Drug Treatment of Disease

CARDIAC ARRHYTHMIAS

BY

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Abnormal rhythms of the heart are commonly causes of heart failure and syncope, and paroxysms of arrhythmia may, over years, cause recurring distress and disability. The drug treatment of such disorders is of importance, since there are rarely any other direct means of preventing attacks or bringing them to an end.

In the treatment of fast abnormal rhythms the three drugs frequently in use are digitalis, quinidine, and procaine amide, while prostigmine is occasionally required. When arrhythmias are slow, as in various forms of heart block, ephedrine, adrenaline, isoprenaline, and atropine are employed. The action of these principal groups of drugs and their administration will now be considered. Subsequently an account will be given of some drugs which aim to redress electrolyte balance such as potassium chloride and sodium lactate, which may play important parts in the control of cardiac arrhythmia.

DIGITALIS

While it has been proved that digitalis in the usual dosage has no influence on the healthy human heart or circulation, it acts on the auricles in heart disease by increasing the refractory period and through the vagus by slowing formation of impulses at the sino-auricular node. It also slows conduction through the bundle of His and the auriculo-ventricular node. Moreover, digitalis improves the power of the failing ventricular muscle and increases cardiac efficiency. Its essential use is in the treatment of heart failure, and it is of special value when this is associated with auricular fibrillation due to rheumatic heart disease.

Auricular Fibrillation

In this condition the heart rate is frequently high and there is a wastage of myocardial power because some contractions are too feeble to assist the circulation, as shown by the weak radial pulse. When the heart is slowed the ventricular filling improves and each contraction contributes to the circulation. Through this effect and its power of increasing the force of myocardial contraction, digitalis relieves the distress of heart failure, slows the rate of the heart, and promotes diuresis, processes which are expressed by the term "digitalization."

The total quantity of digitalis needed to achieve this state will vary according to the speed with which control is to be secured. The digitalizing dose needed for a patient weighing 11 stone (70 kg.) is about 22 gr. (1.4 g.) of the tablet digitalis folia, or about 3–4 mg. of digoxin ("lanoxin"). In severe heart failure treatment should start with an intramuscular injection of lanoxin 0.5 mg. or "cedilanid" 0.4–0.8 mg. Treatment may then be continued orally.

If large doses are given initially a smaller total amount is needed because there is less time for excretion. In general, a good plan is to use tablets of digitalis folia gr. 1 (65 mg.), giving on the first day 6 to 9 gr. (0.4 to 0.6 g.), on the second day 4 to 6 gr. (0.26 to 0.4 g.), and thereafter 3 gr. daily (0.2 g.), depending on the response in terms of heart rate and the clinical state. When it is judged that full benefit has been secured, or when the first indication of toxicity occurs, a lower dose, such as gr. 1 (65 mg.) twice daily, should be given. The ultimate maintenance dose will be that needed to keep the heart rate at about 60–70 per minute.

Digitalis is not expected to convert auricular fibrillation to normal rhythm, though the restoration which sometimes occurs may appear to be due to the action of the drug. The term digitalization also implies that the gradual accumulation which takes place in the body does not reach the degree needed to produce the evidences of intoxication, which are (i) coupled rhythm, (ii) nausea and vomiting, and sometimes (iii) an abnormally slow rate of the heart.

Auricular Flutter

Digitalis given in substantial dosage is the most effective means of restoring normal rhythm when auricular flutter exists. The quantity then needed may be above that already described for digitalization. Treatment is continued until auricular fibrillation is induced; if at this stage the administration is stopped, sinus rhythm returns in about two-thirds of cases. If flutter resists this treatment, digitalis may be continued in doses needed to control the rate, perhaps as 4 : 1 flutter, while at the same time quinidine is given in increasing dosage (see below) until normal rhythm is restored. As the conversion of auricular fibrillation or flutter to normal rhythm requires close clinical and cardiographic control, these procedures should generally be undertaken in hospital, unless special facilities are available elsewhere. There are a few patients in whom flutter resists conversion, or in whom flutter persistently recurs. In them, long-term control by digitalis has to be used.

