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β-ADRENERGIC RECEPTOR BLOCKADE IN HYPERTENSION, PAST, PRESENT AND FUTURE

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β-adrenoceptor blocking drugs—Classification

All β-adrenoceptor blocking drugs that have been described share the common property of being competitive inhibitors. They differ in their associated properties, the presence or absence of cardioselectivity, membrane stabilizing activity, and partial agonist activity. Recently some β-adrenoceptor blocking drugs have been reported which also possess α-adrenoceptor blocking activity. The associated properties have been used as a basis for classifying β-adrenoceptor blocking drugs (Fitzgerald, 1969, 1972).

The presence or absence of cardioselectivity is most useful for dividing β-adrenoceptor blocking drugs. The non-selective drugs (Division I) can be further divided according to the presence or absence of intrinsic sympathomimetic activity (ISA) and membrane stabilizing activity (Fitzgerald's groups I–IV). Group I possess both membrane activity and ISA, e.g. alprenolol, oxprenolol, group II just membrane action, e.g. propanolol, group III ISA but no membrane action, e.g. pindolol. Fitzgerald placed pindolol in group I but it should be placed in group III as it possesses a high degree of β-adrenoceptor blocking potency in relation to its membrane activity (Prichard, 1974). Finally drugs in group IV have neither ISA nor membrane action, e.g. sotalol, timolol.

The cardioselective drugs (Division II) can be similarly sub-divided into groups I–IV according to the presence or absence of ISA or membrane action (Fitzgerald grouped all these together as group V).

Lastly there are new β-adrenergic receptor blocking drugs which in addition have α- adrenergic receptor blocking properties (Division III).

Introduction

Most studies have shown little change in blood pressure after acute administration of β-adrenoceptor blocking agents, but there is immediately a marked reduction in the rise of blood pressure on exercise (Shinebourne, Fleming & Hamer, 1967; Thadani, Sharma, Meeran, Majid, Whitaker & Taylor, 1973) or in the overshoot after Valsalva's manoeuvre (Prichard & Gillam, 1966).

The original observations of the hypotensive effect of β-adrenoceptor blocking drugs were made in a trial of pronethalol in angina pectoris performed in 1962; this, and its use in the treatment of hypertension, was reported in 1964 (Prichard, 1964). The first report of the use of propanolol in hypertension also appeared the same year (Prichard & Gillam, 1964). After a slow start to the acceptance of propranolol in hypertension the value of this drug and other β-adrenoceptor blocking drugs in hypertension has come to be widely accepted (Simpson, 1974).

There are a number of reasons for the delay in general acceptance of β-adrenoceptor blocking drugs in hypertension. First, conservatism existed as β-receptor antagonists inhibited cardiac contraction. This was regarded as a basically undesirable effect and in addition this had been associated with untoward reactions in acutely ill patients. Secondly the effect had not been first seen in animals and the mode of action in hypertension was unknown. Thirdly no antihypertensive effect is seen acutely and peripheral resistance increased, an action which seemed disadvantageous. Another reason was the use of inadequate dosage. A large number of early investigators used fixed inadequate doses even though the original reports (Prichard & Gillam, 1964, 1966)

emphasized the importance of a variable dosage regime. The use of fixed and low doses meant that unimpressive results were often obtained and this delayed the acceptance of these drugs. Misconceptions about dosage arose from erroneous concepts of completed β-adrenoceptor blockade that were based on the observation that a relatively small dose of propranolol blocked the effect of a dose of isoprenaline that previously gave a maximal tachycardia. It was necessary to give a considerably larger dose of propranolol to produce maximum inhibition of exercise induced tachycardia or even the supine or standing resting heart rate (Boakes, Boeree & Prichard, 1973). It is these larger doses that are often needed to give an adequate anti-hypertensive effect.

Lastly, because of these misconceptions, the use of larger doses was widely ascribed to a 'direct depressing action' ('quinidine-like effect', 'membrane action' local anaesthetic effect) on the heart. This membrane action is indeed seen with large doses in animals (Fitzgerald, 1972) and results in a depression of myocardial function independent of β-adrenoceptor blockade. The membrane effect is a pharmacological curiosity and has been subsequently shown to be irrelevant in the treatment of hypertension, neither is it responsible for the haemodynamic effects of β-adrenoceptor blocking drugs. It is inhibition of the sympathetic activity *per se* indeed produces a negative inotropic and chronotropic effect on the heart in man. The use of the term 'negative inotropic effect' when applied to β-adrenoceptor blocking drugs, should be confined to this sympathetic blocking action. As confusion has arisen it would perhaps be best to avoid the term.

All β-adrenoceptor blocking drugs, regardless of associated properties, exert a hypotensive effect, and this lends support to the concept that this effect is needed due to β-adrenoceptor blockade not to a non-specific action.

Non-selective β-adrenoceptor blocking drugs (Division I)

Group I

These β-adrenoceptor blocking drugs possess both membrane stabilizing action and intrinsic sympathiomimetic action (ISA). The original observations were made with pronethaolol (Prichard, 1964) and other members of this group have been shown to have an anti-hypertensive effect.

Oxprenolol Leishman, Thirkettle, Allen & Dixon (1970) performed a trial of oxprenolol in nineteen patients using up to 420 mg/day. Pressures on placebo were 173/102 supine and 165/106 mmHg standing in a double-blind phase, and for oxprenolol 160/99 and 151/99 mmHg respectively. No side effects were experienced, but five were withdrawn prior to the double-blind part of the trial because of inadequate pressure control, so that those taking part were necessarily preselected. Tuckman, Martin & Hodder (1972) reported an open trial of oxprenolol in doses of 60–600 mg/day (average 374 mg daily) in 17 patients; they too failed to note any orthostatic hypotension. In a recent open study it appeared that oxprenolol was similar in efficacy to propranolol, pindolol and practolol (Waal-Manning, 1976).

Alprenolol Alprenolol, another member of this group, is also an effective hypotensive agent. Furberg & Michaelson (1969) performed a double-blind cross-over using up to 400 mg/day in twelve patients. The blood pressure after 12 weeks on placebo was 180/111 mgHg, and after alprenolol 162/104; the reduction in systolic pressure was statistically significant. There have been other studies which have also shown that alprenolol is effective, Tiblin & Ablad (1969), Bengtsson (1972), Nik-Akhtar, Rashed & Khakpour (1975), Hartikainen & Heikkila (1976).

Group II

Propranolol It was with propranolol that the value of β-adrenoceptor blocking agents in hypertension has been established (Prichard & Gillam, 1964, 1966; Baczko, Dabrowska & Wocial, 1967; Frohlich, Tarazi, Dustan & Page, 1968; Tewari & Grant, 1968; Zacharias & Cowen, 1970; Karlberg & Hornkvist, 1971; Zacharias, Cowen, Vickers & Wall, 1972). Prichard & Gillam (1969) reported the first large study, 109 patients treated for up to 4 years.

Degree of blood pressure control with propranolol Propranolol appears to produce similar control to that obtained with bethanidine, guanethidine and methyldopa (Prichard & Gillam, 1969; Zacharias, 1969; Prichard, Gillam & Graham, 1970b; Zacharias *et al.*, 1972). There have been some investigators who have found a less favourable response of blood pressure to propranolol (Humphreys & Devlin, 1968; Paterson & Dollery, 1966; Richards, 1966; Richardson, Freund, Gear, Mauck & Preston, 1968; Waal, 1966). In all these instances the maximum dose used was less than the average dose of about 400–500 mg a day used by Prichard & Gillam (1969), who in addition (unlike the investigators mentioned above) used a diuretic in more than half of their patients. On the other hand, Seedat & Reddy (1971) using full dosage (up to 1920 mg a day) found only 4 of 13 Bantu patients were controlled by propranolol. These investigators did not use a diuretic or any other drug. They found a better response in their Indian patients.

Zacharias *et al.* (1972) in his series of 311 patients, found a larger number achieved satisfactory blood

pressure control than usually observed with other hypotensive drugs.

