Antagonists acting on the beta- or alpha-adrenoceptors are used widely in medicine and in anaesthesia. The major indications for beta-adrenoceptor blockade are coronary artery disease and arterial hypertension, while those for alpha-adrenoceptor blockade include arterial hypertension, paroxysmal hypertension and chronic cardiac failure. The adrenoceptor antagonists interfere with important regulatory mechanisms of the circulation. Detailed knowledge of their effects on the circulation is essential because many patients presenting for surgery receive these drugs. Moreover, this knowledge is required in order to use adrenoceptor antagonists to the patient's best advantage, during anaesthesia and surgery.

As a preamble, the adrenergic receptors will be very briefly described.

ADRENERGIC RECEPTORS

As early as 1906, Dale predicted the existence of two types of adrenergic receptors (Dale, 1906). The criteria for distinction between alpha- and beta-adrenoceptors were defined by Ahlquist (1948). The beta-adrenoceptors were further subdivided into two types, beta-1 and beta-2 (Lands et al., 1967). Similarly, the alpha-adrenoceptors were further subdivided into alpha-1 and alpha-2 receptors (Langer, 1977).

Receptors have two main characteristics, one is affinity for a specific molecule, the transmitter, the other is the triggering, by a change in the configuration of the receptor, of a chain of reactions, leading to a physiological response. Usually, the chain involves an enzyme system which acts as a multiplier. Chemicals other than the natural transmitters may bind to the receptor and cause either activation (agonists) or inactivation (antagonists).

The development of radiolabelled agonists and antagonists has made it possible to demonstrate the presence of adrenergic receptors, to determine their location and to measure the density of their distribution. Using photoaffinity labelling techniques, several peptides have been identified which appear to contain adrenergic receptor sites (Lefkowitz, Stradel and Caron, 1983). Receptors may be located on the cell membrane, in the cytoplasm or at the surface of intracellular organelles. The wide variety of locations of adrenergic receptors (table I) explains the multiplicity of the effects of adrenergic stimulation.

TABLE I. Distribution of adrenergic receptors. (The differentiation between Alpha-1 (postsynaptic) and Alpha-2 (presynaptic) is not precise (Langer and Hicks, 1984))

<table>
<thead>
<tr>
<th>Type of receptor</th>
<th>System, tissue or organs</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-1</td>
<td>Heart</td>
<td>Increased automaticity, increased conduction, increased contractility, increased excitability</td>
</tr>
<tr>
<td></td>
<td>Coronary arteries</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Increased renin release</td>
</tr>
<tr>
<td></td>
<td>Adipose tissue</td>
<td>Enhanced lipolysis</td>
</tr>
<tr>
<td></td>
<td>Intestinal muscle</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Beta-2</td>
<td>Heart</td>
<td>Increased automaticity</td>
</tr>
<tr>
<td></td>
<td>Peripheral vessels</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Bronchial muscle</td>
<td>Relaxation</td>
</tr>
<tr>
<td></td>
<td>Uterus</td>
<td>Relaxation</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Increased insulin release</td>
</tr>
<tr>
<td>Alpha-1</td>
<td>Peripheral vessels</td>
<td>Vasconstriction</td>
</tr>
<tr>
<td></td>
<td>Bronchial muscle</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>Dilator pupillae</td>
<td>Mydriasis</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Decreased insulin release</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation promoted</td>
</tr>
<tr>
<td>Alpha-2</td>
<td>Adrenergic transmission</td>
<td>Presynaptic inhibition</td>
</tr>
</tbody>
</table>

BETA-ADRENOCEPTOR ANTAGONISTS

Pharmacology

Beta-adrenoceptor antagonists exhibit specific affinity for the beta-adrenoceptor, where they act by competitive inhibition. This implies that agonists and antagonists compete for the same binding sites. The binding is reversible and so the antagonist may be displaced from the receptor if sufficiently large quantities of the agonist are present. Competitive blockade causes a displacement to the right of the dose–response curve to the agonist, but the slope of
the dose-response curve remains unchanged and a full effect can develop. Recent evidence indicates that prolonged administration of beta-adrenoceptor antagonists may cause an increase in the number of beta-receptors (Boudoulas et al., 1977).

**Receptor selectivity**

The structure of the beta-adrenoceptor antagonists is relatively similar to that of the sympathomimetic amines. However, because of differences in their chemical structure, some beta-adrenoceptor antagonists have greater affinity for the cardiac (beta-1) than for the peripheral (beta-2) adrenoceptors. Propranolol is considered non-selective, since it is almost equally as effective in blocking beta-1 as beta-2 adrenoceptors. Agents which block both types of receptors are liable to cause bronchoconstriction and peripheral vasoconstriction. These unwanted effects have led to the search for selective adrenoceptor antagonists which act predominantly on the cardiac beta-receptors. Practolol and other cardioselective antagonists reduce the positive inotropic and chronotropic responses to isoprenaline without inhibiting peripheral vasodilatation and bronchodilatation. These agents appear to be selective for the beta-1 receptors (Dunlop and Shanks, 1968; Ablad, Carlsson and Ek, 1973). Selectivity should not be interpreted as specificity; when large doses of beta-1 adrenoceptor blockers are administered, they eventually block both beta-1 and beta-2 receptors.

