Treating mild hypertension

One of the main current medical controversies centres on the treatment of patients with mild hypertension. Wherever this matter is discussed—and especially in Britain—a temporising conclusion is usually reached: to await the results of the Medical Research Council's trial in mild hypertension. Temporisation is now over, for the main results of the trial are published at p 97.

The size of the trial is immediately impressive with some 85 572 patient years of observation. No other trial of this magnitude on the treatment of hypertension seems likely to be done again in our time. Thus its conclusions are of great importance and will rightly form the basis of widespread discussion in the months ahead. If—as might have been predicted—not all aspects of the controversy have been settled this is perhaps not so much the fault of design of the trial as a reflection of the heterogeneous nature of hypertension.

The study was designed to examine whether treatment of patients aged 35 to 64 with diastolic blood pressures of 90-109 mm Hg would reduce the number of strokes and coronary events, known to be the commonest causes of morbidity and mortality in patients with mild hypertension.

The two agents used in the trial were the diuretic bendrofluazide and the β blocker propranolol, members of the two most widely used drug groups used to treat mild hypertension; thus a further aim was to compare their relative benefits and risks. Bendrofluazide was given in a fixed dose of 10 mg/day, while the dose of propranolol was adjusted to a maximum of 240 mg/day. Patients whose blood pressure did not reach a target of 90 mm Hg with either treatment were given supplementary treatment with methyl-dopa or guanethidine. The study was carried out in general practice, was placebo controlled, and incorporated 17 354 participants of both sexes who were followed for some five and a half years. The results were analysed on an "intention to treat" basis—that is, patients in the bendrofluazide, propranolol, or placebo groups included those, firstly, who took only that drug throughout the period of trial; secondly, those who were given additional treatment; and, thirdly, those who for any reasons were withdrawn from treatment. For various reasons some 44% of men and 37% of women stopped the treatment to which they were initially randomised. These

are high figures and must be kept in mind when we are considering recommendations with respect to individual drugs.

The results may be subdivided into the therapeutic and non-therapeutic. Both are important, because as well as giving guidance on the treatment of mild hypertension this study provides a large database for cardiovascular risk factor analysis.

Active treatment reduced the number of strokes but did not influence the rate of coronary events. When all cardiovascular events—stroke, heart attack, ruptured and dissecting aneurysms—were considered together, treatment did cause a reduction. Active treatment did not reduce the overall death rate; but here there was a sex difference, for the death rate decreased in men but increased in women owing to more non-cardiovascular deaths, principally malignancies.

A unique aspect of the study relates to the risks and benefits of the drugs used. Bendrofluazide caused a greater fall in blood pressure than propranolol, but this may reflect the fact that more patients treated with bendrofluazide required supplemental treatment than those given propranolol. β Blockers were more effective in lowering blood pressure in non-smokers than smokers. This is thought provoking; while on the one hand cigarette smoking is known to increase the rate of metabolic degradation of propranolol,^{1,2} and hence decrease its plasma concentration, no good correlation has ever been shown between plasma concentration of propranolol and its hypotensive response,^{3,4} so there may be other reasons for this finding. Propranolol was more effective in lowering blood pressure in younger than in older patients (as has been shown for angiotensin converting enzyme inhibitors⁵), perhaps because maintenance of blood pressure in the young depends more on the renin-angiotensin system than in the elderly.⁵ In spite of its hypotensive effect bendrofluazide did not influence the incidence of coronary events, reflecting the complex and ill understood relation between hypertension and coronary artery disease. Non-smokers given propranolol showed a decrease in strokes and a trend towards reduction in coronary events, but this did not reach the level of significance. Smokers taking propranolol showed no reduction in strokes or coronary events. Neither drug influenced non-cardiovascular deaths.

The non-therapeutic results are equally interesting. Systolic blood pressure at entry was a good predictor of strokes and coronary events, but this was not related to the extent of benefit associated with treatment, which shows an interesting comparison with the results of the Australian Therapeutic Trial in Mild Hypertension.⁶ The MRC trial showed that age, male sex, and cigarette smoking are important predictors of all cardiovascular events; with respect to coronary events, an ischaemic electrocardiographic pattern, high serum cholesterol concentration, and obesity were further important predisposing factors. While these data are important on population basis they must be interpreted with caution in the individual patient.

