Treating hypertension *The place of beta blockade*

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Hypertension is now usually discovered at routine examination or in patients who present with symptoms unrelated to the level of blood pressure. Investigation will rarely reveal a curable cause. Age, sex, and height of blood pressure usually decide whether medication should be started. These symptomless patients then face many years of swallowing tablets. Clearly, the ideal treatment regimen should lower blood pressure independently of posture, without inducing troublesome side-effects, and should be simple to prescribe and take. To the prescriber simplicity means confidence in potency and a dose range that is easy to adjust. To the patient it will seem a poor bargain to have to swallow a large number of tablets several times a day for a statistical chance of a longer life, especially if the tablets are not innocuous.

How closely does beta blockade approach this ideal?

POTENCY

All beta blocking drugs at present available have been shown to lower blood pressure (Morgan *et al.*, 1974; Davidson *et al.*, 1976). After recognising the hypotensive action of propranolol, Prichard and Gillam (1969) assessed its potency in a group of patients previously used in a trial to compare guanethidine, bethanidine, and methyldopa. They found propranolol to be of similar potency to the previously used drugs. Our own within-patient double-blind comparison of oxprenolol and methyldopa (Barritt *et al.*, 1976) showed virtually identical pressure falls with both drugs. Thomas and co-workers (1976) also compared methyldopa, oxprenolol, and spironolactone and found no significant differences between the hypotensive effects of the three agents.

Hydrochlorothiazide 50 mg daily was compared with timolol in a double-blind within-patient trial by Chalmers and co-workers (1976) and found to be

slightly less potent. Petrie *et al.* (1975) have also shown that beta blockade causes a slightly greater fall in blood pressure than a thiazide diuretic in a trial which compared atenolol with 5 mg bendrofluazide daily.

We assessed oxprenolol used alone in 40 patients and found the range of fall in mean blood pressure was 0 to 40 mmHg (average fall 20 mmHg) (Barritt and Marshall, 1977). The maximum sustained fall in pressure in any patient was 62 mmHg systolic, and 42 mmHg diastolic (phase 5). These results are based on multiple measurements made before and during a prolonged period of treatment. It seems to be the case that when beta blocking drugs are compared with adrenergic neurone blocking drugs, methyldopa, or diuretics there is little to choose between them in terms of potency. Whichever agent is used, there will be a good fall in blood pressure in some patients and little in others. This is the trial and error element in the treatment of each hypertensive patient.

DOSE RANGE, ASSESSMENT OF RESPONSE, AND FREQUENCY OF ADMINISTRATION

Beta-blockade was slow to gain popularity partly because it was first suggested that the range of dosage with propranolol and oxprenolol was wide, and that the full effect might take as long as two months to be evident. It was disappointing to find that as the dose was slowly increased little further was achieved. Recent investigations leave little doubt that the effective dose range is in fact relatively narrow with most beta blocking agents, and that their full effect is known in as little as two weeks (Galloway *et al.*, 1976; Barritt and Marshall, 1977; Marshall *et al.*, 1977b).

It can now be predicted with confidence that, if a group of hypertensive patients is given propranolol or oxprenolol in a dose of 80 or 160 mg twice daily or atenolol 100 mg once daily, the average fall in mean blood pressure will be 20 mmHg and the range 0 to 40 mmHg. The result of treatment will be

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evident at the first out-patient visit. Though the plasma half-lives of these drugs suggested that they would need to be given three times daily, it is clear that the effect on heart rate, and especially blood pressure, may last 24 hours or more. The evidence that atenolol is as effective when given once daily as in divided doses appears conclusive (Woolfson and Knapp, 1976; Marshall *et al.*, 1977b). The same may well be true of propranolol and other beta blocking drugs (Wilson *et al.*, 1976). Beta blockade can be used as a simple once daily regimen for hypertension, and its effect fully assessed within two weeks.

SIDE-EFFECTS

Postural hypotension is exceptional with beta blockade, as is impairment of sexual performance or mental slowing, which are the major disadvantages of other current therapy. Used carefully in selected patients, side-effects are few. Nevertheless, beta-blockade invariably lowers cardiac output and is, therefore, quite unsuitable for patients with left ventricular failure. Though some beta blocking agents appear to have little effect on airways resistance, it seems wise to regard a history of wheezing as a contraindication to their use. The only common and undisputed side-effect of beta blockade is the development of cold hands and feet. When the specific question is asked, over one-quarter of patients taking beta blocking drugs admit to the development of cold hands and feet (Marshall *et al.*, 1976). Cold extremities are associated with absence of foot pulses and it is our practice to look for symptoms and signs of peripheral vascular disease, and if these are present to avoid beta blockade or use it with caution. Propranolol and atenolol commonly produce resting heart rates of 50 beats a minute. This is a good guide to the physician that the tablets have been taken, but bradycardia is not usually associated with symptoms unless the patient also has sinoatrial disease. Beta blockade is best avoided in insulin-dependent diabetics. Not only may the treatment mask the symptoms and signs of hypoglycaemic attacks, but may also help to induce hypoglycaemia by inhibiting hepatic gluconeogenesis.

No discussion of long-term treatment with beta-blockade can ignore the emergence of the practolol syndrome. All who prescribe these agents must be aware of its severity (Marshall *et al.*, 1977a). The use of beta blocking agents in therapeutics is an example of the oscillations in the popularity of a new drug, as described by Lawrence (1966). Initial interest was small, but through the persistent work of Prichard and his colleagues, they became acceptable antiarrhythmic and hypotensive agents.