**Intrinsic sympathomimetic activity (ISA)**

Ariens has differentiated between affinity and specific activity at receptor sites (Ariens, 1964, 1967). Drugs with high affinity and high specific activity are pure agonists, drugs with high affinity and no specific activity are pure antagonists and drugs with high affinity and low specific activity are partial agonists. Partial agonists stimulate beta-1 or beta-1 and beta-2 adrenoceptors but, by their presence at receptor sites, prevent the effect of other agonists. Stimulation of the beta-receptors by partial agonists is often called intrinsic sympathomimetic activity. With some partial agonists, up to 50% of the effect of isoprenaline may be elicited (table II). Partial agonists increase heart rate and contractile force in experimental models (Ablad, Brogard and Ek, 1967; Barrett and Carter, 1970). In man, partial agonists cause less resting bradycardia and, in the case of borderline heart failure, may be tolerated more readily than pure antagonists (Epois et al., 1972).

**Classification of beta-blockers**

Beta-adrenoceptor blockers may be classified into selective and non-selective and into partial agonist and pure antagonists (table III). One agent, labetalol, combines alpha- and beta-adrenoceptor blocking properties. Unwanted side-effects and cardiac depression are least likely to occur with the cardioselective partial agonists.

**Table II. Intrinsic sympathomimetic activity (ISA) of some partial agonists (after Ablad and others (1980))**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Partial agonist activity (ISA) (% of isoprenaline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pindolol</td>
<td>50%</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>30%</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>25%</td>
</tr>
<tr>
<td>Practolol</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Table III. Classification of the beta-adrenoceptor blockers.**

*Labetalol is also an alpha-1 adrenoceptor antagonist

<table>
<thead>
<tr>
<th></th>
<th>Cardioselective (beta-1)</th>
<th>Non-selective (beta-1 and beta-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure antagonist</td>
<td>Atenolol</td>
<td>Nadolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>Timolol</td>
<td></td>
</tr>
<tr>
<td>Labetalol*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial agonist</td>
<td>Acebutolol</td>
<td>Alprenolol</td>
</tr>
<tr>
<td>Practolol</td>
<td>Oxprenolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pindolol</td>
<td></td>
</tr>
</tbody>
</table>

**Membrane stabilization**

Membrane stabilization is caused by inhibition of sodium transport. With the exception of atenolol and nadolol, the beta-adrenoceptor antagonists cause some membrane stabilization in the heart and, therefore, resemble quinidine. The rate of increase of action potentials recorded intracellularly is decreased (Singh and Vaughan Williams, 1971) and contractile performance is reduced (Nayler and Chang, 1973). However, these effects are detectable only at concentrations that are considerably greater than those required to obtain adequate clinical beta-adrenoceptor blockade (Fitzgerald, Wale and Austin, 1972). Depressed conduction and negative
inotropy, when they are observed, are not caused by membrane stabilization, but by removal of sympathetic support to the heart.

Antiarrhythmic action

The major antiarrhythmic effect of beta-adrenoceptor blockade is the prevention of the arrhythmogenic effect of the endogenous and exogenous catecholamines. Membrane stabilization (quinidine-like effect) is probably of little importance with the usual clinical doses of beta-adrenoceptor antagonists. Perhaps of more importance is the increase in duration of the action potential which occurs following chronic administration of some beta-blockers (Vaughan Williams et al., 1975). Sotalol is the only beta-adrenoceptor antagonist that increases the duration of the action potential immediately after i.v. administration (Edvardsson et al., 1980; Bennett, 1982).

Morphology of the myocardium

Vaughan Williams and co-workers have examined the effect of long-term beta-adrenoceptor blockade on the morphology of the myocardium. In rabbits, they observed a greater decrease in the dry than in the wet weight of the heart in relation to body weight. This indicated an increase in the fluid content of the ventricles of treated animals (Vaughan Williams et al., 1975). More detailed analysis revealed a significant reduction in the mean intercapillary distance at the epicardial and endocardial zones (Tasgal and Vaughan Williams, 1981). If such an increase in capillary density occurs in man, it would protect the myocardium by a mechanism independent from reduction in oxygen consumption.

Haemodynamic effects of beta-adrenoceptor blockade

All beta-adrenoceptor blockers reduce heart rate and cardiac output because they reduce or remove the effect of beta-1 receptor stimulation. The magnitude of the change is greater when sympathetic activity is exaggerated and smaller when it is depressed. Stroke volume is maintained unless a non-selective beta-blocker is administered. With these agents, beta-2 adrenoceptor blockade increases peripheral vascular resistance to left ventricular ejection and this causes the reduction in stroke volume. There is general agreement that changes in heart rate and cardiac output are of smaller magnitude with partial agonists than with pure antagonists. During exercise, the heart rate response is minimized and cardiac output increases less than in the absence of beta-blockade. The effect of beta-adrenoceptor blockade on the ischaemic myocardium, in arterial hypertension and during anaesthesia is discussed below.

Effect on respiratory function

Beta-adrenoceptor blockade may be associated with a worsening of asthma and a decrease in forced expiratory volume. Non-selective beta-adrenoceptor antagonists are more likely to be poorly tolerated than cardioselective blockers. However, amongst the latter, practolol and metoprolol appear to have greater adverse effects than atenolol (Vilsvik and Schaanng, 1976; Benson et al., 1978). Another adverse effect which may be relevant to the peri-operative situation is the decrease in ventilatory response to carbon dioxide which appears to develop after beta-adrenoceptor blockade (Mutschin et al., 1976). However, the inter- and within-subject variability is considerable and it is difficult to discern any alteration in central sensitivity to increasing carbon dioxide concentration (Twum-Barima et al., 1982).