Recently, we have been performing a formal within-patient, randomized comparison of bethanidine, methyldopa and propranolol (Prichard, Boakes & Graham, 1976) closely following the design of Prichard, Johnston, Hill & Rosenheim (1968). This confirms that the three drugs are of similar efficacy, propranolol producing a significantly different response to posture and exercise.

Dosage We have usually commenced at about 10 mg or 20 mg three or four times daily and increments of about 25% per dose can be made at each time the blood pressure is assessed, usually every 2 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 80–100 mmHg (unless clinically contraindicated—e.g. associated cardio-vascular disease), unless the pulse rate falls below 55 beats/min in standing position. A total of 1 g a day is not exceptional, we have used up to 4 g a day, on the other hand a few patients need a total of 40–80 mg a day. Diuretics were used as indicated and in a few instances small doses of other hypotensive drugs. In severe and moderately severe hypertensives the average dose is about 400–500 mg a day with about half of the patients needing a diuretic in addition. Initially propranolol was given three or four times a day but later trials indicated that dosage may be simplified to a twice daily regime (Hansson, Olander & Aberg, 1971a), or even once a day (Wilson, Morgan & Morgan, 1976).

There is some evidence that there is a considerable margin of safety with propranolol as suggested in a double-blind multi-dose level trial of propranolol in angina pectoris (Prichard & Gillam, 1971). Here a group of six mild hypertensive patients' blood pressure fell from a mean 115 (154/96) (standing) to a mean of 102 (135/85) ($P<0.005$) standing as dosage was increased from zero to an average of 320 mg daily; doubling the dose resulted in no change of blood pressure, at an average dose of 640 mg daily, the standing blood pressure averaged 103 mmHg (137/86).

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

There has been much written about the variation of dosage seen with propranolol and also other β-adreno-ceptor blocking drugs. Three points can be emphasized. First, the fact that the dosage is variable and that therefore patient requirements will vary and fixed dose trials, versus placebo or other drugs are in-appropriate. There are many trials in the literature satisfactory in all save one respect: the dosage used in the study has been sub-optimal. Secondly the dosage variation with propranolol is not unique for propranolol; it is no greater than that seen with a sympathetic inhibitory drug as guanethidine or benthanidine or methyldopa (Prichard & Gillam, 1969). Finally, as β-adrenoceptor blocking drugs are recently introduced drugs, they have been subject to more careful pharmacokinetic study than has hitherto been performed. It seems that the principle reason for dosage variation is difference in absorption of propranolol, this may vary over a 20-fold range (Shand, 1976).

Group III

Pindolol While not necessarily conferring any advantage pindolol weight for weight is the most potent β-adrenoceptor blocking drug in use. It was found that pindolol 13 mg daily was approximately equivalent to propranolol 160 mg daily, or oxprenolol 200 mg a day in a group of hypertensive patients known to respond to β-adrenoceptor blocking drugs (Waal-Manning, 1970b), however Laver, Fang & Kincaid-Smith (1974) found a 1 to 5 ratio for pindolol and propranolol.

A number of subsequent trials have shown pindolol to be an effective anti-hypertensive. Feltham, Watson, Peel, Dunlop & Turner (1972) performed an open and double-blind study in eighteen patients using a dosage between 15 and 80 mg a day. There was evidence of a delay in the maximum hypotensive effect in the double-blind phase, a lower blood pressure being observed after 4 weeks active treatment than after 2 weeks. Thorpe (1972) used 15 to 60 mg daily (average 26 mg) in an open study in twenty patients, and then in a between subject comparison in fourteen of the patients, blood pressure on placebo ($n=8$) averaged 182/100 mmHg; after 2 weeks of active treatment blood pressure was 150/92 mmHg ($n=6$) while after 8 weeks active treatment, 139/86 mmHg. There was no later decline in the blood pressures in the placebo group. Morgan, Louis, Dawborn & Doyle (1972) obtained a good response in 59% of their series of 86 patients. In these 45 patients who responded, 39 required 30 mg a day or less, the other 10 between 30 and 50 mg, while increasing the dose to 80 mg a day did not affect the remainder. In four patients there was a rise in blood pressure with pindolol, a phenomenon observed by others (Collins & King, 1972).

Waal-Manning & Simpson (1974) altered treatment to pindolol in 43 patients continuing diuretic unless this was the only treatment used. They found that blood pressure control was better on pindolol with fewer side effects than in drugs which 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 40–50 mg daily was not of value.

In a double-blind cross over study in 22 patients, pindolol (average 25 mg) resulted in a more consistent fall in blood pressure from placebo, compared to the effect of alprenolol (average 533 mg) (Hartikainen & Heikkila, 1976).

Seedat, Stewart-Wynne, Reddy & Randeree (1973) found pindolol (range 15–75 mg a day, average 45 mg a day) in 24 patients had a superior hypotensive effect than propranolol ($n=25$) (average 760 daily) in Indian and Bantu patients; however this was an open study. A more clearly controlled study was that of Laver *et al.* (1974) who performed a double-blind variable dose study in 35 patients which compared pindolol (average dose 57.5 mg daily) with propranolol (average dose 289.3 mg daily); patients received a diuretic throughout. The blood pressures on both drugs, pindolol supine 138/92 mmHg, standing 132/90 mmHg, and propranolol supine 137/90 mmHg, standing 132/88 mmHg, were similar. They found less postural effect than on previous treatment, which was methyldopa (average dose 1.160 mg daily) in 26 patients. There is evidence that pindolol may be given once daily (Wilson *et al.*, 1976).

Group IV

Recently drugs of this group, i.e. β-adrenoceptor blockade without intrinsic sympathomimetic effect or significant membrane activity, have been found to be effective antihypertensive agents, e.g. sotalol (Prichard & Boakes, 1974; Verniory, Staroukine, Telerman & Delwiche, 1974). Berglund (1977) compared propranolol and sotalol and found them equi-effective antihypertensive drugs with propranolol, having twice the potency of sotalol. Timolol is also an effective antihypertensive (Brogden, Speight & Avery, 1975; Lohmoller & Frochlich, 1975; Lund-Johansen, 1976a; Castenfors, 1977). Alcocer, Aspe & Gomez (1975), compared timolol and propranolol in 12 patients and found that 30 mg of timolol appeared equivalent to 120 mg of propranolol. Cahalmers, Horvath, Tiller & Bune (1976) in a double-blind factorial trial demonstrated an additive effect of timolol (10 mg three times a day) and hydrochlorothiazide (50 mg once daily).

Cardioselective β-adrenergic receptor blocking drugs (Division II)

Recently a number of cardioselective agents have been described; they have all been found to be effective anti-hypertensive drugs.

Group I

Acebutolol possesses both intrinsic sympathomimetic activity and membrane activity. It has been found effective in hypertension (Letac, Fillastre & Wolf, 1974; Hansson, Berglund, Andersson & Holm, 1977).

Group III

Practolol has intrinsic sympathomimetic action but not membrane action. It has been demonstrated to have an anti-hypertensive effect (Leishman *et al.*, 1970; Prichards, Boakes & Day, 1971). It was the first of the cardioselective agents but recent reports of serious adverse reactions, in the eye, skin, a sclerosing peritonitis, have led to the cessation of this drug's use other than for acute intravenous administration.

Group IV

Drugs from this group, i.e. without ISA or membrane activity, have been shown to be effective hypotensive drugs. This has been shown with atenolol (Hansson, Aberg, Karlberg & Westerlund, 1975; Lund-Johansen, 1976b; Douglas-Jones & Cruickshank, 1976; Zacharias, Cowen, Cuthbertson, Johnson, Prestt, Thompson, Vickers, Simpson & Tuson, 1977; Zacharias & Cowen, 1977; Zacharias, Hayes & Cruickshank, 1977).

Some studies have indicated that atenolol is more effective than bendrofluazide (Petrie, Galloway, Webster, Simpson & Lewis, 1975; Fagard, Amery, Deplaen, Lijnen & Missotten, 1976). Metoprolol is also active (Bengtsson, Johnsson & Regardh, 1975; Hansson, Dymling, Hadeland & Hulthen, 1977a).

