Diuretic Agents and $\beta$-Blockers in the Treatment of Hypertension

Sir Colin Dollery

Benzothiadiazine diuretic agents and $\beta$-adrenergic receptor-blocking drugs are two of the main groups of drugs used to treat mild hypertension. Recently, questions have been raised about their relative efficacy in preventing morbidity and mortality from vascular disease in addition to their effect on lowering blood pressure. Attention has been focused on the unfavorable metabolic effects of diuretic drugs and the proven value of $\beta$-adrenergic receptor blockade in secondary prevention after myocardial infarction. Four randomized controlled trials comparing drugs in these two classes have been published: the Medical Research Council trial, the International Prospective Primary Prevention Study in Hypertension, the Heart Attack Primary Prevention in Hypertension trial, and the Metoprolol Atherosclerosis Prevention in Hypertension study. These trials, especially that of the Medical Research Council, have raised some questions about the relative efficacy of these two classes of drugs in preventing stroke in smokers and nonsmokers. Overall, there is little evidence of a reduction in morbidity and mortality after myocardial infarction. The predicted advantage of $\beta$-adrenergic receptor blockade over diuretic therapy has not been realized although there are sufficient hints of a differential benefit to encourage the performance of further trials. (Hypertension 1989;13[suppl I]:I-62–I-65)

The thiazide diuretic drugs were introduced into medicine in 1958 after the discovery of chlorothiazide by Karl Beyer and his associates at Merck Sharp & Dohme. The $\beta$-adrenergic receptor-blocking drugs were discovered by Sir James Black and his team at the Imperial Chemical Industry in 1964. Both drugs were originally intended for the treatment of other diseases (chlorothiazide for edema and propranolol for angina), but their most extensive use has been in the treatment of hypertension. Clinical experience with these drugs has been very extensive, and millions of patients have been treated with each of these drugs during the last 20–30 years. Both drugs have had a good safety record although a large number of minor adverse reactions have been identified with each.

Clinical suspicion has been one of the most effective methods of detecting adverse reactions to drugs. There has been a long-standing clinical suspicion that thiazide diuretic agents might have an unfavorable effect in patients with coronary disease. The main basis of this suspicion has been that several of the metabolic effects of benzothiadiazine diuretic drugs may have adverse consequences in patients with cardiac ischemia.

Hypokalemia caused by thiazide diuretic drugs has been one of the principal reasons for concern. Patients who develop serious ventricular arrhythmias are more difficult to treat when the serum potassium is low, and it is standard practice to administer potassium. However, interpretation of such data is difficult because life-threatening ventricular arrhythmias are often complications of acute myocardial infarction. Patients with acute myocardial infarction often have high plasma concentrations of epinephrine, and this condition causes potassium to enter cells, thereby reducing the extracellular potassium concentration. The relation between cause and effect in acutely ill patients with severe ventricular arrhythmias and hypokalemia may not be straightforward. There is also evidence that treatment with benzothiadiazine diuretic drugs increases the frequency of ventricular ectopic beats although the relation to hypokalemia is by no means clear. Magnesium depletion caused by diuretic therapy may also be a factor, but there are few long-term data.

Benzothiadiazine diuretic agents are also reputed to have adverse effects on a number of cardiovascular risk factors, for example, by increases in blood glucose, low density lipoprotein cholesterol, and serum uric acid. The magnitude and importance...
of these effects have been subjects of disagreement in the literature, probably because of differences in dose and susceptibility. All these changes, if they occur, would tend to increase the incidence of myocardial infarction.

In contrast, β-adrenergic receptor blockade appears to have a more favorable profile of effects. The β-blockers were introduced for the treatment of angina pectoris, and they are effective for controlling catecholamine-induced cardiac arrhythmias,7,8 A number of randomized, controlled, clinical trials have demonstrated a 25–30% reduction in mortality when β-adrenergic receptor–blocking drugs have been used in the chronic phase after myocardial infarction,9–11 and, more recently, a reduction in mortality has also been demonstrated in the acute phase of acute myocardial infarction.12,13

All this background information had created an expectation that benzothiadiazine might have a mildly adverse effect on the risk of a hypertensive patient suffering a myocardial infarction, and that the effect of β-adrenergic receptor blockade might be favorable. Although consumption of social drugs like nicotine, caffeine, and alcohol is known to have short-term effects on blood pressure, there had been no suggestion of an interaction between these factors and the response to individual antihypertensive drugs.

Relevant Clinical Trials

Three randomized controlled trials in hypertension have addressed the question of the comparative efficacy of β-blocking and thiazide diuretic agents, the Medical Research Council (MRC) Hypertension trial,14,15 The International Prospective Primary Prevention Study in Hypertension (IPPPSH),16 and the Heart Attack Primary Prevention in Hypertension trial (HAPPHY).17 Only the MRC trial contained a placebo control group, so only this trial can be used to investigate the absolute as opposed to the relative efficacy of the two classes of drugs. The HAPPHY trial contained only men, whereas the IPPPSH and MRC trials included both sexes.