Absorption and elimination

Beta-adrenoceptor antagonists are absorbed rapidly and almost completely in the gastrointestinal tract. Notable exceptions are atenolol and nadolol, which are absorbed to a much smaller extent than other compounds (table IV, column 2). Because of degradation in gut wall and liver (first-pass effect), the dose available to the systemic circulation may be reduced substantially. The most lipophilic drugs have the lowest bioavailability (table IV, column 3). Protein binding is variable. If protein binding is high, relatively high plasma concentrations are necessary to achieve adequate blockade because only the unbound fraction is effective. Elimination may be via hepatic metabolism or renal excretion, or both (table IV, column 5). The most lipophilic beta-blockers have a clearance that approaches liver blood flow. Because of the important role of the liver for the clearance of the beta-adrenoceptor antagonists, cumulation may occur in the presence of liver disease. Normal elimination half-life is shortest for metoprolol, pindolol, timolol and propranolol, intermediate for atenolol (5–7 h) and longest for nadolol and sotalol (table IV, column 4).

Data on bioavailability are very important when oral administration is to be replaced by i.v. administration during the perioperative period in patients unable to take drugs orally. If bioavailability is
### Table IV. Absorption and elimination of some β-adrenoceptor antagonists (after Regardh (1980), Frishman (1981) and Feely, deVane and Maclean (1983))

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gastro-intestinal absorption (%)</th>
<th>Bioavailability (%)</th>
<th>Elimination half-life (h)</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprenolol</td>
<td>&gt; 90</td>
<td>~10</td>
<td>2–3</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Atenolol</td>
<td>40–50</td>
<td>~50</td>
<td>6–9</td>
<td>Renal</td>
</tr>
<tr>
<td>Labetalol</td>
<td>&gt; 70</td>
<td>~30</td>
<td>3–4</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>&gt; 95</td>
<td>~50</td>
<td>3–4</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Nadolol</td>
<td>25</td>
<td>~25</td>
<td>16–24</td>
<td>Hepatic and renal</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>70–95</td>
<td>~30</td>
<td>2</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Pindolol</td>
<td>&gt; 90</td>
<td>50–100</td>
<td>3–4</td>
<td>Hepatic and renal</td>
</tr>
<tr>
<td>Propranolol</td>
<td>&gt; 90</td>
<td>&gt;30</td>
<td>2–6</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Sotalol</td>
<td>100</td>
<td>100</td>
<td>15–17</td>
<td>Renal</td>
</tr>
<tr>
<td>Timolol</td>
<td>&gt; 90</td>
<td>~50</td>
<td>3–4</td>
<td>Hepatic and renal</td>
</tr>
</tbody>
</table>

high (atenolol, pindolol, sotalol, timolol) the i.v. dose should approximate to the oral dose. If, however, bioavailability is low (nadolol, labetalol, oxprenolol, propranolol), the i.v. dose should be substantially smaller than the oral dose. In practice, it is necessary to titrate the i.v. administration to obtain the desired effect.

**Reversal of beta-adrenoceptor blockade**

Reversing the effect of beta-adrenoceptor blockade is seldom warranted. However, bradycardia may cause concern and this may be treated with atropine. If it becomes necessary to increase the inotropic state of the myocardium, beta-adrenoceptor agonists are effective, but the dose required may be 5 to 20 times the usual dose. When non-selective beta-adrenoceptor antagonists have been administered, large doses of isoprenaline are effective. When cardioselective beta-adrenoceptor antagonists have been administered, a pure β-1 agonist, such as dobutamine or prenalterol, should be administered. Isoprenaline would cause marked vasodilatation and hypotension (β-2 effect) before the inotropic effect develops (Waagstein, Malek and Hjalmarson, 1978; Hjalmarson, Reiz and Waagstein, 1980). Dopamine is not recommended because substantial vasoconstriction is likely to occur with the doses required to overcome beta-adrenoceptor blockade. Intravenous calcium increases the inotropic state of the myocardium for short periods, while glucagon may increase it for longer periods.

**Clinical uses**

**Ischaemic heart disease**

Treatment of angina pectoris should be aimed at improving the coronary reserve which is reduced by coronary artery stenoses, and at reducing myocardial oxygen consumption. Blockade of the sympathetic outflow to the cardiac beta-receptors decreases myocardial oxygen requirement. If increases in heart rate, arterial pressure and contractility caused by exercise are minimized, the balance between oxygen demand and oxygen supply will be better preserved. Indeed, beta-adrenoceptor antagonists have been the first really effective means of preventing angina (Gillam and Prichard, 1965). During exercise, their efficacy is demonstrated by the normalization of ejection fraction and wall motion (Katz et al., 1981).

Beta-adrenoceptor antagonists benefit the patients suffering from acute myocardial infarction because of their anti-arrhythmic action and ability to salvage the ischaemic myocardium. Experimentally, beta-adrenoceptor antagonists minimize the extent of the ischaemic damage caused by acute coronary artery occlusion (Maroko et al., 1972; Levken, 1975). Similarly, in man, marked improvement of ST segment has been observed (Gold, Leinbach and Maroko, 1976). The early administration of beta-adrenoceptor antagonists decreases the release of cardiac enzymes (Yusuf et al., 1980) and reduces the occurrence of both ventricular arrhythmias (Rossi et al., 1983) and mortality (Herlitz et al., 1983).