Auricular Paroxysmal Tachycardia

If pressure on the carotid sinus has failed to restore normal rhythm, and if an injection of prostigmine 0.5–1 mg. subcutaneously or intramuscularly has also been unsuccessful, digitalization should be accomplished either by cedilanid 0.5 mg. as a slow intravenous injection or by lanoxin 0.5 mg. intramuscularly. Oral dosage will follow, and after digitalization has been achieved a daily maintenance dose should be continued for three months. Sometimes neither prostigmine nor digitalis converts the rhythm to normal, but either may render the patient sensitive to carotid-sinus pressure, so that this manœuvre, previously unavailing, becomes effective.

QUINIDINE

This isomer of quinine has for more than 40 years been recognized as having a favourable effect on the rhythm of the heart. It lengthens the refractory period of the myocardium by its influence on the vagus, the myocardium, and the conducting system. Its main clinical uses are in the conversion of auricular fibrillation to normal rhythm, in the control of extrasystolic rhythm, in the conversion of auricular flutter to normal rhythm, and in the treatment of ventricular paroxysmal tachycardia.

Auricular Fibrillation

It has been seen that digitalis cannot be expected to do more than control the rate of this arrhythmia. If the irregularity is of recent onset and not due to acute or advanced degenerative lesions of the myocardium, the physician may decide to attempt restoration to normal rhythm. For this purpose administration of quinidine is necessary. Quinidine sulphate gr. 5 (0.32 g.) is given orally at two-hourly intervals for six doses. The same dose should be given for the next two days. This will bring the plasma level to about 6–8 mg. per litre. If abnormal rhythm persists, the dosage may be increased a little but only under cardiographic control. Thus if the QRS interval increases to 0.14 sec., or if multifocal extrasystoles appear, or if vomiting or diarrhoea occurs, administration must be stopped. If the heart rate rises to 130 or more during treatment, administration should be discontinued pending control by digitalis; another trial by quinidine should then be made. Once normal rhythm has been restored and proved cardiographically, the dose of quinidine is reduced to gr. 5 (0.32 g.) three times daily and continued for a month. If relapse to fibrillation occurs readily and repeatedly after conversion, the attempt to restore normal rhythm should be abandoned.

Auricular Flutter

It has been said that digitalis is the treatment of choice for the correction of this arrhythmia, but if it is unavailing quinidine may be successful either alone or in conjunction with digitalis. If used alone, it should be given by the procedure described above for conversion of auricular fibrillation. Sometimes quinidine may be needed to supplement digitalis in the treatment of flutter. Thus, if digitalis fails to convert flutter beyond the stage of fibrillation, its administration is continued while quinidine is given orally gr. 5 (0.32 g.) thrice daily. Once normal rhythm has been restored, a maintenance dose of digitalis folia gr. 1 (65 mg.) t.d.s. or quinidine sulphate gr. 5 (0.32 g.) t.d.s. should be given for a month.

Extrasystoles

Very often no cause can be found for these arrhythmias, whether they arise from the auricle or the ventricle or in nodal tissues. If a cause such as focal sepsis is found, appropriate preventive action should be taken. Sometimes ectopic beats denote ischaemic or other heart disease, heart failure, thyrotoxicosis, or chronic alcoholism, and the treatment of the irregularity will then be that of the underlying disorder. In the absence of a causal disease requiring treatment, extrasystoles should be treated medicinally only if they weigh in the patient's mind or disturb sleep at night. In such events, quinidine gr. 3–5 (0.2–0.32 g.) thrice daily is the drug of choice, or procaine amide or ("pronestyl") 250 mg. four times a day may be tried. Sometimes a simple sedative such as amytal gr. ¾ (50 mg.) twice daily, is more effective. The arrhythmia may remain refractory to treatment.

