Uses of Beta-adrenoceptor Blocking Drugs

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Beta-adrenoceptor blocking drugs are now widely used in therapeutics. The original clinical evaluation of these agents was in the treatment of angina pectoris, arrhythmias and phaeochromocytoma, but many uses that were not originally predicted from an understanding of their pharmacology have been found. One of these, their ability to lower the blood pressure in hypertension, now represents a major indication for the use of these compounds. Other situations in which their use has been advocated include thyrotoxicosis, anxiety, schizophrenia, drug addiction withdrawal syndromes, migraine, obstruction of the outflow tract of the heart, and glaucoma. By far the largest clinical experience has been gained with propranolol, but uses that have also been demonstrated with this drug are likely to be shared by the newer beta-adrenoceptor blocking drugs, because the associated properties some of these drugs have seem unlikely to be of relevance to their efficacy (McDevitt *et al.*, 1976).

ANGINA PECTORIS

Although increased sympathetic activity becomes progressively more important in the cardiac response to higher levels of exercise, it also plays a part in the tachycardia of exercise at the low levels commonly achieved by patients with angina pectoris (Black and Prichard, 1973).

Mode of Action of Beta-adrenoceptor Blocking Drugs

Beta-adrenoceptor blocking drugs reduce the heart rate, systolic intraventricular pressure, and the inotropic state of the myocardium, all factors that will reduce myocardial oxygen consumption. This beneficial effect is to a modest degree antagonised by the increase in ejection time but, more importantly, by the increase in left ventricular size (Robinson, 1971). The reduction in heart rate,

besides reducing work done, allows more time for diastolic filling of the coronary vessels. There is also a reduction in the rise of pressure on exercise, and a reduction in the velocity of cardiac contraction (Sonnenblick *et al.*, 1965; Furnival *et al.*, 1970; Thadani *et al.*, 1973). Beta blockade reduces oxygen consumption at the onset of pain from acute exercise at any given work load (Wolfson and Gorlin, 1969).

All beta-adrenoceptor blocking drugs increase acute working capacity before pain is produced in patients with angina. This benefit appears to be due to their common property of blockade of cardiac beta-adrenoceptors. The presence or absence of the associated properties does not appear to influence anti-anginal activity (Wilson *et al.*, 1969; Prichard *et al.*, 1970a; Boakes and Prichard, 1973). The d-isomer of propranolol, which has membrane stabilising activity but only minimal beta-adrenoceptor blocking activity, has been found to be ineffective in angina pectoris (Wilson *et al.*, 1969) even in doses of up to 80 mg intravenously (Boakes and Prichard, 1973). The d-isomer of alprenolol is also inactive (Bjorntorp, 1968).

The product of heart rate and systolic pressure was found to be relatively constant in an individual patient when angina was precipitated by a number of factors, e.g. exercise, mental arithmetic or spontaneously (Robinson, 1967). When exercise tolerance improves following the administration of a beta-adrenoceptor blocking drug, the pressure-rate product has been found to be lower than the value that was reached during a control run (Battock *et al.*, 1969; Gianelly *et al.*, 1967a; Robinson, 1971), although it is constant for various beta-adrenoceptor blocking drugs regardless of the presence or absence of the various associated properties (Prichard, 1971).

The occurrence of this lower product of systolic pressure x heart rate is probably due to an adverse effect of beta-receptor blockade itself on left ventricular size. This means that increased tension, therefore increased oxygen consumption, in the ventricular wall is required for a given pressure (Robinson, 1971).

Coronary Blood Flow. Observations in dogs anaesthetised with barbiturates show a reduction in coronary blood flow after propranolol (Parratt and Grayson, 1966). There was no change in flow in conscious dogs (Bergamaschi *et al.*, 1971). Other investigations, also in dogs, have indicated that internal shunting occurs in the coronary circulation after beta-receptor blockade so that flow to an ischaemic area is maintained (Pitt and Craven, 1970), particularly in the subendocardial region (Becker *et al.*, 1971). This alteration of regional blood flow could be an important factor in minimising exercise-induced shifts of the S-T segment of the electrocardiogram which is observed after beta-adrenoceptor block (Gianelly *et al.*, 1969; Prichard *et al.*, 1970a; Sowton and Smithen, 1971; Sandler and Pistevos, 1972; Thadani *et al.*, 1973). The decrease in coronary flow is in proportion to the reduction in myocardial oxygen consumption and an increase in calculated

coronary vascular resistance has been found in man (Wolfson and Gorlin, 1969). No change in coronary venous oxygen saturation has been seen in man (Lewis and Brink, 1968; Mendel and Byrne-Quinn, 1966). This supports the concept that the fall in oxygen consumption is responsible for the reduction in blood flow.

The Effects of Beta-adrenoceptor Blocking Drugs

All beta-adrenoceptor blocking drugs have been shown to relieve anginal pain. The various studies of beta-adrenoceptor blocking drugs in angina have recently been discussed in more detail (Prichard, 1974). The lack of a convincing anti-anginal effect seen in some studies can generally be traced to inadequacies of trial design. Pronethalol, the first clinically useful beta-adrenergic receptor blocking drug, was found effective in reducing the number of attacks of angina (Fulton and Green, 1963; Prichard *et al.*, 1963; Robinson and Pilkington, 1963) but, at the dosage required, many adverse effects were encountered and its use was discontinued when it was found to produce tumours in mice (Alcock and Bond, 1965).