Secondary prevention of myocardial infarction is important because of the high first year mortality. Many deaths are caused probably by ventricular fibrillation. The evidence from several studies is that long-term administration of adrenergic beta-receptor antagonists reduces mortality (The Norwegian Multicenter Study Group, 1981; Julian et al., 1982; May et al., 1982). Protection against
excessive increases in myocardial oxygen consumption and against arrhythmias caused by sympathetic overactivity play a very important role in the efficacy of beta-adrenoceptor blockade. Other factors to be considered are increased threshold for ventricular fibrillation, reductions of platelet aggregation and thromboxane A2 release, increased collateral coronary blood flow and redistribution of flow to the subendocardium (Vatner et al., 1977; Vatner et al., 1978) and, perhaps, increased capillary density (Tasgal and Vaughan Williams, 1981).

Arterial hypertension

The efficacy of beta-adrenoceptor antagonists in the treatment of arterial hypertension is well established. Lack of orthostatic hypotension and low frequency of side-effects ensures that these drugs are widely acceptable. The mode of action remains controversial. Animal studies have suggested an important effect on the central nervous system and it is known that most beta-adrenoceptor antagonists penetrate the central nervous system. Another mechanism is the reduction in release of renin. Beta-adrenoceptor antagonists reduce the plasma renin activity in normal subjects and in hypertensive patients, particularly those with high renin hypertension (Buhler et al., 1972). However, a correlation between renin inhibition and efficacy of beta-adrenoceptor blockade has not always been found (Bravo et al., 1975). A reduction in plasma volume has been implicated, but this failed to correlate with the reduction in arterial pressure (Tarazi, Frohlich and Dustan, 1971). A common denominator for the immediate and long-term effects of beta-adrenoceptor blockade is the reduction in cardiac output (Gibson, 1971). Peripheral vascular resistance may be increased in the initial stages of treatment, but decreases after long-term administration of beta-adrenoceptor blockers (Tarazi and Dustan, 1972). This may be attributed to alteration in baroreceptor reflexes (Pickering et al., 1971). Long-term treatment of arterial hypertension with beta-adrenoceptor blockers reduces left ventricular mass, minimizes electrocardiographic signs of left ventricular hypertrophy and reduces the number of cardiovascular deaths and non-fatal myocardial infarction (Berglund et al., 1978).

Arrhythmias

Beta-adrenoceptor antagonists are particularly effective in the treatment of arrhythmias caused by sympathetic overactivity or administration of catecholamines. In the case of arrhythmias caused by digitalis toxicity, release of noradrenaline at sympathetic nerve endings in the heart plays an important role and these arrhythmias respond well to adrenergic beta-receptor blockers (Chung, 1972). Beta-adrenoceptor antagonists are effective in the control of sinus tachycardia, ectopic atrial tachycardia, re-entrant tachycardias, atrial fibrillation and atrial flutter and in the treatment of premature ventricular ectopics associated with myocardial ischaemia (Kortman, Remme and Roelandt, 1976).

Other uses for beta-adrenoceptor blockers

In obstructive cardiomyopathies, including hypertrophic subaortic stenosis and tetralogy of Fallot, beta-adrenoceptor stimulation is known to increase the obstruction while beta-adrenoceptor blockade minimizes it. Other indications include treatment of the cardiovascular effects of hyperthyroidism (Das and Krieger, 1969), phaeochromocytoma (Bingham, Elliott and Lyons, 1972) and the sympathetic overactivity that accompanies the most severe forms of tetanus (Kerr et al., 1968; Prys-Roberts et al., 1969). Some of the undesirable circulatory responses to haemorrhagic or septic shock may also be controlled by beta-adrenoceptor blockade (Halmagyi, Kennedy and Goodman, 1971). In a number of stressful situations, sympathetic activity is greatly increased and increases in arterial pressure and heart rate are observed, often accompanied by arrhythmias. Prolonged increases in plasma concentrations of free fatty acids and triglycerides (Taggart and Carruthers, 1972) are also observed. Beta-adrenoceptor blockade is highly effective in blocking the physical manifestations of anxiety and stress and may improve performance. This has been particularly well documented in the case of musicians (James et al., 1977). Beta-adrenoceptor blockers have beneficial effects in anxiety states and also in the control of familial, senile and essential tremor (Winkler and Young, 1974). They are useful in the treatment of the cardiovascular toxicity of the tricyclic antidepressant (Freeman and Loughhead, 1973). When propranolol was introduced in the treatment of angina, it was found that patients often obtained relief from co-existent migraine, and this condition may be improved by beta-adrenoceptor blockade.