What, then, are the implications of these data for the practising doctor? The entrails of the study will be pored over and examined in great detail—but what are the initial questions to which the practising doctor will want answers?

Firstly, is it worth treating patients with mild hypertension? Since treatment prevented stroke the answer must be yes, but qualified by the fact that there was no reduction in heart attacks or in the overall death rate. While the trial did not examine the effects of stopping smoking, the difference in the rate of strokes and coronary events between non-smokers and smokers was impressive, for these differences were much greater than the effects of treatment. In advising hypertensive patients we must continue to emphasise the great importance of stopping smoking, for this may turn out to be a more important therapeutic manoeuvre than the prescription of blood pressure lowering drugs.

Should both men and women be treated? Untreated men had a much higher rate of stroke and heart attack than women; and, while treatment did lower the proportion of strokes similarly in both sexes, the absolute number of women so protected was small. The excess overall mortality in treated women over those given placebo must be a cause for concern, and it seems justified to conclude that to treat all women with mild hypertension is not worth while.

Is the extent by which blood pressure is lowered important? Surprisingly this did not appear to matter greatly. At least the extent of benefit was not related to pressure control in this group of mildly hypertensive patients.

Does the treatment which we use matter? As with any long term therapeutic study, our interpretation of the MRC study is constrained totally by the regimens used. It is easy with hindsight to be critical of this aspect of the trial, but we must remember that it was designed in the mid-1970s and there has been much progress in antihypertensive treatment in the past 10 years. Today we would probably not use as large a dose as 10 mg bendrofluazide since there is a strong suspicion from the Multiple Risk Factor Intervention Trial and other analyses that in high doses thiazides may themselves predispose to vascular damage.^{7,8} At one stage of the MRC trial there was concern about a trend towards an excess mortality from coronary events in men given bendrofluazide, and a separate study within the main trial did show an excess of ventricular premature beats, whose causal relation to hypokalaemia was suggestive if not proved.⁹

We would, therefore, recommend a smaller dose of thiazide diuretic (say, bendrofluazide 2.5 mg/day), since the hypotensive effect of thiazides does not appear to be dose related, although their adverse effects are. It seems unlikely that a large study investigating the risks and benefits of different doses of thiazide diuretics in hypertension will ever be conducted, since most available preparations are now generic. With respect to the choice of β blocker prescribing

fashions change, but it is uncertain if real advantages can be attributed to any one of the many β blockers currently available.¹⁰ The effects of cigarette smoking on propranolol efficacy are interesting, raising the question whether a β blocker which is not extensively metabolised (such as atenolol or sotalol) would be influenced in a similar manner. Treatment with propranolol cannot be said to prevent heart attacks in hypertensive patients, although there was a trend towards this in patients who did not smoke, a trend which was also manifest in the Australian therapeutic trial.¹¹

Calcium antagonists have gained an important place in the treatment of mild hypertension over the 10 years since the MRC trial was designed, but we cannot yet clearly assign their place in treatment. What about the risks of bendrofluazide and propranolol in the MRC trial? Some of these have already been published⁹ and most are predictable—that is, impaired glucose tolerance, hypokalaemia, and gout in patients treated with a bendrofluazide, and Raynaud's phenomenon and dyspnoea in those given propranolol. The relatively high incidence of lethargy and impotence in both treatment groups compared with that in those taking placebo is noteworthy.

This is an important summer for those interested in the results of treatment of hypertension. Last month saw the publication of the trial of the European Working Party on High Blood Pressure in the Elderly,¹² carried out in patients over the age of 60 and with results which in fact conflict with those of the MRC trial. In the trial of the European Working Party on High Blood Pressure in the Elderly deaths from myocardial infarction but not from cerebrovascular events decreased with treatment, but as in the MRC trial the overall death rate was not influenced. Again, the drugs used were perhaps not those which we would prescribe today, and it is difficult to be certain how far the results can be extrapolated to other forms of treatment. Next month will see the publication of the results of the International Prospective Primary Prevention Study in Hypertension, in which the effects of oxprenolol have been compared with those of placebo in a study incorporating some 25 000 patient years of observation. The MRC trial has given answers to some of the parts of current therapeutic dilemma on mild hypertension, but it is probably asking too much even of all these trials together to solve all the problems.

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