Most studies have been performed with propranolol, the first beta-adrenergic blocking drug to be widely used. A number of studies showed it to be effective intravenously (Hamer *et al.*, 1966; Prichard *et al.*, 1970a). Oral studies have demonstrated the pattern of increased effectiveness as dosage has been increased (Prichard, 1974). A log-dose response study has been performed (Prichard and Gillam, 1971). In the 'run-in' period, the dose of propranolol was adjusted so that a supine heart rate of 55 to 60 beats per minute was produced if this was not prevented by the occurrence of adverse effects. The doses used varied from 80 to 1,280 mg/day with an average of 417 mg. The average dosages used were 417, 208, 104, 52 and 0 mg. In a trial lasting 30 weeks (after the 'run-in' dosage adjustment period) each patient received each treatment for six weeks. There was a progressive reduction in the number of anginal attacks and in glyceryl trinitrate consumption as dosage increased, from an average of 85 attacks of angina per 6 weeks on placebo to 38 on the highest dose of propranolol. As the dosage of 417 mg was still on the straight-line part of the dose-response curve and, therefore, suboptimal, we now adjust dosage to produce a standing heart rate of 55 to 60.

Studies of a similar nature with other beta-blocking drugs have shown that they are effective in the treatment of angina.

In a fixed dose study, oxyprenolol (80 mg t.d.s.) failed to show a convincing effect (Sandler and Pistevos, 1972), but benefit was seen when a large number of patients were used (Bianchi *et al.*, 1969). However, a variable dose trial (40 to 400 mg/day) produced a much more convincing result (Wilson *et al.*, 1969). Trials with alprenolol have also shown it to be an effective prophylactic in angina (Bjorntorp, 1968, 1971; Aubert *et al.*, 1970; Hickie, 1970).

Pindolol, given acutely, increased exercise tolerance (Storstein-Spilker, 1970; Boakes and Prichard, 1973). Oral pindolol has been found effective in reducing

the number of attacks of angina (Nair, 1972; Sainani and Mukherjee, 1972).

The acute administration of sotalol increases exercise tolerance (Prichard *et al.*, 1970a; Atkins *et al.*, 1971). It has also been found effective given orally (Toubes *et al.*, 1970; Horn and Prichard, 1973). Horn and Prichard (1973), in a comparative study in a group of 14 patients, found that sotalol, average dose 786 mg, was significantly better than propranolol, average dose 93 mg, but not so effective as propranolol, average dose 746 mg.

Intravenous practolol improves acute exercise tolerance (Wilson *et al.*, 1969; Prichard *et al.*, 1970a; Coltart, 1971). George *et al.* (1970) found that practolol reduced the incidence of angina attacks, but Sandler and Clayton (1970) did not find a significant benefit. Prichard *et al.* (1971a) found practolol, average dose 1,004 mg, no different from propranolol, average dose 95 mg, and less effective in reducing anginal attacks or trinitrin consumption than propranolol, average dose 766 mg.

Beta-blocking Drugs Combined with Other Drugs

There is some evidence that the combination of isosorbide with propranolol (Russek, 1968), or pindolol (Adolfsson *et al.*, 1972) may be synergistic. Davies *et al.* (1969), however, did not find any synergism between isosorbide and propranolol. Pentaerythritol tetranitrate in combination with alprenolol showed no synergism (Hansen *et al.*, 1973), nor did it in a sustained release form when combined with propranolol, and the sustained release form on its own was ineffective (Prichard and Richardson, unpublished data).

Dosage Regulation of Beta-blocking Drugs

It appears that dosages of beta-blocking drugs vary between patients and, for optimum effect, dosage has to be adjusted to individual requirements. Propranolol has been studied in most detail and it has been shown that greatest benefit is obtained with maximum tolerated doses (Prichard and Gillam, 1971); probably other beta-blocking drugs are similar. The most dramatic change in the sympathetic environment of the heart takes place when treatment with a beta-blocking drug is begun, i.e. with the small starting dose. The greatest danger of precipitating heart failure is, therefore, at the beginning of treatment. Once treatment has begun even an increase of 25 per cent per dose represents a small pharmacological increment, as there is no great change in the sympathetic drive to the heart. The dosage of beta-blocking drugs required for optimum treatment of angina may be gradually approached; it has been our experience that heart failure is not likely to be precipitated at larger doses, provided they are not used initially. Only one of our patients has suffered overt heart failure and this occurred after two days on 10 mg four times daily of propranolol. We have not had difficulty with large doses of beta-blocking drugs, e.g. up to 4,000 mg propranolol, or 4,000 mg sotalol.

The Place of Beta-blocking Drugs

The use of these drugs is relatively safe provided that the contra-indications of asthma and cardiac insufficiency are observed and that treatment begins with a low dosage. It seems reasonable to use an effective prophylactic such as a beta-blocking drug in any anginal patients who are experiencing regular attacks of pain. Glyceryl trinitrate should also be used in the conventional manner. Although beta blockade does not usually relieve pain totally, it does allow more pain-free exercise. It has been suggested that some patients with coronary artery disease-induced angina pectoris fail to respond to beta-blocking drugs. This might occur in a patient on the verge of heart failure if the increase in heart size from beta blockade is greater than usual, thus requiring a greater increase in wall tension for ejection. An extra large increase in oxygen consumption from this source might outweigh the beneficial effects of beta blockade. However, if this occurs, the sequence is not invariable. Gillam and Prichard (1965) reported a patient who developed heart failure after two days on propranolol 10 mg q.d.s. but subsequently tolerated the drug (50 mg 4 times daily) after treatment with digitalis and diuretics. Later, she once more became breathless on exertion, and this was relieved by a reduction in the propranolol dosage, but the angina increased. The symptoms of heart failure and angina were inversely related according to the dose of propranolol taken, so a compromise of some breathlessness on exertion was acceptable for some relief of her angina. Misdiagnosis may be a cause of failure of chest pain to respond to beta blockade. Amsterdam *et al.* (1969) had 77 per cent of failures on propranolol in 'angina' patients without arteriographic changes, while the failure rate was 14 per cent in those with coronary arteriographic changes. Inadequate dosage is the usual cause of failure in angina pectoris. Higher dosages with individual dosage adjustment are associated with a very low incidence of non-responders.