A comparative study of metoprolol and methyldopa found that these agents were of similar efficacy in the treatment of mild and moderate hypertension (Bergstrand, Vedin, Wilhelmsson & Berglund, 1976).

β-adrenoceptor blocking drugs with α-adrenoceptor blocking properties (Division III)

Recently the use of labetalol, a β-adrenergic receptor blocking drug possessing α-adrenoceptor blocking properties (Richards, 1976), has been reported in the treatment of hypertension (Prichard & Boakes, 1976; Brown, Lever, Cumming & Robertson, 1977).

Inhibition of the sympathetic supply to α-adrenoceptors

Although there are differences between sympathetic inhibitory drugs such as guanethidine, bethanidine, debrisoquine or methyldopa (Oates, Seligmann, Clark, Rousseau & Lee, 1965; Prichard *et al.*, 1968; Heffernan, Carty, O'Malley & Bugler, 1971) these drugs all interfere with important cardiovascular homeostatic reflexes that are mediated largely by sympathetic constrictor fibres to α-adrenergic receptors.

There are therefore several important physiological factors that increase the hypotensive action of sympathetic inhibitory drugs:

1. The tone of blood vessels is maintained by

alteration in sympathetic vasoconstrictor tone and this tone is much greater when standing to counteract the hydrostatic effect of the weight of the column of blood, than in the supine position. Sympathetic blocking drugs produce a larger fall of blood pressure in the standing position when the need for sympathetic constriction is greater.

2. While posture is the most important example, increased demand of various vascular beds, muscle dilatation from exercise, skin dilatation from a hot environment, splachnic dilatation after a meal, all tend to result in a further fall of blood pressure when vasoconstriction that would otherwise occur is inhibited.

3. Obstruction to venous return as seen in straining at the stool or more convenient for the laboratory, Valsalva's manoeuvre, results in a need for vasoconstriction to maintain arterial pressure because of the reduced cardiac output secondary to the reduced venous return to the heart. Any potentially dangerous greater fall in blood pressure from this source is clearly much more likely to occur if the agent producing sympathetic inhibition also results in constipation. When ganglion blocking drugs were used in hypertension, constipation resulted from their parasympathetic blocking action.

4. Any reduction of blood volume requires additional vasoconstriction to maintain blood pressure. There is a reduced blood volume in the early hours of the day, a fluctuation that is greater in hypertensive than normotensives. This diurnal variation in blood volume is probably responsible for the greater incidence of excessive hypotension seen in the early hours of the day, on standing or after exercise.

The effect of these various physiological stresses is additive and clearly an excessive fall in blood pressure in patients being treated by these drugs is more likely to occur for instance in the early hours of the day, performing exercise in the standing position, in a hot environment after a good meal, e.g. 02.00 h at a 'dinner dance'.

Response of blood pressure to physiological stimuli in hypertensive patients treated with β-adrenergic receptor 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 oral propranolol and other β-adrenoceptor 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, Shinebourne, Fleming & Hamer, 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 to the effects seen on sympathetic inhibitory drugs. However, the rise in blood pressure on exercise after β-adrenoceptor blockade is less than that seen in the absence of a β-adrenoceptor blocking agent (Shinebourne *et al.*, 1967).

Studies with other β-adrenoceptor blocking drugs have shown an absence of postural hypotension when blood pressure is lowered by β-adrenoceptor blockade. For instance, in a multicentre open study in 195 patients, pretreatment blood pressure averaged 194/114 supine, 187/113 standing, after treatment with pindolol supine blood pressure was 158/97, standing 154/97 mmHg (Collins & King, 1972).

2. *The effect of increasing environmental temperature*

Increasing temperature from 7° to 30°C produced 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 vasoconstriction occurring in other vessels to compensate. 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 (Prichard *et al.*, 1970b).

3. *The action on Valsalva's manoeuvre and the blood pressure response to other stresses*

A β-adrenergic receptor blocking drug given intravenously reduces the overshoot after cessation of effort without reducing the vasoconstriction that occurs during effort. A similar effect is seen after both propranolol (Prichard & Gillam, 1966) and pronethalol (Prichard, 1966) or practolol (Prichard, 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 to painful stimuli (Nicotero, Beamer, Moutsos & Shapiro, 1968), or cold water (Guazzi, Fiorentini, Polese, Olivari & Magrini, 1976). However, it has been found that the rise in blood pressure from the stress of sorting ball bearings was reduced or abolished by 6 weeks oral propranolol or metoprolol (Lorimer, Dunn, Jones, Clark & Lawrie, 1976), and the rise in pressure in response to mental arithmetic was reduced by propranolol 320 mg a day (Guazzi *et al.*, 1976). However, Nyberg, Graham & Stokes (1977) using lower doses of propranolol, or metoprolol, or alprenolol, found that although the

peak pressures were reduced in response to mental arithmetic, the rise from base line was not.

Mode of action

The reason that β-adrenoceptor blocking drugs lower the blood pressure seems to be a property of their β-receptor inhibitory action. Regardless of associated properties, the presence or absence of membrane stabilizing or sympathomimetic action, hypotensive effect is seen. In addition, it has been shown that the (+)-isomer of propranolol has no hypotensive effect in contrast to normal (±)-racaemic propranolol (Waal-Manning, 1970a, 1976; Prichard, 1970).

A number of suggestions have been made to explain the hypotensive effect of β-adrenergic receptor blocking drugs, an effect on the central nervous system, an adrenergic neurone blocking effect, an anti-renin effect, an effect secondary to the reduced cardiac output, and, finally, a mechanism consequent on resetting the baroreceptors.

Effect on the central nervous system

Observations have been made in animals that suggest a possible central mode of action for the antihypertensive effect of β-adrenergic receptor blocking drugs. The intra-arterial injection of propranolol (0.1 mg/kg) into either the carotid or vertebral artery in the anaesthetized dog produced a fall in blood pressure that was of more rapid onset than when the drug was administered via the femoral artery (Stern, Hoffman & Braun, 1971). However, Offerhaus & van Zwieten (1974) found that the (+)-isomer of alprenolol and propranolol were as effective as the racemic mixtures when injected into the vertebral arteries of the chloralose anaesthetized cats has a hypotensive effect that was abolished by reserpinization, but this was also seen with the (+)-isomer (Kelliher & Buckley, 1970). These observations must be regarded as due to a non-specific effect, as the (+)-isomer is devoid of antihypertensive effect in man.

A variety of β-adrenoceptor antagonists, propranolol, alprenolol, pindolol, practolol, atenolol, sotalol and oxprenolol, have been found to produce a fall in blood pressure, preceded by a transient rise, when given intracerebroventricularly to conscious normosensitive cats. On the other hand, the (+)-isomer of both propranolol and alprenolol, devoid of β-receptor antagonism, were without any hypotensive effect, solely the initial pressor response was seen (Day & Roach, 1974). A similar hypotensive effect has also been seen with propranolol in conscious rabbits (Myers, Lewis, Reid & Dollery, 1975). They used doses that resulted in concentrations in brain tissue after 1–2 h similar to those obtained following the intravenous infusion of 1.0 to 2.0 mg kg^{-1} h^{-1} over a period of 1–2 h. Myers *et al.* (1975) also demonstrated brain penetration by propranolol in man.

Garvey & Ram (1975a), have made some interesting observations in hypertensive and normotensive conscious rats. The administration of oral or subcutaneous propranolol and pindolol for 14 days reduced blood pressure and heart rate. Propranolol was concentrated particularly in the hippocampus, pindolol in the septum. On the other hand, sotalol failed to reduce the blood pressure or produce significant concentrations in the central nervous system. All three drugs produced persistant peripheral β-adrenoceptor blockade. Likewise injection of propranolol into the hippocampus, and pindolol into the septum, produced the greatest reduced blood pressure and heart rate in chloradose anaesthetized cats and dogs, while less effect was seen at other brain sites (Garvey & Ram, 1975b). This effect was associated with a reduction in efferent sympathetic and an increase in parasympathetic nerve activity. The injection of sotalol at various brain sites failed to produce any effect. Lewis & Haeusler (1975) infused racaemic propranolol intravenously into the conscious rabbit and it produced a significant fall of blood pressure and splanchnic efferent nerve activity after 2 h; the (+)-isomer was without effect. However, practolol failed to reduce sympathetic nerve activity and when pressure fell in conscious rabbits after large doses there was a rise in sympathetic nerve activity (Lewis & Haeusler cited by Dollery & Lewis, 1976).

