Treatment of Hypertension with Beta-adrenoceptor Blocking Drugs

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Beta-adrenoceptor blocking drugs are very widely prescribed in the treatment of hypertension, often as drugs of first choice, and are regarded as being remarkably free of serious adverse effects[1]. The purpose of this study was to assess the efficacy of treatment with such drugs, and in particular the incidence and range of adverse effects.

Method

We reviewed the records of 346 hypertensive patients seen consecutively at our hypertension clinic over the years 1978–1980 who were currently or previously on treatment with beta-adrenoceptor blocking drugs.

Beta-adrenoceptor blocking drugs are prescribed in our clinic following unsuccessful treatment with a thiazide diuretic alone, or as agents of first choice, provided the standard contra-indications are absent (a history of obstructive airways disease, cardiac failure, cardiac conduction defects, peripheral vascular disease and Raynaud’s phenomenon or insulin dependent diabetes). The blood pressure is considered to be controlled when the standing diastolic pressure (phase IV) is maintained below 100 mm Hg.

Specific adverse effects of treatment are not routinely sought, but volunteered symptoms are recorded. All patients are weighed at every attendance (by the same nurse throughout this study). The records were analysed for: (a) number and efficacy of drugs required in treatment; (b) major adverse effects specifically attributed to the beta-adrenoceptor blocking drug, which were of sufficient severity to require withdrawal of treatment; (c) minor adverse effects not necessitating withdrawal, but sometimes leading to reduction in dosage, and (d) weight change greater than 2.8 kg (6 lb), with details of duration of therapy and dose of drug.

A supplementary study determined the effect on pulse and blood pressure of doubling the dose of beta-adrenoceptor blocking drug in nine out-patients with mild to moderate hypertension, controlled on treatment with propranolol alone, in divided doses ranging from 80–400 mg daily. Pulse and blood pressure were recorded with the patients at rest and on exercise. All recordings were made in an independent clinic by a single observer using a standard mercury sphygmomanometer and employing a standardised two-step exercise test. Measurements were made on two separate occasions before doubling the dose of propranolol (the second test being taken as a base-line), and again six weeks after doubling the dose.

Results

The great majority of patients had mild to moderate essential hypertension. Hypertension was secondary to chronic renal disease in five per cent. There were approximately equal numbers of males and females in the study.

Hypertension was controlled in 30 per cent (101 patients) with beta-adrenoceptor blocking drugs alone; in 40 per cent (134 patients) using a combination of beta-adrenoceptor blocking drug and a thiazide diuretic; and in 30 per cent (111 patients) using three drugs, beta-adrenoceptor blocking drug, thiazide diuretic, and vasodilator or adrenergic neurone blocking agent.

Table 1 records the specific beta-adrenoceptor blocking drug used and shows the number of patients and numbers who required the drug to be withdrawn. This indicates that the majority were treated with propranolol, and one in four of these patients stopped the drug because of major adverse effects. Thirteen per cent of patients taking atenolol and 16 per cent taking oxprenolol stopped the drug. Overall, 22 per cent of patients on beta-blockers stopped therapy as a result of major adverse effects.

Table 1. Beta-blocker used and withdrawals because of adverse effects.

| Drug        | No. of patients | Withdrawals | %   |
|-------------|-----------------|-------------|-----|
| Propranolol | 235             | 57          | 24  |
| Atenolol    | 79              | 13          | 13  |
| Oxprenolol  | 25              | 4           | 16  |
| Acebutolol  | 3               | 1           | 33  |
| Labetalol   | 4               |             |     |
| Total       | 346             | 75          | 22  |

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Table 2. The major adverse effects necessitating withdrawal.

| Symptoms                      | No. |
|-------------------------------|-----|
| Cold extremities              | 18  |
| Raynaud’s phenomenon          | 24  |
| Lethargy                      | 10  |
| Weight gain                   | 10  |
| Headaches/nightmares          | 10  |
| Depression                    | 6   |
| Nausea/diarrhoea (atenolol)   | 6   |
| Dyspnoea, bradycardia         | 2   |
| Impotence                     |     |
| Total                         | 75  |

Table 3. Minor adverse effects not necessitating withdrawal.

| Symptoms                  | No. |
|---------------------------|-----|
| Vascular                  | 14  |
| Weight gain               | 6   |
| Central nervous system    | 17  |
| Lethargy                  | 14  |
| Cardio-respiratory        | 4   |
| Gastrointestinal          | 2   |
| Total                     | 57  |

Tables 2 and 3 show the nature of the major and minor adverse effects experienced, lethargy, Raynaud’s phenomenon and cold extremities being the most frequent. Less common were weight gain, nightmares and depression (depression usually with propranolol), dyspnoea, mild bronchospasm, and diarrhoea (the latter only with atenolol). Aggravation of intermittent claudication occurred in four patients, two of whom had frank peripheral ischaemia of the toes.

Weight gain greater than 2.7 kg while on treatment with beta-adrenoceptor blocking drugs occurred in 110 patients (59 males and 51 females). Sixteen patients either stopped beta-adrenoceptor blocking drugs or were placed on dietary restriction due to weight gain. The details of weight gain in relation to specific agents are shown in Table 4. It can be seen that weight gain was more frequent and severe with propranolol than with atenolol.