MYOCARDIAL INFARCTION AND BETA-ADRENERGIC BLOCKADE

Recent investigations with alprenolol (Ahlmark *et al.*, 1974; Wilhelmsson *et al.*, 1974), and practolol (Multicentre Study, 1975) have demonstrated that beta-adrenergic blocking drugs reduce mortality once the acute phase after myocardial infarction is passed. Previous investigators have not found any benefit when propranolol was administered after the acute phase (Balcon *et al.*, 1966; Norris *et al.*, 1968), but it should be noted that a low dosage was used in these studies.

The study of Ahlmark *et al.* (1974) also demonstrated a significant reduction in re-infarction rate, but this was not seen in the study of Wilhelmsson *et al.* (1974). These studies were very similar, with the same total daily dosage of 400 mg, but Wilhelmsson *et al.* used 200 mg b.d., and Ahlmark *et al.* 100 mg q.d.s. In the Multicentre Study (1975) there was a reduction in non-fatal infarct but this was not significant. Dosage in this study, 200 mg b.d. of practolol, was

low, particularly for the heavier patients who had considerably lower blood levels. It was also found that the most dramatic reduction in death rate was seen with anterior infarction, while no benefit was seen with inferior infarction. The death rate was lower in patients with diastolic blood pressures of 78 mmHg or below treated with practolol.

Another report examined the effect of beta-adrenergic blockade on patients who had experienced an infarct (Fox *et al.*, 1975). Those patients on beta-adrenergic blocking drugs had a significantly lower incidence of transmural infarction, severe arrhythmias, and incidence of delayed heart failure. Other complications, such as sinus bradycardia, hypotension, syncope, and radiological evidence of pulmonary oedema, showed a similar incidence.

Finally, there have been some reports to suggest that sudden cessation of beta-adrenergic blocking drugs in patients with angina pectoris may precipitate a myocardial infarction. This may be because the progressive disease process was previously masked and with the cessation of beta-blockade the oxygen supply becomes insufficient to meet even resting requirements (Diaz *et al.*, 1974), but it is possible that other factors are involved (Miller *et al.*, 1975).

HYPERTENSION

The antihypertensive effect of beta-adrenergic blocking drugs was first observed in a trial of pronethalol in patients with angina pectoris (Prichard *et al.*, 1963). These observations were extended and reported later (Prichard, 1964).

Mode of Action

The hypertensive action of beta-receptor blocking drugs seems to be a property of their beta-receptor inhibitory action. Regardless of associated properties, the presence or absence of membrane stabilising or sympathomimetic action, an antihypertensive effect is seen (Simpson, 1974). It has also been shown that the d-isomer of propranolol has no hypotensive effect, in contrast to the normal dl-racemic form; i.e. ordinary propranolol (Waal-Manning, 1970a; Prichard, 1970).

Tarazi *et al.* (1971) found that oral treatment with propranolol reduced plasma volume in a series of 14 hypertensive patients, but this did not correlate with the fall in blood pressure. Julius *et al.* (1972) observed a fall in plasma volume after intravenous propranolol. However, Sedenberg-Olsen and Ibsen (1972), using higher doses of propranolol than Tarazi *et al.* (1971), found that four months of treatment of hypertensive patients with propranolol failed to affect plasma volume, but did significantly increase extracellular fluid volume. There was no increase in body weight, which confirmed previous reports (Prichard and Gillam, 1969). The change in extracellular fluid volume did not correlate with the hypertensive effect of propranolol. Similarly, an increase in extracellular fluid volume, correlating poorly with fall of blood pressure, was observed with other antihypertensive drugs (Hansen, 1968; Ronnov-Jessen and Hansen, 1969).

It has been suggested that a central nervous system site may be at least partly responsible for the hypotensive action of beta-blocking agents. Large doses of racemic propranolol, but not the (+)-isomer, result in a fall of blood pressure when injected into the ventricle of the rabbit (Myers *et al.*, 1975). Injection of propranolol into the vertebral or carotid artery produces a more rapid fall of blood pressure than when administered into the femoral artery (Stern *et al.*, 1971). However, these central effects were acute, which is unlike the hypotensive effect seen in man. Another piece of evidence against a central mode of action comes from the observation that practolol, while having an antihypotensive effect, has poor brain penetration (Scales and Cosgrove, 1970).

Plasma renin levels are lowered by beta-adrenergic blockade in normal people (Winer *et al.*, 1969) and hypertensive patients (Michelakis and McAllister, 1972; Buhler *et al.*, 1972). The findings of the latter suggest that patients with a high plasma renin respond much better to propranolol than those with a low plasma renin, and it has been suggested that this effect is responsible for the antihypertensive effect. Others, however, have found a poor correlation with the antihypertensive action of propranolol and its antirenin action (Hannson, 1973; Morgan *et al.*, 1975). A similar poor correlation has been reported with sotalol (Verniory *et al.*, 1974) and pindolol (Morgan *et al.*, 1975). Stokes *et al.* (1974) observed that propranolol lowered plasma renin and blood pressure; with substitution of pindolol for propranolol, blood pressure remained lowered but renin rose to control levels. However, their observations were in 9 patients only and the observations on pindolol were made after only 48 hours of drug administration.

Most of the hypotensive effect of beta-adrenoceptor blocking drugs is observed in the first two weeks, and sometimes, particularly in less severe hypertension, within the first two days. Prichard and Gillam (1969) analysed the blood pressure in groups of patients seen under standardised clinic conditions. There was a signficant fall in blood pressure between the visit to outpatients after stabilisation of the dosage of propranolol, and one month later. The visit to outpatients after stabilisation took place on average three weeks after the final adjustment of propranolol. There was no further drop after another two months. The average heart rate was constant throughout. There was no such fall after stabilisation of dosage at one month or up to three months in groups of patients treated with bethanidine, methyldopa or guanethidine. A similar delay in full hypotensive effect has been observed under double blind conditions with sotalol (Prichard and Boakes, 1974). This delayed fall of blood pressure does not present a problem in management; once normotensive levels are reached, increments of beta-blocking drugs may often be made without any untoward effects.

