in the depolarization and repolarization of the myocardium. The drugs in this category include procainamide, lignocaine, and epanutin as well as quinidine. Propranolol, though best known as a beta-adrenergic-blocking drug, also has quinidine-like properties which play a part in its effect upon dysrhythmias.

Of these drugs, quinidine has been longest in use but is now out of favour because of its toxic effects. It may be used orally or parenterally in the treatment and prevention of supraventricular and ventricular dysrhythmias, and was widely employed before the introduction of direct-current reversion and of other antidysrhythmic drugs. When used in high dosage quinidine gives rise to serious disturbances of conduction and has a bad reputation for causing sudden death. It certainly should be used for intensive treatment of dysrhythmias only when the electrocardiogram can be continually monitored, and, because of its depressant effect on myocardial function, is not the drug of choice in treating patients with dysrhythmias after myocardial infarction.

Procainamide, which may be used orally or intravenously, has very similar effects to quinidine in slowing conduction and depressing myocardial irritability. It is less toxic to the myocardium than quinidine, and has proved valuable in treating supraventricular and ventricular tachycardia. When used in prophylaxis of paroxysmal dysrhythmias the long-term administration of procainamide commonly gives rise to the syndrome of systemic lupus erythematosus, a complication which must be considered in patients on oral procainamide.

Lignocaine has come into wide use in the management of ventricular dysrhythmias after myocardial infarction. Its depressant effect on myocardial function is less than that of other drugs of this group so that it can be used in this delicate clinical situation with reasonable confidence. It has to be given intravenously and can be administered in a loading dose of up to 2 mg per kg body weight, as well as by continuous infusion. It is given for the treatment of ventricular dysrhythmias and also for their prophylaxis, and numerous reports testify to its efficacy and safety.

BETA-ADRENERGIC BLOCKING DRUGS

The beta-adrenergic blocking drugs, which have some quinidine-like actions as well, have a part to play in the treatment of dysrhythmias. The beta-receptors normally respond to circulating catecholamines so as to enhance myocardial performance—with acceleration of the heart-rate and an increase in the force of myocardial contraction—and the beta-adrenergic blocking drugs interfere with this response. Since catecholamines probably play an important part in causing disturbance of cardiac rhythm, the use of beta-blocking drugs has a rational basis. They have proved effective antidysrhythmic drugs, particularly when given intravenously. How much of their effect is due to beta-blockade and how much to their quinidine-like effect has been difficult to judge. Propranolol, the most widely used beta-blocking drug, has a serious depressant effect on myocardial function, and its use in post-infarction dysrhythmias is fraught with danger. Practolol, which is a more cardioselective beta-blocker, has a less depressant effect on myocardial function than pro-

pranolol, and is safer to use in the treatment of dysrhythmias. Nevertheless, the very nature of beta-blocking drugs is such that they must be used with great caution in ill patients with myocardial infarction or after major cardiac surgery.

Digitalis, quinidine, procainamide, lignocaine, and practolol all have their place along with direct-current reversion in managing dysrhythmias, and epanutin and bretylium have been recommended as well for dysrhythmias not responsive to more conventional treatment. But dysrhythmias are capricious in their behaviour, and no hard and fast rules should be laid down for treatment of the individual patient.

Sinus bradycardia usually has an extracardiac mechanism—that is, excessive vagal tone—and is best treated by vagal inhibition with atropine. The bradycardia which often interferes appreciably with cardiac function in myocardial infarction responds very well to this.

Disturbances of Conduction

Disturbances of conduction within the heart comprise sinoatrial block, atrial standstill, and atrioventricular block of varying degree. They may lead to ventricular standstill with Adams-Stokes syncope, or an escape rhythm may establish itself in the heart from a focus beyond the site of block. These disturbances of conduction are most frequently caused by degenerative changes and by ischaemic injury, but are sometimes congenital and may be from digitalis intoxication. Faintness from bradycardia, and syncope from ventricular standstill, are the commonest symptoms, but sometimes heart block is responsible for intractable cardiac failure. While electrical pacemaking is often the proper treatment for the various forms of heartblock, drug therapy does have a significant role with the use of sympathomimetic amines, which improve transmission through the conducting system and also accelerate the rate of impulse generation at all levels in the myocardium.

