THE PHARMACOLOGY OF THE NORMAL AND DISEASED HEART IN RELATION TO CARDIAC SURGERY

BY

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The two main groups of drugs which influence cardiac activity and which are important in relation to cardiac surgery are those with anti-arrhythmic activity and those which increase myocardial contractility.

DRUGS USED IN CARDIAC ARRHYTHMIAS

Recent advances in the treatment of arrhythmias have stemmed from careful observation and monitoring in postoperative intensive care areas and from the renewed interest of physicians in the arrhythmias after myocardial infarction. The basic treatment of arrhythmias is the same whenever they occur.

Although a knowledge of the electrophysiological changes leading to arrhythmias (Hoffman and Cranefield, 1964; Hoffman, Cranefield and Wallace, 1966) is helpful, it is seldom possible to define precisely what the mechanism is in a particular case. Much is known about the pharmacological properties of anti-arrhythmic drugs and their action on myocardial cells (Singer and Ten Eick, 1969) and this has led to some rationalization of therapy, but there are still wide gaps in our knowledge between the basic causes of arrhythmias and the ways in which drugs act to influence them. Therapy is still largely based on clinical experience.

Anti-arrhythmic drugs can be divided into four main groups.

(1) Drugs having a direct action on the cell membrane.

In general drugs in this group diminish excitability, decrease the rate of diastolic depolarization in automatic cells, depress conduction and prolong the refractory period. A disadvantage is that they depress myocardial contractility, perhaps in part due to depression of conduction leading to loss of synchronization in myocardial contraction (Angelakos, 1966).

Quinidine.

This drug is mainly used in the prevention of supraventricular arrhythmias but plays little part in therapy related to cardiac surgery.

Procaine amide.

When given orally procaine amide may be useful postoperatively to suppress ventricular ectopic beats and recurrent ventricular tachycardia; it is often given as a supplement to intravenous lignocaine. Procaine amide is less effective against supraventricular arrhythmias. It is seldom given intravenously as it tends to produce hypotension, due partly to arterial dilatation and partly to a reduction in cardiac output from diminished contractility. As an initial treatment its intravenous use has been almost entirely superseded by lignocaine—but it may be successful when lignocaine fails.

Lignocaine.

Lignocaine was described as having an anti-arrhythmic action in experimental animals by van Dongen in 1953. Later it was used in the management of arrhythmias following cardiac surgery (Likoff, 1959; Weiss, 1960). In the last few years it has been used extensively as an anti-arrhythmic drug and particularly in the management of arrhythmias following acute myocardial infarction. Bigger and Heissenbuttel (1969) have recently reviewed the pharmacological properties of lignocaine and compared them with procaine amide. There have now been numerous observations on the haemodynamic changes occurring after intravenous lignocaine in animals and man (Jewitt, Kishon and Thomas, 1968; Cullhed, 1969; Grossman, Cooper and Frieden, 1969; Binnion et al., 1969). All investigators agree that in therapeutic doses lignocaine has a negligible effect on cardiac output, blood pressure and cardiac contractile force.

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Lignocaine is usually ineffective in supra-ventricular arrhythmias (Jewitt et al., 1967) and, like quinidine, is contraindicated in atrial flutter in patients who have not previously been digitalized. Its main use is in the suppression of ventricular ectopic beats and the termination and prevention of ventricular tachycardia and fibrillation. Lown and others (1967) suggested that ventricular ectopic beats should be suppressed by lignocaine if they had one of four characteristics:

(i) they were of the "R on T" type;
(ii) if they were of multiform configuration;
(iii) salvos of two or more;
(iv) sustained occurrence at a frequency greater than 5 per minute.

Of these the most important is the "R on T" type and it may well be that late ectopic beats (i.e. not "R on T") are far less dangerous however frequently they occur.