Arterial pressure is a function of cardiac output and peripheral resistance; as propranolol reduces cardiac output blood pressure tends to become lower. However, intravenous propranolol has little effect on arterial pressure

(Shinebourne *et al.*, 1967; Ulrych *et al.*, 1968) and the reduction in cardiac output seen after its injection is associated with a rise in peripheral resistance. Beta-receptor blockade of the heart would, however, be expected to reduce the cardiac contribution to any pressor event, and this would be attenuated. Thus, after administration of beta-adrenoceptor blocking drugs there is a reduced rise in blood pressure with exercise (Shinebourne *et al.*, 1967; Thadani *et al.*, 1973) and the pressor overshoot of Valsalva's manoeuvre is reduced (Prichard and Gillam, 1966; Prichard *et al.*, 1970b).

In view of the delay in onset of full hypotensive effect, it has been suggested (Prichard and Gillam, 1969) that an attenuation of the pressor response to various stimuli results in a conditioning of the baroreceptors to produce their inhibitory impulses at a lower level of blood pressure, and the mean pressure falls. The fall in peripheral resistance that this implies has been observed after prolonged oral use of propranolol (Tarazi and Dustan, 1972). A similar state of affairs exists when a hypertensive patient is put to bed. Here there is reduction in sensory input and, hence, pressor events, and over a period of a few days the baroreceptors lower blood pressure by a variable amount.

Propranolol

Soon after the hypotensive effect of beta-receptor blocking drugs was found with pronethalol, a similar effect was seen with propranolol (Prichard and Gillam, 1964) and it was with this drug that the value of beta-receptor blocking agents in hypertension was established (Prichard and Gillam, 1966, 1969; Baczko *et al.*, 1967; Frohlich *et al.*, 1968; Tewari and Grant, 1968; Zacharias and Cowen, 1970; Karlberg and Hornkvist, 1971; Zacharias *et al.*, 1972).

Degree of Blood Pressure Control. The degree of blood pressure control with propranolol appears to be similar to that obtained with bethanidine, guanethidine and methyldopa (Prichard and Gillam, 1969; Zacharias, 1969; Prichard *et al.*, 1970b; Zacharias *et al.*, 1972). Some investigators have found a less favourable response of blood pressure to propranolol (Humphreys and Delvin, 1968; Paterson and Dollery, 1966; Richards, 1966; Richardson *et al.*, 1968; Waal, 1966). In all these instances the maximum dose used was less than the average dose of about 400 to 500 mg a day used by Prichard and Gillam (1969) who, in addition, unlike the investigators mentioned above, used a diuretic in more than half of their patients. However, Seedat and Reddy (1971) using full dosage (up to 1,920 mg a day) found that only 4 of 13 Bantu patients were controlled by propranolol. This was without the use of a diuretic or any other drug. There was a better response in their Indian patients.

Zacharias *et al.* (1972) in a series of 311 patients, found that the use of propranolol resulted in a larger number of patients achieving satisfactory blood pressure control than was usually observed with other hypotensive drugs.

Dosage

The dosage of propranolol and other beta-receptor blocking drugs required to lower the blood pressure varies considerably, which is also true with other hypotensive drugs such as bethanidine, guanethidine or methyldopa. Dosage should be started at a low level and increments of about 25 per cent per dose can be made at each succeeding visit to outpatients, usually every two weeks. If the patient is more closely observed, increments may be made more frequently, even daily. Dosage can be increased until diastolic blood pressure supine and standing is in the range of 80 to 100 mmHg (unless clinically contra-indicated, e.g. in the case of associated cardiovascular disease, or if the pulse rate falls below 55 beats per minute after resting for three minutes on a couch). In younger patients, dosage may be increased, if necessary, to reduce heart rate to this level in the standing position. Dosage of over 250 mg four times daily is not exceptional. The largest dosage ever used was 4,000 mg a day. On the other hand, a few patients need only 10 to 20 mg three times daily. Diuretics should be used as indicated and, in a few instances, small doses of other hypotensive drugs. In severe and moderately severe hypertension the average dose is 400 to 500 mg a day, about half the patients also needing a diuretic. There is evidence that dosage may be simplified to a twice daily regime (Hansson *et al.*, 1971a).

There appears to be a considerable margin of safety with propranolol as suggested in a double blind multi-dose level trial in angina pectoris (Prichard and Gillam, 1971). In this study the blood pressure of a group of six mildly hypertensive patients fell from a mean of 115 mmHg (154/96) to a mean of 102 mmHg (135/85) ($p < 0.005$) in the standing position as dosage was increased from zero to an average of 320 mg daily; doubling the dose to 640 mg daily resulted in no further change of blood pressure.

The degree of success that other investigators have found with propranolol can usually be correlated with the dosage used. Several have used too low a dose or the same dose for each patient, and, as would be expected, have found little or no effect (Prichard and Gillam, 1969; Zacharias, 1969).

Oxprenolol

Leishman *et al.* (1970) conducted a trial of oxprenolol in 19 patients using up to 420 mg/day. In a double blind phase, pressures on placebo were 173/102 supine and 165/106 mmHg standing and for oxprenolol 160/99 and 151/99 mmHg respectively. There were no adverse effects, but five patients were withdrawn prior to the double blind part of the trial because of inadequate pressure control, so that those taking part were necessarily pre-selected. Tuckman *et al.* (1972) reported an open trial of oxprenolol in doses of 60 to 600 mg/day (average 374 mg daily) in 17 patients; they, too, failed to note any orthostatic hypotension.