Withdrawal syndrome

Sudden withdrawal of adrenergic blockade may be dangerous. The syndrome of withdrawal comprises
development of ventricular arrhythmias, worsening of angina, myocardial infarction and even sudden death (Zsoter and Beanlands, 1969; Slome, 1973; Alderman et al., 1974). The most convincing evidence for this syndrome was obtained by Miller and colleagues, who noted a 50% frequency of the condition after crossover to placebo during a double-blind trial of propranolol in the treatment of angina. Ten patients had untoward experience, one had a fatal myocardial infarction, one died a sudden death, one developed ventricular tachycardia and seven reported significant worsening of angina (Miller et al., 1975). Alderman and co-workers observed that six of a group of 107 patients with stable angina developed unstable angina within 12-24 h of propranolol withdrawal. Within 2-21 days, three suffered myocardial infarction and one died suddenly (Alderman et al., 1974). A number of factors may contribute to these complications. First, after withdrawal, the patient whose exercise tolerance has improved during beta-adrenoceptor therapy, may subject his myocardium to exaggerated oxygen demand. Second, sympathetic tone may be increased during treatment and its effect on the beta-receptors unmasked by withdrawal. Third, chronic treatment may increase the number of active beta-adrenoceptors (Boudoulas et al., 1977) and, therefore, increase the effect of sympathetic activity and catecholamines (Nattel, Rangno and Van Loon, 1979; Rangno, Langlois and Lutterodt, 1982). Despite the risk of withdrawal syndrome, discontinuation of treatment with beta-adrenoceptor antagonists has often been recommended in the past (Ayescue et al., 1972; Viljoen, Estafanous and Kellner, 1972; Hillis and Cohn, 1978) and still often occurs in practice because the last dose of beta-blockers is given the evening before surgery, and treatment is not recommended until the patient can take oral medication again. With the anxiety, stress and cardiovascular instability which characterizes the perioperative period, beta-adrenoceptor blockade withdrawal is likely to be tolerated poorly. In a prospective study, Slogoff, Keats and Ott (1978) have shown that patients withdrawn abruptly from propranolol exhibited a high frequency of intraoperative myocardial ischaemia and arrhythmias. Ponten and co-workers (1982a, b) have compared the effects of continuation of beta-adrenoceptor blockade and those of gradual withdrawal before surgery. Even gradual withdrawal was associated with a high frequency of arrhythmias, angina pectoris and electrocardiographic signs of myocardial ischaemia—this led to postponement of surgery in some patients.

Against this background of the danger of withdrawal syndrome, considerable concern has been expressed that beta-adrenoceptor antagonists may potentiate the negative inotropy of the volatile anaesthetic agents, thus causing severe reduction in cardiac output and arterial pressure. Such reductions have not been observed in detailed haemodynamic studies of the interactions between beta-adrenoceptor blockade and anaesthesia. In 1973, Prys-Roberts and his colleagues demonstrated that beta-adrenoceptor blockade did not reduce cardiac output in hypertensive patients under anaesthesia. Not only were there no adverse effects, but the hypertensive responses to laryngoscopy and intubation were found to be attenuated substantially and the occurrence of arrhythmias reduced. These observations led to the recommendation that treatment with beta-adrenoceptor antagonists should be maintained until the few hours before surgery (Prys-Roberts et al., 1973; Foëx and Prys-Roberts, 1974a; Prys-Roberts, 1976; Foëx, 1981), even in patients treated with very large doses of beta-adrenoceptor antagonists (Prys-Roberts, 1979; Prys-Roberts, 1982; Prys-Roberts and Meloche, 1980). Kaplan and his colleagues, comparing withdrawal and maintenance of beta-adrenoceptor blockade, found that treatment could be given to within 24 h of coronary artery surgery (Kaplan et al., 1975). In their study, the risks of withdrawal were obvious, five of 143 patients developing myocardial infarction within 48 h of drug withdrawal. More recently, several authors have demonstrated the safety of continuing beta-adrenoceptor antagonist therapy to within 1-5 h of coronary surgery (Kirsh et al., 1978; Kopriva, Guinauz and Barash, 1978).

Maintenance of beta-adrenoceptor blockade until coronary artery surgery has been shown to reduce the occurrence of supraventricular tachyarrhythmias in the period after operation (Boudoulas et al., 1979). Not only are arrhythmias less common if beta-adrenoceptor blockade is continued until the day of surgery, but the cardiovascular system of the patients remains more stable (Manners and Walters, 1979; Oka et al., 1980). Treatment with beta-adrenoceptor blockers should be continued to within a few hours of surgery and throughout the perioperative period, so that the myocardium is not left unprotected at a time when it is highly vulnerable.
Deliberate use of beta-adrenoceptor blockers in anaesthesia

Beta-adrenoceptor antagonists may be used deliberately in order to prevent arrhythmias associated with laryngoscopy, endotracheal intubation and bronchoscopy (Jenkins, 1970; Prys-Roberts et al., 1973), those developing during dental surgery (Ryder, Charlton and Gorman, 1971; Rollason and Russel, 1980) cardiac and vascular surgery (Moran et al., 1973; Oka et al., 1980), neurosurgery (Whitby, 1963), surgery of the thyroid gland (Bird et al., 1969; Trench et al., 1978), phaeochromocytoma (Bingham, Elliott and Lyons, 1972) and those caused by the administration of catecholamines (Katz, 1965; Pontinen, 1978). They are used also to prevent or minimize the tachycardia associated with induced hypotension (Hellewell and Potts, 1966) and to suppress the arrhythmias caused by inducing hypothermia (Finlay and Dykes, 1968).

Adrenergic beta-receptor antagonists may also be used in the prevention and treatment of the hypertensive episodes caused by sympathetic overactivity. During such episodes, increases in heart rate and systolic pressure contribute to large increases in myocardial oxygen consumption which result frequently in arrhythmias and myocardial ischaemia. Electrocardiographic signs of myocardial ischaemia may be observed (Prys-Roberts et al., 1971), in addition to reduction in ejection fraction (Barash et al., 1980; Giles et al., 1982) and abnormal patterns of wall function (Elliott et al., 1980). Hypertension and tachycardia may be prevented successfully by i.v. and oral beta-adrenoceptor blockade (Prys-Roberts et al., 1973; Manners and Walters, 1979; Prys-Roberts, 1979; Oka et al., 1980).