Ephedrine and isoprenaline have largely given way to Saventrine—a preparation of isoprenaline which is released slowly in the small bowel, giving a slow and prolonged absorption of the drug. Isoprenaline increases the rate of sinus discharge and may also improve atrioventricular conduction and increase an idioventricular rate. It may therefore be helpful in any kind of heart block or cardiac standstill. Unfortunately the mechanism of syncope in patients with heart block is often ventricular tachycardia or fibrillation rather than standstill. It is therefore advisable not to use Saventrine in long-term therapy without first monitoring its effect on the cardiac rhythm over a short period of oral or intravenous administration. Once assured that Saventrine does not aggravate the situation by precipitating ventricular dysrhythmias, the doctor may try oral administration with increasing doses. It seems to have a beneficial effect in preventing ventricular standstill and increasing the heart rate in complete heart block in up to half of all patients, and limits the number of patients needing an electrical pacer.

Myocardial Failure

The cause for myocardial failure may be a pressure overload (as in hypertension or aortic stenosis), a volume overload (as in mitral or aortic regurgitation), or a myocardial injury (as with myocardial infarction or cardiomyopathy.) When overload is the problem the cause may often be treated directly, as with antihypertensive therapy or surgical treatment of valve disease. In the management of myocardial failure treatment is in fact directed as much to other systems and organs as to the heart itself. Diuretic therapy is nearly always necessary, and occasionally the removal of fluid by dialysis—while sometimes an infusion of fluid to increase

ventricular filling pressure may improve myocardial performance. In the seriously ill patient acidosis and anoxia are serious consequences of myocardial failure, which should be corrected if possible. Tissue perfusion may be seriously impaired when the cardiac output is low, and in the patient with cardiogenic shock alpha-sympathetic blockade with phenoxybenzamine, together with large doses of hydrocortisone, may be used in an attempt to improve this. Nevertheless, benefits of improved tissue perfusion may be obtained at the price of increasing the myocardial load and dropping the arterial pressure. The value of hypertensive drugs in this situation, such as L-noradrenaline and angiotensin, is doubtful, as they may increase myocardial load without comparably improving the performance.

Digitalis is the most important drug in general use for improving the function of the failing myocardium—that is, as a positive inotropic agent. Positive inotropic drugs increase the speed of contraction of myocardium and shorten its total duration. In normal heart muscle the contractility is increased but output is unaffected, whereas in the failing heart cardiac output increases. This effect appears to be brought about by the influence of digitalis on the rate of calcium uptake by the myocardial cell, which is diminished in the failing myocardium and which is restored to normal by digitalis. The effect of digitalis on the failing myocardium as distinct from its effect on rhythm and conduction makes it beneficial in almost all patients with congestive heart failure, and it sometimes proves valuable in patients with cardiogenic shock. Isoprenaline, given intravenously, has a positive inotropic effect, and is sometimes worth using when only short-term support for the myocardium is needed, as in the postoperative management of patients having major cardiac surgery.

The insulin-potassium-glucose regimen has been found to improve myocardial function in the failing heart in animals. It is presumed to work by increasing the transfer of potassium from the extracellular compartment into the myocardial cells. Favourable results in patients with myocardial infarction have been reported, which are ascribed to the improvement of myocardial contraction and the diminution of the incidence of dysrhythmias. In general, however, this form of treatment has proved disappointing.

Interest has been centred more recently on another positive inotropic agent, glucagon, a hormone secreted by the alpha cells of the pancreatic islets. This substance has been shown to have an inotropic and chronotropic effect in animals and appears to act in a similar fashion to beta-adrenergic stimulating drugs. It has also been found to be effective in patients with heart disease, increasing the blood pressure and cardiac output without increasing the vascular resistance. It has the advantage over catecholamines in that it does not cause ventricular tachyarrhythmias. The place of glucagon in the treatment of patients with myocardial failure and, in particular, in cardiogenic shock, is still uncertain, but it may well prove to be of value.

