Antihypertensive drugs and plasma lipids

There has been increasing concern expressed about the possible adverse effects upon lipid metabolism of the two major classes of agent used in treating blood pressure—thiazide diuretics and \( \beta \) blockers. Although these effects of diuretics have been recognised for over 15 years,\(^1\) only recently have they begun to have a major impact upon prescribing policy. There are two reasons for this. Firstly, newer classes of agents that are free of these effects were intensively marketed in the 1980s. The competitive advantage of agents such as angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and \( \alpha \) adrenoceptor blockers in terms of their effects upon plasma lipids has been pressed home and has led to a decline in the prescription of diuretics and \( \beta \) blockers in several countries. Secondly, and perhaps more legitimately, it has been suggested that adverse metabolic disturbances account for the apparently disappointing impact of antihypertensive drug therapy upon the incidence of ischaemic heart disease. Thus in the large major multicentre trials of antihypertensive treatment, myocardial infarction was reduced only in the Hypertension, Detection and Follow-Up Programme (HDFP).\(^2\) A meta-analysis of the large trials showed a non-significant reduction in coronary morbidity and mortality that was only a third of the excess risk borne by the patients with hypertension.\(^3\) This contrasted with apparent complete reversal of the stroke risk attributable to hypertension. A later meta-analysis subtly altered the conclusion, largely because several smaller trials in moderate as well as mild hypertension were included.\(^4\) This meta-analysis calculated a 14% fall in the incidence of coronary heart disease compared with an expected fall of 20-25%. Unfortunately, the wide 95% confidence limits (4-22%) for this pooled analysis are compatible with virtually no effect on the one hand or complete reversal of risk on the other.

It is perhaps not entirely surprising that there are residual uncertainties about the impact of antihypertensive therapy on coronary artery disease. Other risk factors play a greater role in coronary artery disease whereas blood pressure is the predominant risk factor for stroke. Though epidemiological associations predict a 35-40% reduction in the incidence of death and the same data predict a reduction in coronary artery disease of only 20-25% as a result of blood pressure reduction.\(^4\)

It is possible therefore that there is no shortfall in the impact of antihypertensive treatment on myocardial infarction and that the uncertainties arise because the existing studies lack statistical power. I think this is unlikely, however. The difficulty with meta-analysis is that it pools studies independently of the rigour of their design. The 14% reduction in the incidence of coronary heart disease owes much to the significant fall of 19.8% in the HDFP group,\(^5\) compared with a fall of only 5-1% in the Medical Research Council (MRC) trial of treatment of mild hypertension.\(^5\) The control group in the HDFP study were patients who had been referred back to their usual medical care whereas the MRC trial had a blinded placebo control group. The fall in incidence in the other 12 trials pooled in a meta-analysis was perhaps closer to the results of the MRC trial than the HDFP study.

It seems likely therefore that there is a shortfall in the impact of antihypertensive therapy upon ischaemic heart disease. How can we identify the adverse effects of the drugs used? Unfortunately the large trials of treatment in mild hypertension have been based upon regimens that largely used diuretics or \( \beta \) blockers. Thiazide diuretics cause a small increase in total cholesterol, low density lipoprotein (LDL) cholesterol, and very low density lipoprotein (VLDL) cholesterol, while \( \beta \) blockers give rise to an increase in triglycerides and a small decrease in high density lipoprotein (HDL) cholesterol.\(^6\) These changes seem to be less pronounced with cardioselective agents and not present in \( \beta \) blockers with considerable intrinsic sympathomimetic activity.\(^7\) Where comparison has been made between \( \beta \) blocker regimens and other regimens\(^8\) or between regimens based upon diuretic therapy and \( \beta \) blocker therapy\(^9\) the failure to show differences in incidence of myocardial infarction may be due to the fact that both agents have an adverse effect.

The most desirable option at this stage would be a trial to compare diuretics or \( \beta \) blockers or both with one of the new classes of agent without adverse metabolic effects. Such an end point trial has not been set up and it is unlikely to be set up in the near future so these questions will not be answered for at least ten years. What advice can be given on the basis of our inadequate evidence? The first indisputable fact is the enormous difference in the price of the older and newer classes of agent. ACE inhibitors cost 50 times as much as thiazide diuretics. Because hypertensive patients require lifelong treatment the cost of selecting an expensive treatment may be very great indeed and may result in failure to meet other equally pressing health needs. For instance, in a recent analysis of the direct and indirect cost of treating hypertension each additional Quality Adjusted Life Year (QALY) gained in a man of 50 with a diastolic blood pressure of 110 mm Hg cost £25588 when diuretic therapy was used and £15 034 when an ACE inhibitor was used.\(^9\) This analysis, however, assumed that neither agent had an impact upon coronary heart disease and theoretically therefore the balance could be tilted more in favour of ACE inhibitors if drug-induced lipid disturbances were relevant. Is this so?