Interactions between beta-adrenoceptor antagonists and anaesthetic agents

All the volatile anaesthetic agents exert a negative inotropic effect on isolated heart muscle (Shimosato and Etsten, 1969). Myocardial depression is dose-dependent and may be more pronounced if the muscle has been obtained from a failing heart (Kemmotsu, Hashimoto and Shimosato, 1973). Similarly, high concentrations of opioids depress the isolated heart muscle (Strauer, 1972). During clinical anaesthesia, however, myocardial depression may be masked by the effect on the heart of sympathetic stimulation caused by the anaesthetic agent or anaesthetic and surgical manoeuvres. While the older volatile agents such as diethylether, cyclopropane and fluoroxyne, increased sympathetic activity, the newer agents halothane, methoxyflurane, enfurane and isoflurane do not (Skovsted and Price, 1972; Skovsted and Sapthavichaikul, 1977). In the case of anaesthetic agents which increase sympathetic activity, or when sympathetic overactivity is present for other reasons, the administration of a beta-adrenoceptor antagonist unmasks the direct negative inotropy of the anaesthetic agent. Indeed, in the case of cyclopropane (Craythorne and Huffman, 1966) and diethylether anaesthesia (Jorfeldt et al., 1967) beta-adrenoceptor blockade has been shown to cause large reductions in cardiac output.

Halothane

In the absence of sympathetic overactivity caused by hypercapnia, hypovolaemia, exogenous catecholamines or unduly light anaesthesia, beta-adrenoceptor antagonists exert little influence on the circulation during halothane anaesthesia. This is confirmed by studies of hypertensive patients in whom the interaction between practolol, a beta-1 selective partial agonist, and anaesthesia with halothane, have been studied (Prys-Roberts et al., 1973). Adrenoceptor blockade was tolerated well and it attenuated the hypertensive response and prevented the tachycardia caused by laryngoscopy. The absence of adverse interaction between halothane and propranolol has also been demonstrated (Kopriva, Brown and Pappas, 1978). Animal studies undertaken with controlled ventilation have shown that the administration of pure beta-adrenoceptor antagonists (propranolol and metoprolol) caused somewhat greater reductions of cardiac output than the administration of partial agonists (oxprenolol and practolol) (Foëx, 1977). Although hypovolaemia increased sympathetic activity, the responses of the circulation to acute haemorrhage were not significantly modified by beta-adrenoceptor blockade (Roberts et al., 1976).

Enflurane

In common with halothane, enfurane causes dose-dependent depression of myocardial performance and decreases sympathetic activity (Gothert and Wendt, 1977, Horan et al., 1977a). In patients with coronary artery disease, no adverse interactions were observed between enfurane and propranolol (Kaplan and Dunbar, 1976) or metoprolol (Morr-Strathmann et al., 1981). Similarly, in experimental studies, no adverse interactions were observed between enfurane and propranolol, provided that the concentration of enfurane was relatively low. How-
ever, significant depression was observed when the enflurane concentration was high or the animal was made hypovolaemic (Horan et al., 1977a). More recently, beta-blockade with the partial agonist, oxprenolol, was found to be compatible even with high concentrations of enflurane (Cutfield et al., 1981).

**Isoflurane**

In contrast with enflurane, isoflurane causes dose-dependent depression of both contractile performance and vascular resistance, while cardiac output is well maintained. Isoflurane does not stimulate the sympathetic nervous system and, therefore, no adverse interaction should occur with beta-adrenoceptor antagonists. Animal studies have confirmed the lack of adverse interactions between propranolol and isoflurane (Philbin and Lowenstein, 1976) even in the case of acute haemorrhage (Horan et al., 1977b).

**Central analgesics**

Myocardial depression is much less marked with these agents than with the volatile anaesthetics. The interactions between fentanyl and beta-adrenoceptor blockade have been studied in patients receiving very high dose beta-adrenoceptor blockade (Prys-Roberts, 1979, 1982). The responses of the circulation were not different in patients on high dose beta-blockade than in patients receiving more conventional doses. The greater stability observed in hypertensive patients treated with beta-adrenoceptor antagonists, has also been observed in patients presenting for coronary artery surgery and anaesthetized with central analgesics (Manners and Walters, 1979). Finally, the effects of i.v. propranolol and fentanyl have been studied in patients suffering from multiple injuries. The two drugs appeared to have additive effects (Delhumeau et al., 1978).

**Methoxyflurane and trichloroethylene**

While these agents do not appear to cause sympathetic stimulation, adverse interactions have been observed in experimental animals between methoxyflurane and practolol (Saner et al., 1975) and between trichloroethylene and propranolol, particularly in the case of hypovolaemia (Roberts et al., 1976). Viljoen, Estafanous and Kellner (1972) had recommended that beta-adrenoceptor antagonists be discontinued before cardiac surgery. It is interesting to note that they used methoxyflurane and may have observed a specific adverse interaction between methoxyflurane and beta-blockade. With trichloroethylene, clinical evidence suggests that its use in cardiac surgery in patients on beta-adrenoceptor blockers is well tolerated (Bethune and Petch, 1980).

From clinical and experimental studies, it seems that compatibility between anaesthesia and beta-adrenoceptor blockade is greatest with opioids, isoflurane, halothane and low concentrations of enflurane. With trichloroethylene, compatibility may be poorer and it is very poor with methoxyflurane.