Experiments in chloralose cats showed that racaemic propranolol, (+)-propranolol and pindolol produced a fall in blood pressure when given into the lateral ventricle at a lower concentration than when administered intravenously, and this decline in blood pressure was associated with a fall in sympathetic nerve activity in response to sciatic nerve stimulation; sotalol however, was without effect (Klevans, Kovacs & Kelly, 1976).

Acutely β-adrenoceptor blocking drugs do not appear to reduce plasma noradenaline levels as has been shown with pindolol (Anavekar, Louis, Morgan, Doyle & Johnston, 1975), however a decline in plasma noradrenaline was seen with chronic administration of the non selective agent pindolol, to levels reached those seen in normotensives (Brecht, Banthien & Schoeppe, 1976). Pretreatment plasma noradrenaline levels co-related with diastolic blood pressure as had been also found by Louis, Doyle & Anavekar (1973). However, others have not found any consistent relationship between arterial pressure and plasma noradrenaline (Reid, Jones & Dargie, 1977). Decline in plasma noradrenaline from pindolol did not correlate with the fall in blood pressure (Brecht *et al.*, 1976) and studies in hypertensive patients with long term penbutolol failed to show a fall in plasma noradrenaline although blood pressure fell (Hansson & Hökfelt, 1975). It should be noted that although supine resting noradrenaline levels may decline with

chronic treatment, there is no fall in the rise on standing or on exercise (Hanssen & Hökfelt, 1975; Brecht *et al.*, 1976).

Studies with cardioselective drug metoprolol did not show any decline in plasma noradrenaline with chronic treatment although blood pressure fell, standing levels were in fact higher on metoprolol (Hansson, Dymling *et al.*, 1977).

There is no doubt that most β-adrenoceptor blocking drugs administered systemically penetrate into the central nervous system. Concentrations rapidly achieve a steady state as no evidence of accumulation in the cerebrospinal fluid was found when 2 weeks' administration to cats of alprenolol and propranolol was compared with acute administration (Offerhaus & van Zwieten, 1974).

Although it seems that β-adrenoceptor blocking drugs can influence central sympathetic activity there are considerations that mitigate against this as being regarded as the explanation for their antihypertensive action in man. First, β-adrenergic receptor blocking drugs that fail to penetrate into the central nervous system, practolol (Scales & Cosgrove, 1970), sotalol (Garvey & Ram, 1975a) are effective antihypertensive drugs in man. Secondly, with the exception of the observations of Garvey & Ram (1975a), the effects described in animals are of acute onset, unlike the response seen in man (Prichard & Gillam, 1969; Prichard & Boakes, 1974).

Adrenergic neurone blocking effects of β-adrenoceptor blocking drugs

An adrenergic neurone inhibiting effect has been demonstrated with propranolol in rats and rabbits, but this action is also seen with the (+)-isomer (Barrett & Nunn, 1970) which is devoid of antihypertensive effect in man. In cats, however, an inhibition of nerve stimulation was seen with recemic propranolol but not the (+)-isomer (Ablad, Ek, Johansson & Waldeck, 1970). There is no evidence in man that innervation of the α-receptor is inhibited. The fact that propranolol (and other β-adrenergic receptor blocking drugs) controls the blood pressure in man without producing postural hypotension characteristic of the adrenergic neurone inhibitory drugs (Prichard & Gillam, 1969) suggests that any effect from this action is not important. The rise in blood pressure during the effort phase of Valsalva's manoeuvre is not inhibited by β-adrenoceptor blocking drugs (Prichard & Gillam, 1966; Prichard, Gillam & Graham, 1970), neither have more direct measurements found any evidence of inhibition of vasoconstriction (Korner, Blombery, Bobik, Tonkin & Uther, 1976). In addition, no depression of the cold pressor test was seen after 3 weeks oral propranolol in male hypertensive patients, suggesting that the innervation of the α-receptor was not impeded (Guazzi *et al.*, 1976).

Renin

β-adrenergic receptor blockade in normal subjects (Winer, Chokshi, Yoon & Freedman, 1969) and hypertensives (Buhler, Laragh, Baer, Vaughan & Brunner, 1972; Michelakis & McAllister, 1972) lowers plasma renin; although the β-adrenergic system is important in the release of renin it is not the only factor (Bravo, Tarazi & Dustan, 1974).

Buhler *et al.* (1972) subdivided their patients according to their pretreatment ambulant peripheral renin levels. They related renin levels to the daily urinary sodium excretion, and divided them into high, normal or low renin groups. The three groups were similar as regards age and severity of hypertension. Propranolol was used in a dosage of up to 540 mg daily. The 12 patients with high renin levels showed the greatest falls of pressure, those with low renin (14 patients) showed only a very small effect, while those with normal renin levels (23 patients) were intermediate. There was overall a good correlation between the fall in blood pressure and plasma renin activity. Propranolol, oxprenolol, LL 21945, and the cardioselective agents atenolol and metoprolol were studied in a further series of 137 patients (Buhler, Burkhart, Lutold, Kung, Marbet & Pfisterer, 1975). The same pattern was observed, high renin patients showed a good fall in blood pressure, it was poor with low and intermediate with normal renin patients. Likewise in hypertensive patients being treated with alprenolol, the fall in diastolic blood pressure observed correlated with the reduction in plasma renin (Castenfors, Johnsson & Oro, 1973).

Fournier, Hardin, Alexandre, Lombaert, Ronco, Bezoc, Desmet & Quichaud (1976) also found a greater fall in blood pressure in hypertensive patients with normal plasma renin activity than in those with low activity, although overall fall of blood pressure did not significantly correlate with initial plasma renin activity, following the administration of acebutolol.

There is, however, evidence against accepting the prime role of renin in the antihypertensive effect of β-adrenergic receptor blocking drugs. A number of workers have not found any correlation with the fall in blood pressure and pre-treatment levels of plasma renin; for propranolol (Hansson, 1973; Stokes, Weber & Thornell, 1974; Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Bianchetti, diSalle, Morselli & Chidsey, 1975; Morgan, Roberts, Carney, Louis & Doyle, 1975; Zweifler & Esler, 1976), pindolol (Morgan *et al.*, 1975; Lancaster, Goodwin & Peart, 1976; Stumpe, Kolloch, Vetter, Gramann, Krück, Ressel & Higuchi, 1976), alprenolol (Pedersen & Kornerup, 1977), sotalol (Verniory *et al.*, 1974), metoprolol (Genest, Dornier, Boucher, Nowaczynski, Roto-Ortega & Kuchel, 1976; Hansson, Dymling *et al.*, 1977), or atenolol (Amery, de Plaen, Fagard, Lijnen & Reybrouck, 1976a).

Also, there was no relationship between the fall in

blood pressure and change in renin when propranolol was added to patients on diuretics for their hypertension and, indeed, in some, renin increased (Bravo, Tarazi & Dustan, 1975). Chalmers *et al.* (1976) found while timolol alone lowered plasma renin, when hydrochlorothiazide was added, plasma renin were not different from levels seen on placebo, although there was an additive antihypertensive effect of timolol and hydrochlorothiazide. Morgan *et al.* (1975) divided their patients as described by Buhler *et al.* (1972); but unlike these investigators, they found equal falls in blood pressure with low, normal and high renin patients. Relatively small doses of propranolol suppress plasma renin levels at dose levels with little effect on blood pressure (Michelakis & McAllister, 1972; Leonetti *et al.*, 1975; Zweifler & Esler, 1976). Leonetti *et al.* (1975) found 40 mg daily produced almost maximal suppression of supine and frusemide stimulated renin levels; and 60% of the fall in standing renin levels. The further fall in the standing levels up to a dosage of 160 mg of propranolol daily was significant. In contrast only a small fall in blood pressure was seen at 40 mg daily; the changes in diastolic pressure were insignificant, the significant fall being seen between 40 and 160 mg of propranolol daily.