The view that drug-induced lipid disturbances should determine selection of a drug for first line treatment depends upon two unproven assumptions. These are firstly that changes in plasma lipids induced by drugs are as powerful risk factors as naturally occurring differences in plasma lipids between individuals. This presupposes identical changes at the cellular level and equivalent effects from quite different durations of exposure in the two cases. Further it has to be assumed that the drug induced lipid changes predominate over other risk factors that can be
influenced by treatment. Atheroma is not primarily a metabolic disease. Its distribution is patchy throughout the arterial tree and influenced by local mechanical factors such as turbulence and pressure. Different classes of antihypertensive agent clearly have radically different effects upon these variables. Even the metabolic picture is more complex than suggested by the simplistic lipid hypothesis. Though non-selective β blockers can influence the pattern of plasma lipids in an adverse way, in some experimental preparations they also have antiatheroma properties. In neither case can we confidently predict an in vivo effect on human atheroma.

Quantitatively, drug-induced changes in cholesterol are insufficient to contribute substantially to the apparently disappointing impact of antihypertensive treatment on myocardial infarction. In the MRC trial bendrofluazide treatment increased cholesterol by 0·1 mmol/l in men and 0·14 mmol/l in women. In this trial differences in plasma cholesterol of this magnitude was associated with a 3·4% increase in the risk of a coronary event, while the shortfall in impact upon infarction was, as we have seen, 15-20%. In a separate analysis of the pooled cholesterol data from the MRC and HDFP trial Collins et al estimated that diuretic therapy increased total cholesterol overall by about 1% and that such an increase would have been associated with an increase in coronary heart disease of only 2% over the duration of the trials if extrapolation from epidemiological associations to clinical trials was valid.4

There is further direct evidence that diuretic or β blocker therapy does not have a pro-atheromatous effect. Thus most strokes in patients with mild hypertension are atherothrombotic rather than haemorrhagic. The complete reversal of stroke risk by effective antihypertensive therapy therefore suggests a beneficial effect on at least one serious atheromatous complication of hypertension.

There is clearly a major role for newer classes of antihypertensive agent in patients whose blood pressure is not controlled by diuretics or β blockers or in whom these drugs are contraindicated for other reasons. Until properly conducted end point trials provide information to the contrary, I do not therefore see any reason to modify the British Hypertension Society guidelines that diuretics or β blockers should be the first-line agents. I would, however, suggest two relevant if not totally conclusive reasons for preferring β blockers normally. Firstly, many hypertensive patients in clinical practice (as opposed to clinical trials) have associated ischaemic heart disease. The benefits of β blockade in preventing secondary infarction are now well established. Secondly, there is some suggestive trial evidence that β blockers do have a beneficial impact on coronary events in hypertensive patients, even those without clinical evidence of ischaemic heart disease. Thus when both clinical coronary events and silent electrocardiographic changes suggestive of an infarction were pooled in the MRC study, the propranolol treated group showed a significant 15% reduction compared with the placebo group.11 Patients fared significantly better in this respect than the diuretic treated group who showed a 15% increase in coronary events compared with the placebo group.11

Although the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial found no difference in outcome between patients randomised to a diuretic or a cardioselective β blocker, a subgroup of patients receiving either metoprolol or a thiazide diuretic were maintained in the trial (MAPHY (Metoprolol Atherosclerosis Prevention in Hypertensives) trial). The metoprolol treated group showed a 24% reduction in fatal and non-fatal myocardial infarctions compared with the thiazide treated group.14 The MAPHY trial is not independent of the original HAPPHY trial and did not feature in the original objectives. Like the analysis of silent coronary events in the MRC trial,11 this is strictly therefore a subgroup analysis and does not carry the same weight as an independent prospective trial. In the absence of other evidence, however, most clinicians will tilt the balance in favour of β blockers as first-line agents in the management of hypertension.

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