Lignocaine is given intravenously in a bolus dose of 0.5–2 mg/kg body weight (usually 50–100 mg). The duration of action is 15–20 minutes and a second dose of 0.5–1.0 mg/kg can be repeated within 3–5 minutes. Successive doses can be given up to a total of 3–4 mg/kg (Killip, 1968). For the suppression of ectopic beats a bolus dose is usually followed by an intravenous infusion of the drug at the rate of 1, 2 or up to 4 mg/min. Satisfactory blood levels can be achieved with intramuscular lignocaine (Dunning, Ketner and Wesdorp, 1969), but postoperatively it is certainly best given intravenously. The possibility of oral lignocaine has been investigated (Eisinger and Hellier, 1969).

The only contraindications to lignocaine are sinus bradycardia and atrioventricular block. Because of problems of excretion and distribution it should be given cautiously to patients with liver disease or pronounced renal failure.

(2) Beta-adrenergic blocking drugs.

Pronethalol, the first beta-adrenergic blocking drug to be used clinically, was originally introduced for the treatment of angina but was found to have anti-arrhythmic actions. The drug which has been most widely studied experimentally and clinically is propranolol, but in recent years many other beta-adrenergic blocking drugs have been synthesized.

In addition to their beta-blocking properties some of these drugs have one or both of two additional effects. The first is a direct action on the myocardium, diminishing the rate of rise and height of the action potential of conducting tissue; this is associated with a local anaesthetic effect. In much higher doses a decrease in myocardial contractility results. Because of the similarity to the effect of quinidine on the action potential and the local anaesthetic effect, this was termed a "quinidine-like" effect. This, however, is not a satisfactory term and most workers prefer the less specific term—a "membrane" effect. The second action which some of these compounds have is a sympathomimetic effect on cardiac tissue.

Table I shows the main beta-adrenergic blocking drugs which are in clinical use at present.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Beta-blocking action</th>
<th>Sympathomimetic action</th>
<th>Membrane effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol (Inderal)</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Alprenolol (Aptin)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oxprenolol (Trasicor)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sotalol</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Practolol (Eraldin)</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Practolol is interesting in that it has a beta-blocking action on the heart but not on bronchi or peripheral vessels—thus it can be used in patients with obstructive airways disease.

The optical isomers of some of these drugs have been studied and as a group all behave in a similar way. In the case of propranolol the dextro isomer has only 1/50th to 1/100th of the beta-blocking action of the laevo form, but has an equivalent membrane effect. The sympathomimetic action of these compounds is confined to the laevo isomer.

The action of propranolol and other beta-blocking drugs in slowing the sinus rate and the ventricular rate in atrial fibrillation and flutter is through beta-blockade. The action of pro-
pranolol in abolishing or preventing supra-
ventricular and ventricular ectopic beats and
tachycardias is due partly to beta-blockade and
partly to its membrane action.

Propranolol is liable to precipitate and intensify
heart failure; this is commonly considered to be
due in part to its membrane effect. Because of
this, and the fact that it may provoke profound
bradycardia, propranolol is seldom used in the
treatment of postoperative arrhythmias. Practolol,
however, has less tendency to produce heart
failure and has been used successfully in post-
operative patients (Gibson, Balcon and Sowton,
1968; Jewitt and Croxon, 1971). It may be used
to slow the sinus rate or, in patients who cannot
be controlled with digitalis, it may be effective in
slowing the ventricular rate in atrial flutter and
fibrillation if this is considered necessary. It must
be stressed, however, that the sinus and ventricu-
lar rates are usually rapid as a secondary mani-
festation of cardiac stress and to lower them may
be not only unhelpful but hazardous.

Practolol may be effective in terminating
supraventricular tachycardia or slowing the
ventricular rate by increasing the degree of
atrioventricular block. It may abolish or prevent
ventricular ectopic beats and tachycardia in some
patients in whom lignocaine has failed. It is
administered intravenously in a dose of 5 mg
but up to 25 mg may be given. Oral treatment of
100 mg or more twice daily may be helpful in
preventing ectopic arrhythmias.

Oxprenolol has been reported to be an effective
anti-arrhythmic agent but so far has been used
less frequently than practolol in this country.
Alprenolol has a greater negative inotropic effect
than practolol (Jewitt, 1970) and is probably not
as safe to use postoperatively as practolol.