Ventricular Paroxysmal Tachycardia

This arrhythmia is often self-limiting, the attacks being so brief that they are over before treatment can be administered. Attacks that last several hours or days may follow cardiac infarction, and these may be very difficult to correct more than temporarily. For such paroxysms quinidine sulphate is the treatment of choice, and is given orally in doses of 5 gr. (0.32 g.) two-hourly for eight doses. If this results in a return of normal rhythm, gr. 5 (0.32 g.) should be given thrice daily for a week or ten days, the dose being then tapered and discontinued. The suppression of recurring brief bouts of ventricular tachycardia may often be achieved by quinidine sulphate gr. 5 (0.32 g.) three or four times daily. If quinidine treatment is not successful in arresting these arrhythmias, pronestyl should be administered as described below.

PROCAINE AMIDE

This substance, introduced into clinical medicine less than ten years ago, has gained some recognition as a safeguard during anaesthesia and as a medicament for the control of cardiac arrhythmia in day-to-day practice. It acts by increasing the refractory period of both the auricle and ventricle and it also depresses vagal activity. Given by injection during anaesthesia, it helps to maintain regular rhythm in subjects known to be liable to arrhythmia, such as ventricular tachycardia, or the multiple extrasystoles that may occur during cyclopropane anaesthesia.

Procaine amide is less likely than quinidine to banish extrasystoles, but it may be given orally in doses of 250 mg. every four hours for two or three days, whether the arrhythmia is auricular or ventricular. Certain toxic effects may be encountered. Gastro-intestinal disturbances such as anorexia and vomiting occur, chiefly with oral administration, and may or may not invalidate its use. The more serious side-effects on the circulation arise when it is given intravenously, and the chief risk is of hypotension. This usually occurs, and sometimes it induces alarming effects by worsening impending shock and causing angina.

Procaine amide is also given in attempts to abolish paroxysmal tachycardia, wherever the focus may be, though it is more likely to be effective in ventricular tachycardia. Bellet (1958) has analysed the results claimed from this treatment in four published reports comprising 279 cases in all. Ventricular tachycardia was brought to an end in 69%, ventricular extrasystoles in 91%, supraventricular tachycardia in 68%, auricular fibrillation in 7%, and flutter in 5%. On the other hand, there is no arrhythmia in which procaine amide is generally regarded as the treatment of choice, though some may prefer it to prostigmine in the treatment of auricular paroxysmal tachycardia. Procaine amide may also be given intramuscularly in the dose already mentioned; though the results may be less certain, toxic effects may thus be avoided.

PROSTIGMINE

If in auricular tachycardia carotid sinus pressure fails to bring the paroxysm to an end, the drug most likely to succeed is prostigmine. It is given subcutaneously in a dose of 0.5 mg. Constitutional upset may follow—notably nausea and vomiting—but sinus rhythm may simultaneously be restored.

POTASSIUM

There has been in recent years an increasing realization of the importance of potassium in the function of the myocardium and in the maintenance of normal rhythm. If this electrolyte exists in excessive amount in the blood stream it may cause cardiac arrest. Conversely, deficiency of potassium increases the effect of digitalis on the heart. Moreover, it is a cause of arrhythmia and may explain the failure of digitalis to benefit the rhythm or the clinical state in some patients with heart failure. In these circumstances the heart still has a fast irregular rhythm but the patient is actually receiving more digitalis than is required, and perhaps more than he should. Estimation of the blood electrolytes may reveal deficiency of potassium. If then potassium chloride is given orally in doses of 5 g. daily, ventricular ectopic beats may disappear while the heart rate slows and the signs of heart failure abate. If the need is more urgent, potassium may be given intravenously as Darrow's solution. Should the potassium level in the blood be too great (a possible cause of rapid nodal rhythm), an infusion of one-sixth molar sodium lactate may correct this and often the associated arrhythmia.

It should be remembered that low-sodium diets and the long-continued use of mercurial diuretics may result in harmful disturbance of electrolyte balance. In this event less restriction of the sodium and correction of the potassium imbalance commonly brings swift improvement.