Within a few years they were widely prescribed and claimed to be the best treatment for diseases varying from schizophrenia to anxiety, thyrotoxicosis, and hypertrophic obstructive cardiomyopathy. Rashes, eye disease, and most important life-threatening peritoneal fibrosis leading to progressive intestinal obstruction, associated with practolol therapy, have justly made many physicians hesitant to use long-term beta-blockade. Such adverse reactions in the few have undoubtedly to be balanced against the unquestioned benefits to the many patients who have been treated. Each new beta blocking agent will need to be monitored with the utmost vigilance, but it does now seem certain that no sinister syndrome will follow the use of propranolol or oxprenolol, both of which have been prescribed in large quantities over a number of years.

How does beta-blockade lower blood pressure?

It has been suggested that beta-blockade may lower blood pressure (1) by reducing both the cardiac output at rest and the increases in output induced by exercise and catecholamine activity, this adjustment leading to the resetting of cardiovascular reflexes; (2) by suppressing plasma renin activity; (3) by a central action in the brain. There are serious objections to accepting any of these three alone as explaining the mode of action.

Certainly the most obvious effect of beta-blockade is a slowing of the heart rate which is accompanied by a measurable fall in cardiac output. Unless the peripheral resistance rises, blood pressure must fall, and after a period of time the baroreceptors may reset at a lower level of activity and a sustained fall in resistance may result. This would lead to the idea that hypertensive patients with high levels of cardiac output might respond better than those with low cardiac output (Ulrych *et al.*, 1968). The resting heart rate gives some indication of the level of cardiac output. Our own analysis shows that the relation between initial heart rate, the fall of heart rate with the drug, and the fall in pressure with oxprenolol, is so variable that reduction of cardiac output alone seems unlikely to account for its hypotensive action. Not only is initial heart rate a poor guide to response to treatment (Fig.) but in addition there is little relation between the fall in heart rate that occurs with the drug and the fall in blood pressure. If a fall in cardiac output is invariable with beta blockade a fall in pressure is not.

Most beta blocking drugs have been shown to depress levels of plasma renin activity (Bühler *et al.*, 1972). The exception is pindolol (Weber *et al.*,

Fig. Initial heart rate plotted against blood pressure fall in 40 patients treated with oxprenolol alone. There is a slight tendency for those with slower initial heart rates to have a greater fall in pressure (correlation coefficient -0.214 , SE 0.160).

1974). Thus the renin state of the patient could play a major part in determining the response. Indeed Bühler and co-workers, who divide their hypertensive patients into high, normal, and low renin groups, have produced evidence that the high renin group respond well to propranolol and the low renin group poorly. Other workers have failed to confirm this. Stokes *et al.* (1974) measured plasma renin activity in hypertensives treated with propranolol. They found a sustained suppression of the renin-angiotensin system during treatment, but the degree of suppression correlated poorly with the fall in blood pressure. Moreover, when pindolol was given instead of propranolol, plasma renin activity increased, but blood pressure did not. Thomas and co-workers (1976) also measured plasma renin activity and divided their hypertensive patients into three groups (according to their renin levels). All patients received oxprenolol and the falls in blood pressure were equal in each group. It seems clear, therefore, that the renin status of the patient is a poor predictor of the response to beta blockade.

A hypotensive effect mediated via the sympathetic neurones in the central nervous system has been suggested. The blood pressure in rabbits can

be lowered by injecting the laevo-isomer of propranolol into the cerebral ventricle, an effect not produced by dextropropranolol which lacks beta-blocking activity (Lewis *et al.*, 1973). This possible mechanism of action needs to be further investigated in man. The fact that beta blocking drugs which freely pass the blood brain barrier are no more potent than others which do not, gives no support to this concept.

Can the physician predict good responders to beta-blockade?

There seems to be no clear answer, for age, sex, initial heart rate, and the initial height of blood pressure are not helpful in predicting the fall in blood pressure. However, if there is a satisfactory record of pretreatment blood pressure each patient's response to this form of treatment can be assessed quite quickly.

Additional agents

As the size of blood pressure fall with all the hypotensive agents is limited, it follows that the higher the initial blood pressure, the more likely it is that more than one agent will be required. If beta-blockade fails to lower blood pressure to an acceptable level, the addition of a different type of hypotensive agent can be expected to cause a further fall. The addition of a thiazide diuretic produces on average a further fall in mean blood pressure of 13 per cent with few side-effects, at the cost of one extra tablet daily (Marshall *et al.*, 1977c). The argument could be put that the rarity of symptomatic side-effects with diuretics should make them the agent of first choice. In our view preference goes to beta blocking drugs in view of their slightly greater potency, their undisputed antiarrhythmic action, and the possibility that they may reduce the incidence of myocardial infarction. A proportion of severe hypertensives will need a third or fourth agent. Success has been reported by adding methyldopa (Scott *et al.*, 1977), hydralazine (Wilcox and Mitchell, 1977), or prazosin (Marshall *et al.*, 1977c) to treatment with beta-blocking drugs and diuretics.

There is still no escaping the element of trial and error in treating hypertension. None the less, a rational approach is easy to see. The four principles are (1) to give one agent and assess its effect; (2) the higher the initial pressure the more likely it is that more agents will be needed; (3) to choose agents in ranking order of their acceptability to the patient; (4) to aid compliance, minimise the number of tablets.

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