(3) Phenytoin.
The pharmacological action of this drug has been
reviewed recently by Vaughan Williams (1970).
He stated that from the evidence available there
appeared to be three ways of explaining its anti-
arrhythmic action:

(1) by a central action, reducing the output of
sympathetic impulses;

(2) by increasing the permeability of the cell
membrane to potassium—analogous to the
action of acetylcholine on atrial muscle;

(3) by having the same class of action on
cardiac muscle as quinidine, lignocaine
and dextro-propranolol.

Eddy and Singh (1969) found it helpful in
suppressing supraventricular ectopic foci whereas
Helfant et al. (1970) found it relatively inefficient
in supraventricular arrhythmias. Both groups and
Mercer and Osborne (1967) found it of value in
ventricular ectopic beats and tachycardia, and
superior to procaine amide. Moffitt, Sessler and
Kirklin (1967) have used it postoperatively in
abolishing ventricular ectopic arrhythmias. It is
given intravenously at the rate of 25–50 mg/min
to a total dose of 5 mg/kg body weight (Helfant
et al., 1970).

As a rule lignocaine would be tried first and
then practolol or phenytoin unless, of course,
cardioversion is more appropriate.

(4) Digitalis.
Digitalis is used either for its anti-arrhythmic
action or its positive inotropic action or both.
Its anti-arrhythmic action is partly due to the
direct action of the drug on atrial muscle and
atrioventricular node and partly by enhancing the
effect of vagal stimulation (table II).

| Table II |
|---|---|
| **Anti-arrhythmic effects of digitalis on cardiac muscle.** | **Atrioventricular node** |
| **Atrial muscle** | Effective | Conduction | Effective | Conduction |
| | refractory | velocity | refractory | velocity |
| Direct effects of digitalis | Increased | Decreased | Increased | Decreased |
| Vagal effect | Decreased | Increased | Increased | Decreased |
| Effect on innervated heart | Slightly decreased | Slightly increased | Increased | Decreased |

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By its action at the atrioventricular node it reduces the ventricular rate in atrial flutter and fibrillation. It may convert atrial flutter to fibrillation by its action on atrial muscle (Moe and Farah, 1965).

The clinical use of digitalis for both effects is discussed below.

**INOTROPIC DRUGS**

Drugs which increase myocardial contractility do so by a direct action on the myocardium or via sympathetic stimulation.

**Adrenergic drugs.**

Adrenergic drugs which have a stimulatory effect on beta-receptors may be used to increase myocardial contractility. They also have a positive chronotropic effect and may precipitate arrhythmias. The drugs in common clinical use are listed in table III.

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Alpha-receptors</th>
<th>Beta-receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Noradrenaline (Levophed)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th>Alpha-receptors</th>
<th>Beta-receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Metaraminol (Aramine)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mephentermine (Mephenine)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Phenylephrine (Neo-synephrine)</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Methoxamine (Vasocon)</td>
<td>+ +</td>
<td>-</td>
</tr>
<tr>
<td>Methyl-amphetamine (Methedrine)</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Although such drugs may be useful when there is some evidence of myocardial insufficiency, there is a good deal of controversy about their use and relative values in the management of cardiogenic shock where the prime fault is a low cardiac output. In this condition there are also profound secondary changes in the peripheral circulation and the alpha-stimulating actions of these drugs as well as their effect on heart rate have to be considered.

Lillehei, Dietzman and Bloch (1967) advocate the use in cardiogenic shock of phenoxybenzamine, an alpha-adrenergic blocking drug, together with adequate fluid therapy. They reported that isoprenaline, which also dilates the blood vessels in the muscle masses, together with fluid therapy was often successful; they found isoprenaline most useful in patients with a bradycardia or a rate below 100/min. However, the majority of patients with cardiogenic shock have a tachycardia and the further increase in heart rate from isoprenaline had a deleterious effect. Fordham and Resnekov (1970) compared the effects of intravenous infusions of adrenaline and isoprenaline in the early postoperative period following aortic valve replacement. They concluded that adrenaline was a more satisfactory drug in that, for a given increase in heart rate, it caused a greater change in stroke volume and arterial pulse pressure and that isoprenaline always aggravated hypoxaemia.