Alprenolol

Alprenolol is also an effective hypotensive agent. Furberg and Michaelson (1969) conducted a double blind cross-over trial in which they used up to 400 mg/day in 12 patients against a placebo. The blood pressure after twelve weeks on placebo was 180/111 mmHg, and after alprenolol 162/104. The reduction in systolic pressure was statistically significant. Other trials have also shown that alprenolol is effective (Tibblin and Ablad, 1969; Bengtsson, 1972).

Pindolol

Although not necessarily conferring any advantage, pindolol weight for weight is the most potent beta-adrenoceptor blocking drug in use, and it has a relatively long duration of action. Pindolol 13 mg daily was found approximately equivalent to propranolol 160 mg daily, or oxprenolol 200 mg a day in a group of hypertensive patients known to respond to beta-blocking drugs (Waal-Manning, 1970b). However, Laver *et al.* (1974) found a 1 to 5 ratio for pindolol and propranolol. There have been a number of other trials that have shown pindolol to be an effective antihypertensive drug, (Feltham *et al.*, 1972; Thorpe, 1972; Collins and King, 1972; Seedat *et al.*, 1973). Waal-Manning and Simpson (1973) altered treatment to pindolol in 43 patients, continuing a diuretic unless this was the sole treatment. They found that blood pressure control was better on pindolol, with fewer adverse effects, than with drugs that produced a postural fall in blood pressure. The average dose used was 15 mg a day and the investigators felt that increase of the dose above 40 to 50 mg daily was not of value. In a double blind variable dose study, Laver *et al.* (1974) compared pindolol (average dose 57.5 mg daily) with propranolol (average dose 289.3 mg daily) in 35 patients who received a diuretic throughout. The blood pressures on both drugs (pindolol supine 138/92 mmg, standing 132/90 mmHg, and propranolol supine 137/90 mmHg, standing 132/88 mmHg) were similar. They found less postural effect in 26 patients than on previous treatment with methyldopa.

Sotalol

Prichard and Boakes (1974) used a dose range of sotalol from 50 to 4,000 mg a day in a trial in 27 patients. Sotalol appeared to be of similar potency to methyldopa.

Practolol

Practolol, with a very high ratio of beta-receptor blockade to membrane activity, has also been demonstrated to have an antihypertensive action (Leishman *et al.*, 1970; Prichard *et al.*, 1971b).

Response of Blood Pressure to Physiological Stimuli in Hypertensive Patients treated with Beta-adrenergic Blocking Drugs

1. *The action on response of blood pressure to posture and exercise.* There is an absence of postural and exercise hypotension when blood pressure has been lowered by beta-blocking drugs. This has been confirmed with intra-arterial recordings of blood pressure, for posture and supine exercise (Prichard *et al.*, 1970b) and for posture and erect exercise (Prichard *et al.*, 1970c). These later investigations showed an increased peripheral resistance on changing from supine to standing position. The absence of exercise and postural hypotension on propranolol is in contrast with the effects seen on sympathetic inhibitory drugs. However, the rise in blood pressure on exercise after beta blockade is less than that seen in the absence of a beta-blocking agent (Shinebourne *et al.*, 1967).

2. *The effect of increasing environmental temperature.* Prichard *et al.* (1970b) studied the response of blood pressure to posture and exercise at various environmental temperatures from 7 to 30° C. As temperature was increased, there was an increased postural and exercise hypotension in patients treated with bethanidine and guanethidine. This is presumably due to increasing vasodilatation of skin blood vessels without adequate compensatory vasoconstriction occurring in other vessels. Repeating the studies after treatment with propranolol showed that alterations in environmental temperature did not affect the response of blood pressure to posture and exercise.

3. *The action on Valsalva's manoeuvre and the blood pressure response to other stresses.* The intravenous administration of a beta-adrenergic blocking drug reduces the overshoot after cessation of effort without reducing the vasoconstriction that occurs during effort. A similar effect is seen after both propranolol (Prichard and Gillam, 1966) and pronethalol (Prichard, 1966) or practolol (unpublished observations). Prolonged oral administration of propranolol does not inhibit the vasoconstriction occurring during the effort phase of Valsalva's manoeuvre, in contrast to the inhibited vasoconstriction on bethanidine, guanethidine or methyldopa (Prichard *et al.*, 1970b). There is some evidence that propranolol reduces the rise in blood pressure that occurs in coitus (Fox, 1970). However, it does not appear to reduce the rise in pressure due to painful stimuli (Nicotero *et al.*, 1968).

Beta-blocking Drugs in Combination with other Antihypertensive Drugs

Propranolol may be administered with diuretics, and approximately equal numbers of patients in the series of Prichard and Gillam (1969) received a diuretic in addition to propranolol, as in previous therapy. Beta-receptor blocking drugs may be given in combination with other hypotensive drugs on those occasions when control is not adequate on beta-receptor blocking drugs alone. Propranolol at least exerts an additive effect or is even potentiated by sympathetic inhibitory

drugs, e.g. bethanidine and methyldopa (Day and Prichard, 1971). The addition of bethanidine or methyldopa to propranolol means that blood pressure control is associated with some postural and exercise hypotension, although less than that seen when blood pressure is lowered by bethanidine or methyldopa alone (Day and Prichard, 1971).

Propranolol given in conjunction with the alpha-receptor blocking drug phenoxybenzamine also results in postural and exercise hypotension (Beilin and Juel-Jensen, 1972). The combination of beta and alpha blockade in the same molecule tends to result in blood pressure control being associated with postural hypotension when larger doses of the drug were used (Prichard *et al.*, 1975).

There have been reports of the value of the beta-adrenergic receptor blocking drugs in combination with vasodilators (Hansson *et al.*, 1971b; Gottlieb *et al.*, 1972; Aenishanslin *et al.*, 1972; Sannerstedt *et al.*, 1972).