It should be noted that the presence of hypercapnia may complicate the situation. Hypercapnia causes a hyperdynamic response of the circulation. This response results from sympathetic overactivity. Blockade of the beta-1 adrenoceptors may unmask the direct depressant effect of carbon dioxide on the myocardium. When hypercapnia is present, depression of the circulation caused by beta-adrenoceptor blockade is greater with the pure antagonists than with partial agonists (Foex and Prys-Roberts, 1974b; Foex and Ryder, 1981).

**Contraindications to beta-adrenoceptor blockade**

The major contraindications are left and right ventricular failure, unless caused by tachycardia. Disorders of atrioventricular conduction are also a strong contraindication to beta-blockade. Patients with peripheral vascular disease may experience substantial worsening of their symptoms after treatment with non-selective beta-adrenoceptor antagonists: however, they are likely to tolerate cardioselective beta-blockers. Non-selective and high doses of selective beta-blockers are contraindicated in patients suffering from multiple injuries. The two drugs appeared to have additive effects (Delhumeau et al., 1978).

**ALPHA-ADRENOCEPTOR ANTAGONISTS**

In the past decade, alpha-adrenoceptor antagonists have been used less extensively than beta-adrenoceptor antagonists. However, these drugs are becoming increasingly important, not only in the treatment of hypertensive emergencies, but also in the long-term treatment of arterial hypertension and of chronic cardiac failure.

With the exception of phenoxybenzamine, the alpha-adrenoceptor antagonists are competitive blockers at the receptor sites. They can exhibit selectivity for the post-synaptic alpha-1 receptors.
(prazocin) or the presynaptic alpha-2 receptors (yohimbine). Phenoxybenzamine and phentolamine are non-selective antagonists while labetalol blocks alpha-1, beta-1 and probably beta-2 receptors. The administration of alpha-adrenoceptor antagonists causes peripheral vasodilatation in addition to some venodilatation. The resulting arterial hypotension causes baroceptor-mediated increases in sympathetic activity and, therefore, of heart rate. Small doses of alpha-adrenoceptor antagonists may be used to reduce left ventricular afterload and improve cardiac output in chronic cardiac failure. Larger doses are effective in the treatment of arterial hypertension, but may cause postural hypotension. The i.v. administration of alpha-blockers is effective in controlling paroxysmal hypertension.

At variance with the beta-adrenoceptor antagonists which are considered best as a group, each alpha-adrenoceptor blocker appears to have its own clinical uses and it is preferable to discuss these drugs individually.

**Phenoxybenzamine**

Phenoxybenzamine is a non-selective non-competitive alpha-adrenoceptor antagonist with a slow onset of action. This slow onset of action is a result of the time required for structural modification in the molecule that renders it active. Because a stable bond is formed with the receptor, phenoxybenzamine has a long duration of action. Phenoxybenzamine has been used in association with beta-adrenoceptor blockers in the treatment of arterial hypertension (Vlachakis and Mendlowitz, 1976). In chronic cardiac failure, phenoxybenzamine reduces the afterload and increases cardiac output, but tachycardia and postural hypotension may develop. The marked vasodilatation produced by phenoxybenzamine may be useful in the short-term preservation of human kidneys for transplantation. Phenoxybenzamine increases the viability of renal cells subjected to periods of interrupted blood flow (Pryor et al., 1971). The major place for phenoxybenzamine is in the treatment and pre-operative preparation of patients suffering from phaeochromocytoma (Sjoerdsma et al., 1966; Pratilas and Pratila, 1979; Desmonts and Marty, 1984), most of the time in association with beta-adrenoceptor blockers. Patients with inoperable tumours may be maintained for years on phenoxybenzamine (Engleman and Sjoerdsma, 1964). In surgical patients, it must be remembered that the hypotensive effect of phenoxybenzamine is potentiated by the volatile anaesthetic agents (Ross et al., 1967).

**Phentolamine**

Phentolamine is a weak, non-selective, competitive alpha-adrenoceptor antagonist. Much less potent an alpha-adrenoceptor blocker than phenoxybenzamine, phentolamine causes vasodilatation mostly by a direct effect on vascular smooth muscle. It has a rapid onset of action and its effects last for approximately 15–30 min. Because of the marked vasodilatation, baroceptor-mediated increases in sympathetic activity are observed and the inotropic state of the myocardium may be enhanced (Singh, Hood and Abelmann, 1970; Gould and Reddy, 1976). Phentolamine reduces the resistance of the systemic and the pulmonary circulations, while causing some increase in vascular capacitance. In recent years, beneficial effects of phentolamine have been observed in patients suffering from myocardial infarction and chronic heart failure. In patients with very high left ventricular filling pressures, stroke volume has been found to increase and the pulmonary capillary wedge pressure to decrease after phentolamine (Kelly et al., 1973; Perret et al., 1975). The occurrence of tachycardia may be a significant disadvantage. However, the reduction in vascular resistance and diastolic wall tension decrease myocardial oxygen demand and improve subendocardial perfusion. Moreover, phentolamine can abolish alpha-adrenoceptor-mediated coronary artery spasm (Gould, Reddy and Gomprecht, 1973). These characteristics make phentolamine a useful drug in the management of intraoperative myocardial ischaemia, provided tachycardia is not allowed to develop. In patients with phaeochromocytoma, phentolamine is effective in the treatment of paroxysmal hypertension during operative manipulations of the tumour (El-Etr and Glisson, 1978). Phentolamine, administered as a bolus dose or by continuous infusion, may be used to control intra- and postoperative hypertension and also to control perfusion pressure during extracorporeal circulation for cardiac surgery.