**Inotropic drugs having a direct myocardial effect.**

1. **Digitalis.**

   The inotropic effects of digitalis have been well reviewed recently by Mason, Spann and Zeglis (1969). They pointed out that digitalis glycosides augment the contractile state of the myocardium in normal, failing and diseased non-failing hearts. In addition they cause arterial and venous constriction. The net result of these actions clinically depends on the initial circulatory state and the degree of sympathetic tone. Thus in the normal heart there is no rise in cardiac output nor any improvement in the response to exercise (Russell and Reeves, 1963). In patients with heart failure cardiac output is increased. If the cardiac output is low in patients with heart disease not in failure, it is restored to normal and the response to exercise is improved. The drug allows less encroachment on the fundamental compensatory mechanisms maintaining circulatory function in these patients and provides some additional inotropic reserve (Mason, Spann and Zeglis, 1969).

**Digitalis therapy in clinical practice.**

Whenever possible digitalis is given by mouth. In this country digoxin is the most popular drug...
and there are a number of schedules for full digitalization (Friedberg, 1966; Cleland et al., 1969). Another advantage of digoxin is that the maintenance dose can be continued intramuscularly. A more rapid effect can be achieved by the intravenous route using digoxin, Cedilanid (lanatoside C) or ouabain.

Although as a general rule intravenous digitalis should not be given if the patient has received any digitalis preparation within the previous two weeks (Friedberg, 1966), the situation may be different after major heart surgery. At this time the therapeutic requirements may change and stable digitalization may have been disturbed by the bypass procedure. Accordingly, should the necessity arise, oral treatment can be increased or small additional intravenous doses of lanatoside C (0.3–0.4 mg) or ouabain (0.2 mg) (Bristow and Griswold, 1965) or digoxin (0.125 mg) may be given, the patient being kept under careful observation for evidence of toxicity.

Pre-operative treatment. There is some controversy as to whether digitalis should be given pre-operatively, for its inotropic effect, to patients who are not already taking the drug. This situation arises, for example, in patients with moderate pulmonary stenosis or atrial septal defects. Since, as indicated above, digitalis may be of value in abnormal but non-failing hearts it seems reasonable to give the drug before operation as a prophylactic measure against the stresses and trauma to the myocardium at operation, and the possible negative inotropic effects of the anaesthetic. In patients undergoing closed mitral valvotomy, in whom atrial fibrillation might be anticipated during or after operation, pretreatment with digitalis permits easier control of the ventricular rate if atrial fibrillation does occur (Bristow and Griswold, 1965; Mason, Spann and Zeglis, 1969). Whilst these workers and others (Deutsch and Dalen, 1969) advocate prophylactic digitalization, others are not in favour of it (Lyons, Dushane and Kirklin, 1960; Moffitt, Sessler and Kirklin, 1967). Recently Selzer and Cohn (1970) put forward a strong case against giving pre-operative digitalis to patients with no overt signs of heart failure. They point out that individual requirements for full digitalization vary widely and there are no clinical or laboratory landmarks for guidance. They criticize the evidence which is quoted in support of the use of digitalis in the prevention of cardiac failure and control of postoperative arrhythmias. Certainly, there is a real difficulty in treating a postoperative arrhythmia when it is not clear whether it is due to digitalis or whether digitalis is necessary to control it.

Patients who are stabilized on maintenance digitalis before operation should normally continue on their usual dose up to the time of operation. Those, however, who are on a heavy diuretic regime may have low tissue stores of potassium even when their serum potassium is normal. In these cases extra oral potassium is given for 2–3 days before operation and digitalis withheld for 1 or 2 days (Lillehei, Dietzman and Bloch, 1967).