Conclusion

Most of the pioneer work in the use of beta-receptor blockade in the treatment of hypertension was performed with propranolol, but other beta-blocking drugs have also been found to possess an antihypertensive effect. This would be expected if the mode of action is a function of beta-adrenergic blockade and not some associated property.

It has been amply demonstrated that for proper use of propranolol in hypertension it is necessary to titrate the dosage according to individual requirements, a situation that is not unusual with potent antihypertensive drugs. Failure to do this leads to poor results. As would be expected, evidence is accumulating that for optimum treatment with other beta-receptor blocking drugs such titration is also necessary.

ARRHYTHMIAS

The treatment of arrhythmias by beta-adrenergic blocking drugs is a useful advance and has emphasised the role of the sympathetic nervous system in their genesis (Singh and Jewitt, 1974).

At beta-adrenergic receptor blocking concentrations these drugs reduce the slope of sinus or ectopic pacemaker potentials, particularly when the slope has been increased by catecholamines (Hoffman and Singer, 1967) or ouabain (Carmeliet and Verdonck, 1967). The concentration of propranolol *in vitro* in isolated cardiac muscle needed to produce a membrane effect is 100 to 500 times that required to suppress cardiac arrhythmias (Coltart *et al.*, 1971; Shand, 1974), hence the membrane depressant properties of beta-receptor antagonists are unlikely to be of relevance in the treatment of arrhythmias. Moreover, practolol is an effective anti-arrhythmic agent even though it has no membrane depressant activity.

Beta-receptor antagonists have been used in a whole variety of cardiac

arrhythmias, and many supraventricular arrhythmias respond. Sinus tachycardia (Schamroth, 1966) and supraventricular ectopics due to digitalis intoxication are reduced by beta-adrenergic blockade. Beta-blocking drugs increase the refractory period of AV conduction tissue, including re-entry circuits that appear to be responsible for many cases of paroxysmal supraventricular tachycardia (Goldreyer, 1972), for which the beta-adrenoceptor blocking drugs are useful both for treatment (Schamroth, 1966) and for prophylaxis (Gianelly *et al.*, 1967b), particularly in the Woolf-Parkinson-White syndrome (Burchell, 1973).

As beta-adrenergic blocking drugs increase the refractory period of the AV node, they reduce the ventricular rate in atrial fibrillation without any effect on the fibrillation itself (Gibson *et al.*, 1968). Sinus rhythm is only occasionally restored in atrial fibrillation, although more often in atrial flutter (Gibson and Sowton, 1970). Their use in atrial fibrillation is limited except when it occurs with thyrotoxicosis. An infrequent use is to slow the ventricular rate when digitalis in maximum tolerated doses has failed to do so satisfactorily (Stock, 1966), the action of digitalis and beta-blocking drugs on conduction tissue being additive.

Ventricular ectopics from a variety of causes are reduced by intravenous or short-term oral administration of beta-blocking drugs (Gibson and Sowton, 1970) but whether these agents reduce the risk of sudden fatal arrhythmias in these patients is not known. There is evidence that patients having ventricular ectopics on their routine electrocardiograms have a higher risk of sudden death (Goldstein and Moss, 1972; England, 1972). Beta-adrenergic blocking drugs are not agents of first choice in acute attacks of ventricular tachycardia, unless the arrhythmias have been precipitated by an excess of catecholamines as by a phaeochromocytoma. As heart failure is readily precipitated, cardioversion is preferable. Beta-blocking agents are of value, however, in the prophylaxis of attacks of paroxysmal ventricular tachycardia, particularly when the attacks have been produced by exercise (Gibson and Sowton, 1970). Intravenous beta-blocking drugs have been used, usually combined with procainamide or lignocaine, in the prevention of recurrences of ventricular fibrillation following electrical defibrillation (Sloman *et al.*, 1965; Ikram, 1968).

It has been well known for a number of years that catecholamines cause arrhythmias in experimental myocardial infarction. Increased levels of adrenaline and nor-adrenaline have been found following myocardial infarction in man (Singh and Jewitt, 1974); however, trials of beta-blockers following myocardial infarction failed to reduce mortality until recently when trials with larger dosage were reported. Beta-blocking agents are useful when administered acutely in the treatment of arrhythmias following infarction. Perhaps practolol should be preferred (Jewitt and Croxon, 1971) as it produces less of a reduction in cardiac output, the long-term complications of practolol treatment not being a risk here. Beta-blockers neither increase the reversion rate when given prior to d.c. shock in

patients with atrial fibrillation, nor reduce the relapse rate. However, sinus rhythm may be maintained for longer periods when they are given in combination with quinidine. Beta-blocking drugs are useful in treating a whole variety of arrhythmias associated with anaesthesia (Gibson *et al.*, 1968) and in suppressing extra systoles in patients during artificial cardiac pacemaking (Harris, 1966). Digitalis-induced atrial and ventricular tachyarrhythmias respond well to beta-blocking drugs (Gibson and Sowton, 1970).

All beta-receptor blocking drugs seem to have comparable anti-arrhythmic properties regardless of the presence or absence of membrane depressant activity. Thus, propranolol, oxprenolol, pindolol and practolol, for instance, are likely to have similar anti-arrhythmic action in similar beta-blocking doses. Any therapeutic superiority is likely to be related to associated adverse effects with the different compounds (Singh and Jewitt, 1974).