**Prazocin**

Prazocin is a selective, competitive, alpha-1 adrenoceptor blocker (Wood, Phelan and Simpson, 1975; Stokes and Oates, 1978) which reduces arterial and venous tone. Because alpha-2 receptors are not blocked, the negative feed-back effect of noradrenaline on its own release is not inhibited. This
explains why tachycardia and renin stimulation do not occur and also why prazocin is more effective than phenoxybenzamine in the control of hypertension (Mulvihill-Wilson et al., 1979). The major side-effects of prazocin are postural hypotension and a precipitous decrease in arterial pressure which may occur after the first dose has been administered (Bendall, Blaloch and Wilson, 1975). In hypertensive patients, prazocin causes little disturbance in the circulation; cardiac output and renal blood flow are essentially unchanged. The hypotensive effect of prazocin is augmented when prazocin is administered with a diuretic. Association with a beta-adrenoceptor antagonist may be necessary, in order to avoid the worsening of angina which has been reported (Simpson, Bolli and Wood, 1977). In common with other vasodilators, prazocin has been used in the treatment of congestive cardiac failure and has been shown to increase cardiac output and decrease the pulmonary capillary wedge pressure. While the reduction of the left ventricular filling pressure persists after prolonged administration of prazocin, the increase in cardiac output does not (Miller et al., 1977). Because of its greater affinity for alpha-receptors in veins than in arteries, prazocin produces haemodynamic effects which resemble glyceryltrinitrate more than phentolamine or hydralazine (Fitzgerald, 1982).

Labetalol

Labetalol differs from other adrenergic receptor antagonists in that it blocks both alpha- and beta-adrenoceptors. Less potent an alpha-blocker than phentolamine, it is also much less potent a beta-blocker than propranolol. While labetalol does not appear to block the presynaptic alpha-2 receptors, it blocks the beta-1 and the beta-2 receptors (Richards, 1976). Although it is more potent a beta-than alpha-adrenoceptor antagonist, it is very often used for vasodilatation. This is the reason why the drug is discussed amongst alpha-adrenoceptor antagonists.

The i.v. administration of labetalol produces a substantial decrease in systemic arterial pressure because of the simultaneous reductions in systemic vascular resistance and cardiac output (Koch, 1977). These reductions are particularly large in exercising subjects. After prolonged administration of labetalol, the reduction of arterial pressure results mainly from reduction of systemic vascular resistance while cardiac output is well maintained (Koch, 1979). Labetalol may be used in the long-term treatment of arterial hypertension, particularly in patients suffering from symptomatic coronary artery disease. In these patients, anginal symptoms are relieved, exercise tolerance is improved and arterial pressure is controlled. Because of its low transfer across the placenta, labetalol has been advocated in the treatment of hypertension during pregnancy (Lamming, Pipkin and Symonds, 1980). In the treatment of hypertensive emergencies, labetalol appears to be effective and provides smooth control of arterial pressure (Wallin and O'Neil, 1983).

In patients anaesthetized with halothane, labetalol causes substantial reductions in arterial pressure mainly by reduction in systemic vascular resistance. Cardiac output is reduced slightly more in patients breathing spontaneously than in those whose lungs are ventilated artificially (Scott et al., 1978). Because heart rate does not increase, labetalol may be a useful drug for deliberately induced hypotensive anaesthesia in adults (Scott et al., 1978) in addition to children, in whom satisfactory hypotension may also be achieved with labetalol and halothane for surgery of aortic coarctation (Jones, 1979). While labetalol appears to minimize the tachycardia and the hypertensive responses to laryngoscopy and intubation (Fischer et al., 1983), it is much less effective in blocking the effects of sympathetic overactivity in tetanus (Wesley et al., 1983) or the cardiostimulatory effects of ketamine (Dundee, Lilburn and Moore, 1978).

The most common side-effect of labetalol is postural hypotension. Because of the blockade of the beta-adrenoceptor it is contraindicated in patients with atrioventricular blocks and probably also in patients with heart failure. Its hypotensive effect is potentiated by halothane and enflurane and the concentration of these agents should be carefully controlled.

Thymoxamine

This alpha-1 selective antagonist causes peripheral vasodilatation. Although it may be effective in the treatment of circulatory failure after cardiac surgery (Cottrell and Pearson, 1981), most of the published work relates to the treatment of peripheral vascular disease. Thymoxamine appears to improve regional peripheral blood flow after oral, i.v. or intra-arterial administration (Rose, 1979; Jaffe and Grimshaw, 1980).
CONCLUSIONS

While alpha- and beta-adrenoceptor antagonists play an important role in the treatment of many patients suffering from cardiovascular diseases and are very useful during the perioperative period, they interfere with the regulation of the circulation and it is essential to monitor the patients carefully, particularly when combined alpha- and beta-adrenoceptor blockade is present. This is even more important with the association of calcium influx blockers and adrenoceptor antagonists. The calcium influx blockers exert a direct effect on the excitation-contraction coupling in the heart and in the vascular smooth muscle and may potentiate the negative inotropy of the volatile anaesthetic agents (Reves et al., 1982). Safe anaesthesia in the presence of potent, modern cardiovascular drugs rests with understanding of their effects in association with intensive monitoring.

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