Slow Cardiac Arrhythmias

It has been seen that fast abnormal rhythms of the heart cause distress which is partly haemodynamic and partly emotional, and which is often incapacitating in varying degree. They may be responsible for heart failure and for syncopal attacks. Abnormally slow rhythms have equally harmful effects on the circulation and commonly lead to cerebral anoxia and syncope. The effects are thus in some ways similar to those of the fast arrhythmias but the problems of treatment are entirely dissimilar. The principal causes of bradycardia are depression of function or disease of the A.–V. node or bundle of His, depression of the S.–A. node or block between this node and the auricles, and overaction of the carotid-sinus mechanism. In any of these slow arrhythmias it is likely that overaction of the vagus contributes to the disorder. The general therapeutic indication is then for drugs which increase the excitability of the heart and its conducting tissue and in less degree those which impair or abolish vagal activity.

EPHEDRINE

This substance, given in doses of gr. ½–1 (32–65 mg.) thrice daily, is the most effective means of increasing the rate of the heart and for lessening the frequency of fainting or syncope. It acts by sympathetic stimulation and by improving the conductivity of the bundle of His. It is thus effective in accelerating the rhythm in partial heart block and in sino-auricular block. Even in complete A.–V. block, when the rhythm depends on the ventricles, ephedrine (like exercise or fever) increases the rate by a few beats a minute.

ADRENALINE

If the patient has Stokes–Adams attacks due to intermittent cardiac arrest or excessive slowing, injections of adrenaline are required. This is given as adrenaline hydrochloride, 5 minims (0.3 ml.) subcutaneously every two hours. A loaded syringe is kept in readiness for immediate treatment should more prolonged ventricular asystole occur. Sometimes Stokes–Adams attacks are associated with ventricular tachycardia. In such cases adrenaline is inadvisable, and quinidine and procaine amide are also contraindicated. The treatment advised is the sublingual administration of isoprenaline 20 mg.

ATROPINE

Through its action in depressing vagal activity atropine sulphate might be expected to increase the rate of the heart, but vagal activity is poor below the A.–V. node. Actually it is of little avail when heart block is present unless in conjunction with adrenaline. Atropine sulphate gr. 1/50 (1.3 mg.) given subcutaneously twice daily is always worth while giving when adrenaline alone does not produce the results expected.

SODIUM LACTATE

Normal solutions of sodium lactate given by intravenous drip have a powerful effect in stimulating the heart and increasing its rate. This effect may be particularly striking when bradycardia is associated with hyperkalaemia and in the Stokes–Adams syndrome. It is believed to act by favouring alkalosis, by the lowering of serum potassium, and perhaps by the direct effect of the lactate ion and an influence on the vagus. As the action of sodium lactate is entirely different from that of other drugs that excite the heart, it may reinforce their effect or even be advantageous when other remedies are without effect.

CORTICOTROPHIN (A.C.T.H.)

The successful use of this steroid in isolated cases of Stokes–Adams syndrome has been reported by Litchfield *et al.*

REFERENCES

Bellet, S. (1958). *Amer. Heart J.*, **56**, 479.
Litchfield, J. W., Manley, K. A., and Pollak, A. (1958). *Lancet*, **1**, 935.

"In the sphere of medicine and in the sense of something of value and based on experience that is handed down by word of mouth from senior to junior, tradition can teach that the very apprehensive patient is a 'bad surgical risk' and likely to make an eventful recovery from any operation, if indeed he does not succumb. This is equally true of the man who changes his religion on the night before a major surgical procedure, the man with piles of books, especially French novels, at each side of the bed, and the man who after a surgery is found reading his newspaper upside down. There is a well-founded tradition that intussusception babies are liable to burst after laparotomy, and that patients with red hair are prone to develop keloid scars." (The Cavendish Lecture, 1958, "On Tradition," by Sir Gordon Gordon-Taylor. *Proceedings of the West London Medico-Chirurgical Society, 1958.)*