CONGENITAL HEART DISEASE

Sympathetic stimulation with isoprenaline was observed to increase outflow tract obstruction in obstructive cardiomyopathy (Braunwald and Ebert, 1962) and acute studies showed that beta blockade reduced the pressure gradient across the obstruction induced by exercise and isoprenaline (Cohen *et al.*, 1964; Harrison *et al.*, 1964). Most prolonged oral studies with propranolol have also demonstrated improvement of symptoms in most patients (Cherian *et al.*, 1966; Flamm *et al.*, 1968; Adelman *et al.*, 1970) but Sloman's (1967) results in five cases were not impressive. Beta-adrenergic blockade has little effect on obstruction at rest and propranolol was of limited value in patients with resting obstruction (Adelman *et al.*, 1970). Likewise with practolol, little reduction on left ventricular and diastolic pressure was found at rest, but on exercise there was a considerable reduction (Webb-Peploe *et al.*, 1971). In a comparative study both propranolol and practolol improved symptoms of hypertrophic cardiomyopathy but propranolol had a better anti-anginal effect (Hubner *et al.*, 1972).

At present it is difficult to draw any conclusions about the value of beta blockade in this rather variable and generally progressive condition, but the drugs are perhaps of some value in latent and labile outflow tract obstruction (Furberg, 1974).

FALLOT'S TETRALOGY

One of the chief dangers to life in infants with Fallot's tetralogy are cyanotic attacks associated with a marked increase in the right to left shunt and a decrease in arterial oxygen saturation because of increased infundibular obstruction. It has been suggested that this obstruction might be due to excess circulatory noradrenaline (Johnson, 1961). Beta-adrenergic blockade with pronetholol (Honey *et al.*, 1964) or propranolol (Cumming, 1970) may reduce this obstruction. Propranolol may be of value in treating acute severe dyspnoeic

attacks and prolonged oral treatment may postpone shunt surgery. Eriksson *et al.* (1969) selected 10 of 65 patients with Fallot's tetralogy by therapeutic assessment that indicated less infundibular obstruction after propranolol. During nine months of treament these 10 patients had improved exercise tolerance, and cyanotic attacks were prevented.

HYPERTHYROIDISM

For many years, the clinical features of hyperthyroidism have been attributed to the potentiation of catecholamines by thyroxine (Harrison, 1964). Although this now seems unlikely to be true (Levey, 1971; Aoki *et al.*, 1972; Spaulding and Noth, 1975) it has been the basis of various attempts to block the sympathetic nervous system in the treatment of thyrotoxicosis. Initially, sympathectomy and sympatholytic drugs such as reserpine and guanethidine were used, but recently beta-adrenergic receptor blocking drugs have been employed with success (Turner, 1974).

Propranolol has been shown to reduce significantly the peripheral manifestations of hyperthyroidism (Shanks *et al.*, 1969; Nelson and McDevitt, 1975). In hyperthyroid patients, it markedly reduces heart rate both at rest and on exercise (Howitt and Rowlands, 1966; McDevitt *et al.*, 1968; Carruthers *et al.*, 1974) and in some patients has resulted in actual fibrillation being converted to sinus rhythm (Parsons and Jewitt, 1967); myocardial contractility and cardiac output are also decreased (Howitt and Rowlands, 1966). The amplitude of tremor is reduced and the achilles reflex time significantly prolonged by propranolol (Marsden *et al.*, 1968) and there is some suggestion that myopathic and neurological signs in hyperthyroidism may improve after propranolol (Pimstone *et al.*, 1968; Kammer and Hamilton, 1974; Weinstein *et al.*, 1975; Yeung and Tse, 1974; Rothberg *et al.*, 1974). Sweating does not appear to be reduced by propranolol (Allen *et al.*, 1973) and no consistent effects of propranolol on the eye signs of thyrotoxicosis have been recorded (Sneddon and Turner, 1966; Crombie and Lawson, 1968). The basal metabolic rate (Howitt and Rowlands, 1966; Pimstone and Joffe, 1970) and thyroid function tests (Hadden *et al.*, 1969) are unaffected by propranolol.

On the basis of their effects on resting heart rate in hyperthyroid patients, beta-adrenergic receptor blocking drugs with intrinsic sympathomimetic activity have been shown to be less effective than drugs without this property and this has been claimed as further evidence for potentiation of catecholamines in this disease (Turner, 1974). However, practolol has been shown to have more effect on exercise heart rate than on resting heart rate in hyperthyroid patients (Carruthers *et al.*, 1974) and the practice of assessing beta-adrenergic receptor blocking drugs in hyperthyroidism by their effect on resting heart rate has been questioned. In addition, in a double-blind controlled trial of the effects of propranolol 160 mg and practolol 480 mg daily in hyperthyroid patients, practolol was found to be inferior to propranolol in its effects on heart rate only; practolol reduced heart

rate by 17 per cent and propranolol by 24 per cent (Nelson and McDevitt, 1975). Other less highly designed studies have given conflicting results, but it would seem that drugs with ISA can be effective if there are compelling reasons for not using propranolol, e.g. in hyperthyroid patients with respiratory disease.

Indications for the use of beta-adrenergic receptor blocking drugs include the management of hyperthyroid crises (Mackin *et al.*, 1974), pre-operative preparation for thyroidectomy (Lee *et al.*, 1973; Michie *et al.*, 1974), and during the period of onset of effect of antithyroid drugs (2 to 3 weeks for drugs such as carbimazole) or of radioiodine therapy (up to 3 months) (Hadden *et al.*, 1968; Montgomery, 1975). It has been used as the only drug in the treatment of hyperthyroidism in several series (Pimstone *et al.*, 1968; McLarty *et al.*, 1973; Montgomery, 1975) with remission rates as high as 40 per cent at one year (Montgomery, 1975). However, it is generally believed that this form of treatment cannot be recommended except in patients intolerant of antithyroid drugs and in whom surgery or radioiodine was not yet considered appropriate (Turner, 1974). This is because it is impossible to select which patients will respond to propranolol alone; those who do not remain thyrotoxic and may continue to lose weight. Lastly, the use of propranolol has also been advocated in the treatment of neonatal and childhood thyrotoxicosis (Smith and Howard, 1973; Pemberton *et al.*, 1974; Buckfield and Davis, 1966) and of hyperthyroidism in pregnancy (Langer *et al.*, 1974; Bullock *et al.*, 1975). Further experience is necessary to substantiate these claims.