Table 4. Weight gain of more than 2.7 kg (6 lb).

| Beta-blocker | No. (%) of patients who gained weight | Average weight gain and range (kg) | Average follow-up (months) | Mean dose (mg) |
|--------------|--------------------------------------|-----------------------------------|----------------------------|---------------|
| Propranolol  | 93 (40)                              | 5.75 (3-26)                       | 36                         | 240           |
| Atenolol     | 11 (14)                              | 4.3 (3-13)                        | 12                         | 100           |
| Oxprenolol   | 6 (24)                               | 6 (3-10)                          | 36                         | 320           |

In the sub-groups of patients treated with propranolol the mean of the recordings of pulse and blood pressure, both before and after doubling the dose of beta-adrenoceptor blocking agent, are shown in Table 5.

From these results it can be seen that despite an increase in beta-blockade (as demonstrated by a reduction in both resting pulse and exercise-induced tachycardia), there is no associated reduction in either systolic or diastolic blood pressure. Unfortunately, due to the small numbers involved, these results do not reach statistical significance.

Table 5. Mean of results.

|                     | Base-line | On exercise |
|---------------------|-----------|-------------|
| Initial dose of propranolol: | | |
| Pulse               | 76        | 74          | 96          |
| BP                  | 147/94    | 154/106     | 154/106     |
| Double dose of propranolol: | | |
| Pulse               | 63        | 66          | 86          |
| BP                  | 147/100   | 151/106     | 157/102     |

Discussion

Although beta-adrenoceptor blocking agents are effective anti-hypertensive agents, this study shows a high incidence of adverse effects associated with their use. The incidence of adverse effects with any drug therapy is frequent when elicited by direct questioning in open studies; we would emphasise that adverse effects are not routinely sought in our clinic, but volunteered adverse effects are recorded. The range of adverse effects we have met is widely quoted in the literature[2], some, such as weight gain and peripheral ischaemic gangrene, being less well documented.

All beta-adrenoceptor blocking agents seem equally effective in the treatment of hypertension[4] but the use of relatively cardio-selective agents does not lessen all adverse effects. For example, fatigue is reported as commonly with metoprolol as it is with propranolol[5]. We feel that fatigue has attracted insufficient attention as an adverse effect. Stone[6] has claimed that at least 30 per cent of patients with 'full beta-blockade' complain of weakness of the leg muscles and an inability to hurry on hills or stairs.

Weight gain has been reported previously[7,8] as a consequence of treatment with beta-adrenoceptor blocking agents, with a much lower incidence and less severity than in our series, but often it is not even mentioned in lists of adverse reactions. In our experience, withdrawal of therapy leads to return to pre-treatment weight. The mechanism of weight gain may be related to the complex effects of blockade of B2 receptors on adipose cells[9]. Few patients reported increased appetite. Weight gain has been shown to be less severe with atenolol compared to propranolol[10] and our experience supports this finding.

Control of hypertension lessens the risk of stroke[11], and with the availability of agents causing less serious adverse effects than those encountered with early drugs, treatment has been applied to vast numbers of patients with increasingly less severe hypertension. We feel scant regard has been paid to the quality of the lives of these patients on treatment. This is shown by the high incidence of minor but troublesome adverse effects in our study, which led to one in five patients stopping their drug. A similar proportion of patients stopped treatment.

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in the recent MRC trial of thiazides and beta-adrenoceptor blocking drugs[12].

In our supplementary study, which involved doubling the dose of beta-adrenoceptor blocking drug in a small group of hypertensives controlled on propranolol alone, we observed no fall in blood pressure, despite an increase in the degree of beta-blockade as demonstrated by the effects on heart rate. Although these results did not reach statistical significance, a similar but more rigorous double-blind crossover study[13] showed no difference in anti-hypertensive effect between oral doses of 120 and 240 mg of propranolol daily.

There is some evidence[14] to suggest that 30 per cent of the hypotensive effect of propranolol occurs at plasma levels of 20 mg/ml and that a plateau of response occurs at levels of 100 mg/ml. This is approximately equivalent to an oral dose of 240 mg daily[15], though there is a wide individual variation in plasma levels at any particular dose. The initial dose of propranolol in the majority of our patients was at or above 250 mg daily, thus a plateau in dose/response at this level might explain the absence of any further fall in blood pressure on doubling the dose. Avoidance of a higher dose of propranolol, which in our experience gave a limited additional hypotensive effect, may be one way of reducing adverse reactions associated with its use.

Better compliance will be obtained only by strategies aimed at reducing unwanted symptoms, and, as the benefits of treatment decline, as they probably do in mild hypertension, questions about the quality of life during prolonged drug treatment become more important.

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Book Review

Clinical Investigation of Respiratory Disease, edited by T. J. H. Clark. Chapman & Hall, London, 1981. 526 pages. Price £22.50.

Professor Tim Clark’s aim with this book is to provide a comprehensive review of those investigations, many of which have been developed since 1970, that are used to supplement purely clinical information in the diagnosis, management and assessment of prognosis in patients with respiratory disease. He has certainly succeeded in bringing together a wealth of expertise bearing upon his objective. He himself introduces the subject, defining the place of clinical investigations, their limitations, their expense and the need for their critical use.

The individual contributions are patchy. Those concerned with lung sounds, physiology, radioisotope imaging, immunology, host defence and occupational lung disease are excellent. Altogether there are 17 chapters, and other subjects include exercise-testing, radiology, biochemistry—a growing field of potential importance—microbiology, bronchoscopy and cytology—an exhaustive introduction with many references—biopsy and nasal investigation.

In some chapters references are too few and, in many, no later than 1979; so there is a lack of up-to-date appraisal of some rapidly advancing methods such as CAT scanning.

This is a useful book of reference for libraries and for perusal by those in the field of respiratory medicine—its expense will probably exclude it from the shelves of those with a general interest, whether undergraduate or postgraduate.

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