More evidence of the dissociation of renin and antihypertensive effect is provided by the observation that intravenous propranolol lowers plasma renin without lowering blood pressure (Bravo *et al.*, 1974; Morgan *et al.*, 1975), although it could be argued that the fall in blood pressure, although delayed, was secondary to an anti-renin effect.

Stokes *et al.* (1974), found propranolol lowered plasma renin but, although the substitution of pindolol for propranolol in nine patients for 48 h maintained the hypotensive effect, plasma rose to control levels.

Similarly Stumpe *et al.* (1976) found that while pindolol and propranolol produced a similar fall in blood pressure in both patients with borderline and ascertained hypertension, the fall in renin was greater with propranolol. While the fall in blood pressure and fall in renin correlated with propranolol it did not with pindolol.

Other work has also indicated that fall in blood pressure after pindolol is not correlated with changes in plasma renin (Lancaster *et al.*, 1976; Anavekar *et al.*, 1975).

Likewise, Amery *et al.* (1976a), when they changed patients from propranolol (480 mg) to atenolol (600 mg) the hypotensive effect continued but renin levels rose and were no longer significantly different from placebo.

Finally, Stumpe *et al.* (1976) took four patients who showed a fall in blood pressure with propranolol and a drop in renin levels and found that the angiotensin antagonist, sar^1-ala^8–angiotensin II, failed to lower blood pressure.

Effect on plasma volume

Tarazi, Frohlich & Dustan (1971), found oral treatment with propranolol reduced plasma volume in a series of 14 hypertensive patients; however, this failed to correlate with the fall in blood pressure and in some patients blood pressure fell without any fall in plasma volume. Julius, Pascual, Abbrecht & London (1972) observed a fall in plasma volume after intravenous propranolol but, as others had shown before, there was no fall in blood pressure.

However, Sedenberg-Olsen & Ibsen (1972) using higher doses of propranolol than Tarazi *et al.* (1971) found that 4 months' treatment of hypertensive patients with propranolol failed to affect plasma volume but that there was a significant increase in extracellular fluid volume. There was no increase in body weight, confirming previous reports (Prichard & Gillam, 1969). The change in extracellular fluid volume did not correlate with the hypotensive effect of propranolol, similar to the poor correlation observed with other hypotensive drugs (Ronnov-Jessen & Hansen, 1969). Parving & Gyntelberg (1973) also found pindolol was without effect on plasma volume in hypertensive patients, and Hansson, Dymling *et al.* (1977) in fact found a small but significant increase after the use of metoprolol to lower the blood pressure.

Gordon (1976) found 1 month's administration of small doses of pindolol (15 mg a day) and propranolol (30 mg a day) increased plasma volume in spite of a fall in blood pressure. The picture was different with larger doses; propranolol, 40 mg three times daily, produced inconsistent effects in fall in plasma volume in 7, no change on increase in the remaining 6 patients. Pindolol (10 mg three times daily) in three out of four patients reduced plasma volume. In patients on diuretics in whom plasma volume was reduced to 93% of the normal values, the addition of propranolol increased plasma volume to 99% of the normal values (Bravo *et al.*, 1975). The changes did not correlate with the further fall of blood pressure seen with propranolol. This further indicates that change in plasma volume is not likely to be important in the hypotensive action of β-adrenoceptor blocking drugs.

Although total blood volume may be reduced by propranolol the cardiopulmonary volume appears to be unaltered (Tarazi, Ibrahim, Dustan & Ferrario, 1974). An unchanged cardiopulmonary volume in the presence of a reduced blood volume would suggest systemic vasoconstriction. Tarazi *et al.* (1974) have used the ratio of cardiac output to control pulmonary volume as an index of cardiac performance. After intravenous propranolol this rate fell from 6.03 to 4.65 ($P < 0.001$); conversely isoprenaline increases the ratio. In patients on diuretics in whom plasma volume was reduced to 93% of the normal values, the addition of propranolol increased plasma volume to 99% of the

normal values (Bravo, Tarazi & Dustan, 1975). The changes did not correlate with the further fall of blood pressure seen with propranolol.

Studies on the effect of propranolol on the ranal handling of sodium (Epstein & Braunwald, 1966) showed that β-adrenoceptor blockade appeared to alter the kidney's ability to eliminate sodium in the normal subject. There was a fall in day-time sodium excretion, with a balancing increase in nocturnal sodium clearance, so that overall sodium retention did not occur. The observation was also made that if, while taking propranolol, normal subjects were given added sodium each day, there was a delay in re-establishing equilibrium though, after a lag of several days, urinary sodium output increased and balanced the increased load. Epstein & Braunwald (1966) found that sodium retention with fluid overload was precipitated only in those patients who were dependent on high adrenergic tone to avoid cardiac failure. Gibson *et al.* (1970) confirmed the production of sodium retention by 5 days' propranolol administration that was not seen with the lower dose of practolol used. Singh, Till & Kelly (1971) found that oxprenolol up to 240 mg/day would, like propranolol, reverse the day/night sodium excretion ratio, but, unlike proranolol, when given for 4 to 10 days to patients with moderately severe cardiac disease, it did not cause sodium retention. Sotalol has also been found to reverse day/night sodium excretion in normals (Rice, Ferguson, Delle & Wilson, 1970). Nies, McNeil & Schrier (1971) suggested that the fall in renal blood flow is part of the overall systemic adaptation to β-adrenoceptor blockade which results in enhanced sodium reabsorption secondary to reduction in peritubular blood flow. They found that the local arterial injection of propranolol had no effect on sodium handling. The micropuncture studies of Blendis, Auld, Alexander & Levinsky (1972) supported these findings.

Delayed response of blood pressure and role of cardiac output in anti-hypertensive action of β-adrenoceptor blocking drugs

The immediate and long-term haemodynamic effects of β-adrenergic receptor blockade have frequently been found to be different. Acute and long-term drug administration reduces cardiac output (Gibson, 1974) usually to a similar extent but it is only after long-term administration that blood pressure falls and there is a decline in peripheral resistance (Tarazi & Dustan, 1972; Hansson, 1973).

Interesting observations have been made in young rabbits by Vaughan-Williams & Raine (1974) who found chronic administration of propranolol or practolol produced a reduction in heat weight without altering the inotropic response to isoprenaline. The relative volume of mitochondria was reduced of vascular elements to interfibrillar volume increased, so the gap between capillary and cell wall was reduced. The relative volumes of myofibrils and nuclei were unchanged (Vaughan-Williams, Tasgal & Rain, 1977). Whether these observations are relevant to adult hypertensives is at present unknown, data in man is not available.

Although it was thought by some earlier investigators that an elevated pretreatment cardiac output might be a reliable guide to the hypotensive response to β-adrenoceptor blocking drugs, later experience indicates that there was no correlation between it and reduction in blood pressure by propranolol (Birkenhäger, Krauss, Schalekamp, Kolsters & Kroon, 1971; Tarazi & Dustan, 1972).

A similar haemodynamic response in seen when propranolol is added to a diuretic. Acutely, there is no fall in blood pressure, cardiac output falls (as does renin), with therefore a rise in peripheral resistance; one month later blood pressure was reduced with an adaptation of peripheral resistance (Niarchos, Tarazi & Bravo, unpublished observations, cited by Tarazi, Dustan & Bravo, 1976). While the lowering of cardiac output *per se* does not generally appear to be the reason for the hypotensive effect of β-adrenergic receptor blocking drugs, an exception is the addition of a β-adrenoceptor blocking drug to a patient receiving a vasodilator. When propranolol was added to minoxidil, this resulted in a further fall in blood pressure with a fall in cardiac output and no change in peripheral resistance (Tarazi *et al.*, 1976).