It is not clear what happens to digitalis stores and levels in patients submitted to bypass and this is used as a reason by some for not giving pre-operative digitalis to patients not on maintenance; they prefer to give the drug in full dosage during or after operation as the necessity arises (Lyons, Dushane and Kirklin, 1960).

During operation. It is seldom necessary to give additional digitalis during cardiac surgery but if atrial fibrillation develops and the ventricular rate is too rapid it may be necessary.

Postoperative treatment. Additional digitalis together with other inotropic drugs may be helpful in a patient who develops cardiogenic shock which does not respond satisfactorily to volume replacement and correction of other factors. It may likewise be beneficial to increase the dose in patients with increasing congestive failure or those with atrial flutter or fibrillation and a rapid ventricular rate.

Digitalis is often successful in terminating supraventricular tachycardias but there are two main problems associated with its use in these arrhythmias. The first is that supraventricular arrhythmias may be the result of digitalis toxicity and to increase the dose might be dangerous. The second difficulty is that if the arrhythmia fails to respond to increased doses of digitalis, d.c. cardioversion is less likely to be successful and is more hazardous in patients who are intoxicated, or nearly so, with digitalis. Lillehei, Dietzman and Bloch (1967) pointed out that if the heart is unstable it is best to ensure that the
patient is not potassium-depleted by giving an infusion of potassium chloride; it is unwise to augment digitalis therapy if there may be potassium deficiency. If stopping digitalis and giving potassium supplements fail then other measures may be tried. Phenytoin is a useful drug in terminating digitalis-induced ectopic arrhythmias and success has also been reported with practolol (Gibson, Balcon and Sowton, 1968). When digitalis intoxication is associated with a slow ventricular rate due to atrioventricular block or nodal bradycardia then isoprenaline or atropine is indicated; phenytoin, practolol and potassium should not be given.

(2) Glucagon.

Glucagon, a polypeptide hormone produced by the alpha cells of the pancreas, has been shown in animal studies (Farah and Tuttle, 1960; Regan et al., 1964; Whitehouse and James, 1966; Glick et al., 1968; Lucchesi, 1968) and in humans (Farnley, Glick and Sonnenblick, 1968; Klein, Morch and Mahon, 1968; Finhart et al., 1968; Williams et al., 1969) during cardiac catheterization to have significant inotropic and moderate chronotropic effects (Manchester et al., 1970). The inotropic effect persists, despite beta-adrenergic blockade, catecholamine depletion or full digitalization and is not associated with increased ventricular irritability.

Parmley, Matloff and Sonnenblick (1969) gave 5.0 mg intravenously to patients on the first day after prosthetic valve replacement. They reported increases in arterial pressure, heart rate, cardiac index and systolic ejection rate. Glucagon did not provoke any arrhythmias. When given intravenously the maximum effect occurs within 10 minutes and the effects are dissipated by 30 minutes (Murtagh et al., 1970). Other dosage schedules were reviewed by Dolgin (1970). Vanden Ark and Reynolds (1970) gave a continuous infusion of glucagon for several days at an average dose of 4 mg/hour. They reported that the drug produced distinct clinical improvement in 12 of 16 patients with low cardiac outputs, 4 of whom were postoperative heart surgery patients. The drug did not induce arrhythmias. Other workers (Brogan, Kozonis and Overy, 1969; Nord, Fontanes and Williams, 1970; Wilcken and Lvoff, 1970) have also used this method of administration with some success.

Diamond et al. (1970) reported that the oxygen cost for an equivalent rise in output was less with glucagon than with noradrenaline, and Polumbo and Leighton (1970) found that both glucagon and isoprenaline enhanced cardiac performance in patients with heart disease, but that isoprenaline tended to be more effective; further improvement resulted when the two drugs were given together.

In summary, it appears that glucagon has some value in heart failure and should be useful in low output states after cardiac surgery. The results of further trials will be awaited with interest.

REFERENCES


PHARMACOLOGY IN RELATION TO CARDIAC SURGERY