Coronary Insufficiency

The drugs used for treating coronary insufficiency do not act directly by increasing coronary blood flow, but indirectly by reducing in one way or another the myocardial work. Glycerol trinitrate has been used for one hundred years for the treatment of cardiac pain, and it has been generally believed that it caused vasodilatation of the coronary arteries and thereby improved the collateral blood flow around an arterial obstruction. Though such dilatation is in fact suggested by coronary arteriography, no increase in total coronary blood flow can be shown after giving nitrites. It is now thought that their beneficial effect stems from their action on the peripheral circulation. As a potent vasodilator, glycerol trinitrate causes a pronounced fall in systemic vascular resistance and thus in left ventricular work. Its value is therefore in reducing the load on the left ventricle and therefore its oxygen

demand. The same mechanism justifies the use of the various other nitrite preparations with slower absorption such as isosorbide nitrate (Vascardin) and pentaerythritol tetranitrate (Mycardol). These drugs, when used in adequate dosage, may help in the management of coronary insufficiency, though they have been superseded almost completely by the beta-adrenergic blocking drugs.

Beta-adrenergic blocking drugs such as propranolol, practolol, and oxprenolol block the type 1 beta-adrenergic receptors in the myocardium, reducing the heart rate and decreasing the force of myocardial contraction—and thereby reducing left ventricular work. Their beneficial effect on coronary insufficiency is therefore similar to that of nitrites, though it is achieved in a completely different way. Effective beta-adrenergic blockade is recognized by the slowing of the heart rate and fall in blood pressure and runs *pari passu* with improvement of the symptoms of coronary insufficiency. The depressant effect of beta-blocking drugs on myocardial function, to which must be added their quinidine-like action, presents a problem in their use, as congestive cardiac failure may occur as a complication of treatment. The choice of the ideal beta-blocking drug will turn on this factor, as all those at present available have slightly different beta-blocking, quinidine-like, and sympathomimetic actions. Propranolol produces blockade, not only of the type 1 beta receptors in the heart but also of the type 2 receptors in the bronchial musculature. This leads to bronchospasm in susceptible people and may preclude its therapeutic use. Practolol and oxprenolol are much more cardioselective and are to be preferred.

Analgesic drugs are rarely employed in treating cardiac pain except when there is severe coronary insufficiency or myocardial infarction. The cardiovascular system in these states is often very seriously affected with hypotension, reduced cardiac output, left ventricular failure, tissue anoxia, and acidosis. Care has to be taken in administering any drug which can upset a very delicately balanced situation. Morphine, which is probably the most widely used analgesic in the treatment of myocardial infarction, often causes quite a pronounced fall in the blood pressure in patients with myocardial infarction. This may be severe enough to interfere seriously with the circulation and possibly the coronary flow in the seriously ill patient. Pethidine closely resembles morphine in this respect, while heroin causes very little fall in blood pressure and seems to be a more satisfactory drug for analgesia after myocardial infarction. Any of these potent analgesics also depress respiration. Since the patient with myocardial infarction may well have a degree of left ventricular failure as well as anoxaemia and acidosis, the effect of this must be kept in mind when giving analgesic drugs.

Conclusion

Nearly all the drugs employed in treating patients with heart disease are potentially dangerous as well as beneficial and their use is always in some degree an experiment. If the best results are to be obtained with the least hazard to the patient, careful and continued clinical observation is necessary. This need not entail continuous monitoring of the pulmonary artery pressure or even the electrocardiogram, but it does require observations of the pulse and blood pressure, the patient's colour, the assessment of cardiac failure both from the venous pressure and from the state of the lungs, and estimation of the cardiac output. The latter may be judged clinically from the pulse, the state of the skin circulation, the mental state, and the urinary output. Decisions about therapy should be positive decisions and must be reviewed periodically if the drugs we employ in heart disease are to be used to their best advantage.

This article is one of the Birmingham series of lectures (see B.M.J., 27 November, p. 510).