Re-setting the baroreceptors

The anti-hypertensive effect of β-adrenoceptor blocking drugs in mild hypertension is seen rapidly. In the more severely affected patients some delay in the anti-hypertensive effect is seen although the greater part is seen in the first 2 weeks (Prichard & Gillam, 1969). Prichard & Gillam (1969) analysed the blood pressure in groups of patients seen under standardized clinic conditions. In patients receiving propranolol they found that there was a significant fall in blood pressure from the visit to outpatients after stabilization of the dosage of propranolol and 1 month subsequent to this. The visit to outpatients after stabilization of dosage was on average 3 weeks after adjustment of the dosage of propranolol. There was no further drop after another 2 months. The average heart rate was constant throughout. There was no such fall after stabilization of dosage at one, or up to 3 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 & Boakes, 1974). Arterial pressure is a function of cardiac output and peripheral resistance: as propranolol reduces cardiac output this will tend to lower the blood

pressure. However, after intravenous propranolol there is little effect on arterial pressure (Shinebourne *et al.*, 1967; Ulrych, Frohlich, Dustan & Page, 1968) and the reduction in cardiac output is associated with a rise in peripheral resistance. Inhibition of the cardiac sympathetic activity by β-receptor inhibition would, however, be expected to reduce the cardiac contribution to any pressor event, which would therefore be attenuated. There is, for instance, as discussed above, a reduced rise in blood pressure on exercise, the pressor overshoot of Valsalva's manoeuvre is reduced, although the response to painful stimuli is not reduced, and the pressor effect of some stresses is inhibited.

In accord with the delay of onset of full hypotensive effect it has been suggested (Prichard & Gillam, 1964, 1969) that an attenuation of the pressor responses to various stimuli leads to the baroreceptors generating their inhibitory impulses at a lower level of blood pressure and mean pressure falls; with prolonged oral use peripheral resistance is reduced (Tarazi & Dustan, 1972). This is similar to conditions that exist when a hypertensive patient is put to bed. Here there is a reduction in sensory input, hence pressor events, and the baroreceptors over a period of a few days lower blood pressure by a variable amount.

Experiments in dogs have shown that pressor response to carotid occlusion is blunted by chronic propranolol therapy (Dunlop & Shanks, 1969) while short-term administration was without effect. If chronic propranolol administration enhanced baroreceptor sensitivity, an acute reduction in carotid sinus pressure (from carotid occlusion) would leave more inhibitory impulses remaining, than in the absence of chronic propranolol administration, and it is possible that with the higher afferent inhibitory traffic that an occlusion would result in a reduced rise in blood pressure. There is evidence that baroreceptor reflexes in response to pressor effects are blunted in hypertension, and that this reflex is enhanced modestly by propranolol in normals (Pickering, Gribbin, Petersen, Cunningham & Sleight, 1972).

It is possible that a drug with such wide actions as a β-receptor inhibitory drug may act to lower the blood pressure by more than one mechanism. In some cases one of the effects of a β-adrenoceptor blocking drug may be of particular importance, e.g. lowering plasma renin in patients with a high renin, in other instances one of its other effects may become dominant.

β-adrenoceptor blocking drugs in combination with other drugs

β-adrenoceptor blocking drugs have been used in combination with diuretics since the earliest studies. Prichard & Gillam (1969) reported approximately equal numbers of patients received a diuretic in addition to propranolol as on the previous therapy. This is the pattern of our recent randomized trial of bethanidine, methyldopa and propranolol (Prichard *et al.*, 1976).

β-adrenergic receptor blocking drugs have also been used in combination with drugs which inhibit the action of vasoconstrictor nerves either at nerve endings or at the receptor site, and also with vasodilators.

Particular interest has recently been directed toward using β-adrenoceptor blocking drugs with agents that directly relax vascular smooth muscle (Pettinger & Mitchell, 1976). These include hydrallazine and the closely related dihydrallazine and minoxidil. Minoxidil is reserved for the treatment of patients with severe refractory hypertension that is often associated with advanced renal impairment, because it causes serious sodium and fluid retention, inexplicable hypertrichosis (Gottlieb, Katz & Chidsey, 1972; Dormois, Young & Nies, 1975), and when given to dogs in large doses it may produce lesions of the right atrium (Du Charme, Freyburger, Graham & Carlson, 1973).

These vasodilators produce baroreceptor mediated reflex increases in heart rate and cardiac output (Ablad, 1963; Montgomery & Du Charme, 1968; Sannerstedt, Stenberg, Vedin, Wilhelmsson & Werko, 1972). When used alone to treat hypertension they have to be given in relatively large doses and this causes unacceptable levels of tachycardia (dangerous in patients with embarrassed coronary circulation), sodium and fluid retention and other side effects such as headaches, nervousness and gastrointestinal disturbances (Gilmore, Weil, Chidsey, 1970; Hammer, Ulrych & Fries, 1971; Kincaid-Smith, 1975). However, they can be used in antihypertensive treatment at much lower doses and with a marked reduction of untoward reactions if they are administered with a diuretic and drugs which inhibit reflex sympathetic activity. The adrenergic blocking agents also inhibit the vasodilator induced increase of plasma renin activity and this may be an important aspect of the combined anti-hypertensive regime (Pettinger & Keeton, 1975).

One approach of using β-adrenergic receptor blocking drugs in combination with vasodilators is to give just large enough doses of the former to inhibit reflex sympathetic activity. Zacest, Gilmore & Koch-Weser (1972) achived good control of supine and standing blood pressure in this manner in 17 of 23 patients without untoward reactions by giving a diuretic, 80–160 mg (average 143 mg) of propranolol daily and 40–400 mg (average 225 mg) of hydrallazine. Chronic oral doses of hydrallazine of this magnitude are unlikely to produce a 'lupus phenomenon' (Zacest, 1975). An alternative approach is to use larger amounts of the β-adrenoceptor blockers than is necessary to inhibit the side effects due to the vasodilators. Hansson, Olander, Aberg, Malmcroud & Westerlund (1971b) reported successful

results in 17 patients with average daily doses of 320 mg propranolol (maximum 640) and of hydrallazine 137 mg (maximum 200 mg).

Other β-adrenergic receptor drugs were used in combination with hydrallazine or dihydrallazine in varied doses and with mixed anti-hypertensive results: oxprenolol (Aenishanslin, Pestalozzi-Kerpal, Dubach, Imhof & Turri, 1972; Tuckman *et al.*, 1972; Tuckman, Messerli & Hodler, 1973; Siitonen, Janne, Keyrilainen, Koskinen, Leskinen, Pitkajarvi & Reinikainen, 1974; Freeman & Knight, 1975), alprenolol (Sannerstedt *et al.*, 1972), pindolol (Persson, 1975), practolol (Dahr, 1972) and atenolol (Wilcox & Mitchell, 1977).

It is probably necessary to use the more effective vasodilator, minoxidil, in patients with severe hypertension that is often associated with poor renal function. Wilburn, Blaufuss & Bennett (1975) gave a combination of average daily doses of propranolol 475 mg, minoxidil 33 mg, and frusemide 578 mg, and found it effective in patients whose hypertension was resistant to more conventional treatment. Other investigators used smaller doses of propranolol in combination with minoxidil and have successfully treated previously severe and refractory cases of hypertension (Gottlieb *et al.*, 1972; Pettinger & Mitchell, 1976; Dormois *et al.*, 1975).

Prazosin hydrochloride is a quinazoline derivative that is a peripheral vasodilator that probably acts distal to the vascular α-receptors and probably at those receptors in an unconventional manner (Constantine, 1974). However, unlike the vasodilators discussed above it does not produce obvious tachycardia or an increase in cardiac output (Lund-Johansen, 1974).

Prazosin lowers blood pressure when used alone and the anti-hypertensive effect is increased when it is administered with propranolol (Stokes & Weber, 1974). Kincaid-Smith, Fang & Laver (1973) reported that it produces marked falls in blood pressure when combined with large doses of propranolol in patients with severe refractory hypertension. Kincaid-Smith (1975) later reported that double-blind studies with a diuretic, β-adrenoceptor blocking drug and hydrallazine or prazosin showed equal hypotensive effects for both regimes. Prazosin, however, caused fewer side effects. The major side effect due to prazosin is episodes of acute hypotension which sometimes occur within 3 h after the initial dose of the drug (Meek, Mamtora & Gabriel, 1976). Symptoms suggestive of postural hypotension were found initially with the addition of prazosin to a diuretic and propranolol, or oxprenolol, or atenolol but more prolonged use up to a dosage of 15 mg daily of prazosin was not associated with postural or exercise hypotension (Marshall, Barritt, Pocock & Heaton, 1977).