PSYCHOTROPIC USES OF BETA-ADRENOCEPTOR BLOCKING DRUGS

Although the first use of beta-adrenergic blocking drugs in the psychiatric field was reported in 1966, there has been a recent increase in interest and in the number of applications (Jefferson, 1974; Whitlock and Price, 1974).

Anxiety

Anxiety state is manifest by a variable component of autonomic symptoms which themselves can cause anxiety. Whether the emotional changes or the autonomic dysfunction cause the condition is a matter for debate; both may arise from a common central origin (Whitlock and Price, 1974).

Granville-Grossman and Turner (1966) found propranolol (20 mg q.d.s.) in a short duration trial superior to placebo in relieving the autonomic symptoms of anxiety. This has been confirmed in single blind studies (Suzman, 1971). The d-isomer (non-beta-blocking) of propranolol was found ineffective (Bonn and Turner, 1971). Evidence that peripheral beta blockage was responsible for the benefit in anxiety was given by the observation that practolol, which has low penetration of the brain (Scales and Cosgrove, 1970), was also effective (Bonn *et al.*, 1972). Propranolol, however, was ineffective in relieving the central

manifestations of anxiety (Ramsay *et al.*, 1973; Tyrer and Lader, 1974a, b).

Beta-adrenergic blocking drugs have also been tried in physiological anxiety. Brewer (1972) used a dose of propranolol (10 to 80 mg) to reduce the resting heart rate to between 55 and 65 and found a reduction in the feeling of nervousness prior to examinations, but the central component of induced anxiety in normals is not affected (Tyrer and Lader, 1974c). These drugs will, of course, reduce the tachycardia associated with stressful situations, e.g. public speaking (oxprenolol) (Taggart *et al.*, 1973), ski jumping (oxprenolol) (Imhof and Brunner, 1970).

Beta-blocking drugs are therefore of value in relieving the somatic symptoms, and any effect on psychic symptoms will be secondary. They are ineffective in contrast to the benzodiazepines in patients with psychic anxiety (Tyrer and Lader, 1974a).

Drug Dependence

There have been reports of the use of beta-blocking drugs in the control of anxiety symptoms associated with alcohol withdrawal (Carlsson and Johannson, 1971) but other reports have not been so encouraging (Gallant *et al.*, 1973). There have also been reports of the reduction of anxiety symptoms associated with opiate withdrawal (Hollister and Prusmack, 1974) and LSD administration (Linken, 1971) by propranolol.

Others have noted a reduction in craving for addictive drugs in two heroin addicts (Grosz, 1972) and in a pethidine addict (Lowenstein, 1973). It will be interesting to see if these findings are substantiated; one can only speculate on the mode of action as propranolol does not appear to influence morphine metabolism (Brunk *et al.*, 1974). Propranolol does not influence the subjective effects of cannabis (Mortz *et al.*, 1972) or amphetamine (Jonsson, 1972).

Psychosis

Atsmon *et al.* (1972) found that propranolol improved patients with acute schizophrenia but had little effect in chronic care. They used an average dosage of 1,400 mg/day (400 to 4,200 mg/day) adjusted to achieve a drop in pulse rate of 60 to 64/minute; lower doses have been found ineffective (Gardos *et al.*, 1973). More recently, however, Rachensperger *et al.* (1974) used larger doses of oxprenolol (3 cases) and propranolol (2 cases) and found only marginal benefit. In contrast, Yorkston *et al.* (1974) found that all schizophrenic symptoms were relieved completely by propranolol in 6 out of 14 patients who had been unresponsive to phenothiazines, one of the remaining patients had a marked improvement and 4 showed moderate improvement. Relapse was seen in 2 patients who stopped their treatment. The dosage used was 500 to 3,500 mg/day, and toxic symptoms were minimised by gradual increase of dosage.

Use of propranolol has been reported in other psychoses due to organic brain

damage, but it was less effective in the manic phase of manic-depressive psychosis (Steiner *et al.*, 1972) but more effective than chlorpromazine in postpartum psychosis (Steiner *et al.*, 1973). These new interesting possible uses of beta-blocking drugs await further evaluation.

MIGRAINE

Rabkin *et al.* (1966) observed that, while treating patients with angina pectoris with propranolol, co-existent migraine was benefited. Recently, there have been a number of trials of the use of beta-blocking drugs in this condition.

Weber and Reinmuth (1966), using 80 mg/day of propranolol, found it was an effective prophylactic in migraine, but a less convincing effect was seen with 60 mg daily (Malvea *et al.*, 1973), while Ludvigsson (1973), in a further double blind study, used 60 mg on children under 35 kg, 120 mg daily above 35 kg and found more impressive results, only 2 out of 28 children not responding. Widerøe and Vigander (1974) found propranolol 160 mg daily effective, all but 2 of the 49 patients showing some effect in an open study. A double blind study was performed in 30 patients who responded well and there was a significant reduction in the average monthly attacks of migraine from 1.7 to 0.4. Open studies with pindolol suggest that it may be effective (Anthony *et al.*, 1972) but a double blind study with 15 mg or 7.5 mg daily of pindolol failed to reveal a significant effect (Sjaastad and Stensruo, 1972).

It seems that beta-blocking drugs may be a useful migraine prophylactic, but at the moment this is only reasonably established with propranolol.

CONCLUSION

The beta-adrenergic blocking drugs represent perhaps the most interesting and useful group of new drugs introduced in the last decade. Many uses have been discovered which were not predicted from the original animal pharmacology, both within the area of cardiovascular disease, e.g. hypertension, and in other fields, e.g. psychiatric uses. The place of these drugs remains to be fully evaluated in some of their indications but they are well-established as useful agents in a number of common conditions, notably hypertension and angina pectoris, and have a modest place in the treatment of arrhythmias.

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