β-adrenoceptor blocking drugs have been used in combination with those drugs that act by inhibiting the action of vasoconstrictor nerves, either at the nerve endings or α-adrenoceptor site. The combination of propranolol with either methyldopa or sympathetic inhibitory bethanidine showed at least an additive effect or possibly a potentiating action. However, the combination of treatment was at the expense of some postural and exercise hypotension, absent on propranolol alone (Day & Prichard, 1971; Prichard, 1976). A similar additive effect has been reported with atenolol and methyldopa (Webster, Jeffery, Galloway, Petrie & Barker, 1977; Wilson, Scott & Abdel-Mohsen, 1977). The use of the α-adrenoceptor drug phenoxybenzamine with propranolol also resulted in marked fall in blood pressure on assuming the erect posture (Beilin & Juel-Jensen, 1972). There have been reports of the use of phentolamine in conjunction with β-adrenoceptor blocking agents but the duration of action of phentolamine is probably too short to be of great value (Dawson, Smith & Johnson, 1977) although others have found more encouraging results (Majid, Meeran, Benaim Sharma & Taylor, 1974). Labetalol is a β-adrenoceptor blocking drug which in addition possesses some α-receptor blocking activity, but less than a quarter that of its β-adrenoceptor blocking action (Richards, Prichard, Boakes, Tuckman & Knight, 1977). Our experience with this drug in the long-term treatment of hypertension indicates that many patients can be controlled without postural or exercise hypotension although this may be seen at large doses (Prichard, Thompson, Boakes & Joekes, 1975; Prichard & Boakes, 1976). Use of labetalol has also been made in the treatment of acute hypertensive emergencies. It has advantages over some of the alternative methods of treatment as given by slow intravenous infusion; it produces a smooth reduction in blood pressure (Brown *et al.*, 1977).

Long term value of β-adrenergic receptor blocking drugs

Besides the long term advantages of the absence of postural or exercise hypotension β-adrenergic receptor blocking drugs have the possible advantages of long term cardioprotective and vasculoprotective effects.

Cardioprotective action

There is evidence that the long-term administration of β-adrenergic receptor blocking drugs may exert a cardioprotective effect. Firstly they reduce the tachycardia and arrhythmias of everyday stress, in pilots undergoing simulated flight (Eliasch, Rosen & Scott, 1967), public speaking (Taggart, Carruthers & Somerville, 1973a) racing car driving (Taggart & Carruthers, 1972) motor car driving (Taylor & Meeran, 1973a) and while travelling as a passenger in car or by air (Taylor & Meeran, 1973b).

Secondly there is evidence that β-adrenoceptor blocking drugs reduce the size of myocardial infarction. Studies in experimental animals suggest that β-adrenergic blocking drugs reduce the size of acute myocardial infarcts and that this is reflected in associated S.T. segment changes (Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971). It has been shown that various β-adrenergic receptor blocking drugs reduce the ECG changes associated with ischaemia at rest and on exercise (Prichard, Aellig & Richardson, 1970). Pelides, Reid, Thomas & Shillingford (1972) using multiple orecardial leads demonstrated that the acute administration of practolol reduces the degree and area of S.T. segment depression in patients with acute myocardial infarction. These observations have been confirmed (Hjalmarson, Waagstein & Waldenstrom, 1976). Further evidence has been afforded by the observations of Fox, Chopra, Portal & Aber (1975). It was found that ischaemic patients matched for severity of pain, sex, age, previous cardiac history, had significantly less severe ischaemic episodes if they were receiving β-adrenergic receptor blocking drugs (a significantly lower incidence of final diagnosis of transmural infarct, and a higher incidence of coronary insufficiency) compared to those patients who were not on β-adrenergic receptor blocking drugs.

Although a number of the studies can be criticized on methodological grounds (Fitzgerald, 1976), a number of studies in post infarction patients have suggested that there is a reduction in recurrence of myocardial infarction and or sudden death in those patients given β-adrenergic receptor blocking drugs (Wilhelmsson, Vedin, Wilhelmsen, Tibblin & Werko, 1974; Ahlmark, Saetre & Korsgren, 1974; Multicentre Trial, 1975). A similar effect has been observed in patients with angina pectoris (Lambert, 1976).

On balance therefore it seems that there is evidence for a cardioprotective effect in high risk patients, i.e. post myocardial infarction. The use of other antihypertensives has not been associated with a reduction in incidence of myocardial infarction even though other complications of hypertension have been reduced. A recent study has suggested that propranolol treated patients with hypertension have a lower incidence of myocardial infarction than those not given β-adrenergic receptor blocking drugs (Stewart, 1976).

Vasculoprotective action

β-adrenergic receptor blocking drugs, other than merely lowering the blood pressure at rest or on exercise, have what could be termed an immediate vasculoprotective effect as they reduce the rate of rise of systolic pressure and therefore the force of the systolic pressure wave. However they have a number of other actions that may be beneficial in inhibiting vascular degeneration.

β-adrenergic receptor blocking drugs do not effect the rise in catecholamines associated with various forms of stress, however they abolish the rise in free fatty acids and triglycerides in response to racing car driving (Taggart & Carruthers, 1972; Taggart, Carruthers & Somerville, 1973b) public speaking (Taggart, Carruthers & Somerville, 1973a) and being a passenger in an airliner (Carruthers, Taggart & Somerville, 1973). This action may be important in breaking a postulated chain on the effect of stress producing atheroma (Carruthers, 1969; Carruthers *et al.*, 1973). Cholesterol levels are not affected in man but experimentally the administration of propranolol to rabbits fed a high cholesterol diet reduces the development of atheromatous lesions (Whittington-Coleman, Carrier & Doublas, 1973).

β-adrenergic receptor blocking drugs have a number of other effects that may be relevant to a long term vasculo-protective effect. Propranolol, in relatively small doses, was found to return the abnormal sensitivity of platelets to aggregation by adenosine diphosphate in patients with angina pectoris to the level seen in normals (Fishman, Weksler, Christodoulou, Smithen & Killip, 1974). Another observation that may help blood flow in compromised vessels is the observation that alprenolol reduces blood viscosity (Dintenfass & Lake, 1976). Lastly, propranolol has been shown to reduce the rise in clotting factor VIII induced by adrenaline (Ingram & Jones, 1966).

Selection of patients for treatment with β-adrenergic receptor blocking drugs

There have been attempts to identify factors that would be of predictive value in forecasting the response of a given patient to a β-adrenergic receptor blocking drug. Renin levels have been suggested to be of value (Buhler *et al.*, 1972, 1975), but others have disputed these findings. Old patients were found to respond less well to β-adrenergic receptor blocking drugs, as renin levels fall with age (Buhler *et al.*, 1975). Contrary views on renin have been discussed above and others have found no useful predictive factors. There has been no correlation found between cardiac output and response to beta blocking drugs (Birkenhager *et al.*, 1971; Tarazi & Dustan, 1972; Hansson, Zweifler, Julius & Ellis, 1974), no predictive value of age and blood volume (Birkenhager *et al.*, 1971; Hansson *et al.*, 1974) peripheral resistance, urinary adrenaline and noradrenaline (Hansson *et al.*, 1974; Meekers, Missotten, Fagard, Demuynck, Harvengt, Pas, Billiet & Amery, 1975) aldosterone levels, heart rate response to isoprenaline all failed to be of any value in predicting response to β-adrenoceptor blocking drugs (Hansson *et al.*, 1974).

Pressor response to β-adrenoceptor blocking drugs

There have been a number of reports of rises in blood pressure in hypertensive patients given β-adrenergic

receptor blocking drugs. It has been observed in β-adrenoceptor blocking drugs regardless of the presence or absence of cardioselectivity, intrinsic sympathomimetic activity or membrane stabilizing action. It was reported with acute administration of pronethalol (Prichard, 1964) in the first report of β-adrenoceptor blocking drugs in hypertension and recently after oral use of a number of agents, atenolol (Amery, Billiet, Boel, Fagard, Reybrouck & Willems, 1976b), oxprenolol (Crook & Raftery, 1972), propranolol (Drayer, Keim, Weber, Case & Laragh, 1976) and pindolol (Waal-Manning & Simpson, 1975; Bjerle, Jackson & Agert, 1975).

It has been suggested that the possession of intrinsic sympathomimetic activity (ISA) was the reason for this penomenon, but as it is seen with drugs without ISA, i.e. atenolol and propranolol, it cannot be the general explanation. Also β-adrenoceptor stimulation would generally be expected to produce a fall in peripheral resistance and thus of blood pressure. It is just possible that stimulation of presynaptic β-adrenoceptors (Adler-Graschinsky & Langer, 1975; Stjarne & Brundin, 1975) could facilitate the release of noradrenaline and thus result in a rise in blood pressure from α-adrenoceptor stimulation. The suggestion that blockade of peripheral β-adrenoceptors allows unopposed α-adrenoceptor activity also seems difficult to accept as the explanation, as the phenomenon is seen with the cardioselective agent atenolol. Fluid retention could be the explanation; this can occur with all β-adrenoceptor blocking drugs. It was seen with the patients on propranolol (Drayer *et al.*, 1976) and atenolol (Amery *et al.*, 1976b), weights of patients were not reported in the reports of a rise in pressure on pindolol.

Side effects

In the large series of 311 patients reported by Zacharias *et al.* (1972) side effects from propranolol in 55 patients that were 'tolerable', in seven dose limiting, and in 26 patients the drug was stopped. It seems that the overall incidence of side effects is probably at least no more than other potent anti-hypertensive drugs (Prichard & Gillam, 1969; Zacharias *et al.*, 1972; Prichard *et al.*, 1976).

Two important untoward effects from β-adrenergic receptor blocking drugs that should be avoided with foresight in patient selection: heart failure and asthma. Patients in heart failure, or patients with incipient left ventricular insufficiency (they may have no signs of heart failure on physical examination or chest X-ray) are critically dependent on sympathetic activity to the heart to maintain their cardiac output. Patients with left ventricular insufficiency should not be given a β-receptor blocking drug without prior administration of digitalis and diuretics. If these drugs alleviate the dyspnoea it is reasonable, with extra caution, to start the patient on a β-adrenoceptor blocking drug. There have been reports that patients who have been put into failure by propranolol have been subsequently able to tolerate the drug after the administration of digoxin and a diuretic (Gillam & Prichard, 1966; Amsterdam, Gorlin & Wolfson, 1969). If heart failure is uncontrolled, β-adrenergic receptor blocking drugs should not be given. β-adrenoceptor inhibitory drugs with intrinsic sympathomimetic stimulating action can also precipitate heart failure; alprenolol (Lund-Larsen & Sivertssen, 1969; Lyon & Nevins, 1971), INPEA (Del Bianco, Bavazzano, Frianchi & Sicuteri, 1966), oxprenolol (Bianchi, Lucchelli & Starcich, 1969; Forrest, 1972) and pronethalol (Apthorp, Chamberlain & Hayward, 1964). There is no evidence that the direct membrane effect contributes significantly to heart failure (Coltart, Gibson & Shand, 1971).

Caution must be exercised with small doses as the most dramatic change in the sympathetic environment of the heart takes place when treatment is commenced with a β-adrenergic receptor blocking drug, i.e. the small starting dose (Prichard, 1974). Reports of adverse reactions have confirmed the greatest danger of precipitating heart failure is at the start of treatment. In one study seven out of eight life threatening adverse reactions due to impaired cardiac function, were receiving a very small dose of less than 40 mg a day of propranolol (Greenblatt & Koch-Weser, 1974). The small percentage increase in dose levels entails less risk of suddenly precipitating heart failure than when dosage is commenced. We have given β-adrenoceptor blocking drugs with a total of over 300 patients with dosage of up to 4000 mg of propranolol or sotalol daily, our only case of sudden cardiac decompensation was at the commencing dose of 10 mg propranolol four times daily.

A precipitate fall in blood pressure is rare after oral propranolol; these have been reported in patients with cardiomyopathy (Bett, 1968; Taylor, 1968). It has occurred after intravenous propranolol (Stephen, 1966) and rarely after oral and intravenous practolol (Wiseman, 1971).

A common side effect from β-adrenergic receptor blocking drugs are cold extremities, presumably as a result of peripheral vasoconstriction due to the reduced cardiac output and peripheral β-adrenergic receptor blockade. It was reported in 25 out of the series of 311 patients of Zacharias *et al.* (1972) necessitating stopping the drug in three patients.

All non-selective β-adrenergic receptor blocking drugs are likely to produce a significant increase in airways resistance in asthmatic subjects due to inhibiting sympathetic tone in bronchial smooth muscle (Beumer, 1974). Even the cardioselective agents only show modest selectivity; a serious increase in airways resistance has been reported with practolol (Waal-Manning & Simpson, 1971).

Glycogenolysis is controlled in part by β-adrenoceptors and therefore β-adrenergic receptor

blockade could interfere with this mechanism of increasing blood sugar. Hypoglycemia is very rare but insulin indiced hypoglycemia may be exaggerated in diabetics on propranolol. It has also been reported in children recovering from anaesthesia, and partial gastrectomy patients (Dollery *et al.*, 1969).

A number of central nervous system side effects occur as most β-adrenergic receptor blocking drugs readily cross the blood brain barrier. They include depression, often dose related, confusion, blurring of vision and visual hallucinations have been reported rarely. Troublesome dreams are not infrequent in patients taking large doses, vivid dreams occurred in eleven of the patients of Zacharias *et al.* (1972). Dreams and insomnia can usually be controlled by taking the last dose no later than early evening, or even before, and also reducing the last dose if necessary. The occurrence of indigestion often with some nausea is a not uncommon side effect which can often be avoided by taking the drug with meals (Prichard & Gillam, 1969). Diarrhoea is unusual (Zacharias *et al.*, 1972), constipation is more common than diarrhoea with practolol (Wiseman, 1971). Skin rashes, purpura (with or without thrombocytopenia) paresthesia and alopecia have been reported after propranolol.

One advantage of β-adrenergic receptor blocking drugs is the lower incidence of notcuria that has been seen on propranolol than with other potent anti-hypertensive drugs (Prichard & Gillam, 1969). Disturbances of sexual function are uncommon. There were no cases of impotence in the series of Zacharias *et al.* (1972); of eight patients who had impotence on previous therapy, in two it was improved, in four it disappeared, while in the other two it was unchanged.

In recent years a number of severe sensitivity reactions have been reported with practolol, so that long term use has ceased. These reactions have included a systemis lupus syndrome (Raftery & Denman, 1973), dry eyes, corneal ulcers, skin lesions particularly a psoriasiform eruption which may occur from 3 weeks and up to 3 years (on average 10 months) after starting practolol (Felix, Ive & Dahl, 1974) and sclerosing peritonitis (Brown, Baddeley, Read, Davies & McGarry, 1974).

The occurrence of adverse reactions to β-adrenergic receptor blocking drugs are uncommon except with practolol, particularly with correct patient selection, i.e. excluding cases of heart failure and asthma. It is soon after initiation of therapy that severe adverse reactions occur, even with small doses, but once therapy has been started gradual increase in dosage is most unlikely to be associated with precipitate adverse reactions.

Conclusion

While most of the pioneer work in the use of beta receptor blockade in the treatment of hypertension was performed with propranolol, other beta blocking drugs that have been tested have also been found to possess an antihypertensive effect. This would be expected if the mode of action is a function of β-adrenergic receptor blockade and not some associated property. Like other potent anti-hypertensive drugs it is important to give proper attention to the dosage required; titration of dose is required for optimum results. There is evidence that β-adrenergic receptor blocking drugs are of similar potency to adrenergic neurone inhibitory drugs and methyldopa. β-adrenergic receptor blocking drugs have the advantage of the absence of postural and exercise hypotension and possible long term benefits in reducing the manifestations of ischaemic heart disease.

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