The β-adrenergic receptor–blocking drugs used were different in all three studies. The MRC trial used the nonselective β-adrenergic receptor–blocking drug propranolol, which has no partial agonist activity. The IPPPSH trial used the nonselective

### Table 1. Treatment Regimens

<table>
<thead>
<tr>
<th>Protocol</th>
<th>MRC</th>
<th>IPPPSH</th>
<th>HAPPHY</th>
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<tbody>
<tr>
<td>Regimen 1</td>
<td>Bendrofluazide 10 mg</td>
<td>Oxprenolol (SR) 160 mg</td>
<td>Bendroflumethiazide 5–10 mg or hydrochlorothiazide 50–100 mg</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>Propranolol 240 mg</td>
<td>Placebo oxprenolol</td>
<td>Atenolol 100–200 mg or metoprolol 200–400 mg</td>
</tr>
<tr>
<td>Main supplement(s)</td>
<td>Methyldopa (18–34%)</td>
<td>Diuretic (67–82%), methylthiopropylamine (23.5%)</td>
<td>Hydralazine (21–24%)</td>
</tr>
<tr>
<td>Control group</td>
<td>Placebo</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

MRC, Medical Research Council; IPPPSH, International Prospective Primary Prevention Study in Hypertension; HAPPHY, Heart Attack Primary Prevention in Hypertension; and SR, slow-release.
achieved in the trial. When the incidence of stroke was plotted against the blood pressures achieved after 6 months in the trial (when most patients had achieved stable control), the relation was shifted downward and to the right, not only in comparison to propranolol but also in comparison to placebo. This finding raised the possibility that diuretic agents may have a favorable effect on stroke in addition to their effect on decreasing blood pressure. However, the HAPPHY trial, which used different $\beta$-adrenergic receptor blockers, found no evidence of this interaction, and the unadjusted figures favored $\beta$-blockade.

Mortality from myocardial infarction and sudden death was almost identical in the diuretic and $\beta$-blocker groups of each trial. Thus, the hope that the beneficial results of acute and secondary prevention trials with $\beta$-blockers in myocardial infarction would persist into primary prevention in hypertension was not fulfilled (Table 2). There was evidence that nonsmoking men treated with $\beta$-blockers in the MRC and IPPPSH trials had a lower mortality from ischemic heart disease than did nonsmoking men treated with diuretic drugs, but this difference was marginally significant in the MRC trial and was not confirmed in the HAPPHY trial. However, a large observational study with treated hypertensive subjects with somewhat more severe hypertension (the Department of Health, Hypertension Care Computer Project) has also demonstrated a lower mortality from ischemic heart disease in nonsmoking men treated with $\beta$-blockers. 18

The link with smoking complicates comparison of results from trials that have used selective (HAPPHY) and nonselective (MRC and IPPPSH) $\beta$-blockers because of the likelihood of differing cardiovascular responses to catecholamines released by smoking. 19,20 There is disagreement concerning the extent to which chronic responses to smoking, coffee, and other agents are modified by selective $\beta$-blockade. 21-23 If the suggestion of a beneficial effect in nonsmoking men is confirmed in further studies, it is not easy to provide an explanation. Smoking causes catecholamine release, and a protective effect of $\beta$-adrenergic receptor blockade in smokers may be expected.

In the MRC trial, a trend toward reduction of sudden death (within 1 hour) was also noted in the $\beta$-blocker group compared with the diuretic group, but this tendency was not evident in either the IPPPSH or HAPPHY trial. The issue of additional benefits from $\beta$-blockade in hypertension is not yet closed, and the argument has been fueled by the favorable result of longer follow-up of the metoprolol subset of the HAPPHY trial, recently reported as the MAPHY trial. 24 The benefits of $\beta$-blockade in MAPHY were not confined to nonsmokers.

It is not easy to translate the results of these trials into a sensible clinical policy. Thiazide diuretic agents are effective in preventing stroke, and they are inexpensive. $\beta$-Adrenergic receptor-blocking drugs may be less effective in preventing stroke (in smokers), and they are more expensive. If the principal benefit of treating hypertension is to decrease the incidence of stroke by 50%, should not every patient be treated with a diuretic agent as the first step? However, in nonsmoking men, $\beta$-blockade is as effective in preventing stroke as diuretic drugs, and the former may have the added benefit of reducing coronary events. Until more evidence is available, one reasonable defensive policy is to favor $\beta$-blockers as the primary regimen in male nonsmokers and to use benzothiadiazine diuretic agents as the first choice in smokers of either sex.

Table 2. Incidence of Fatal Myocardial Infarctions and Sudden Death

<table>
<thead>
<tr>
<th>Treatment group*</th>
<th>Diuretic or non-$\beta$-blocker</th>
<th>$\beta$-Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>n</td>
<td>Rate†</td>
</tr>
<tr>
<td>MRC</td>
<td>50</td>
<td>4.6</td>
</tr>
<tr>
<td>HAPPHY</td>
<td>50</td>
<td>4.09</td>
</tr>
<tr>
<td>IPPPSH</td>
<td>41</td>
<td>3.26</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>...</td>
</tr>
</tbody>
</table>

*Treatment groups included male hypertensive subjects treated with diuretic agents or $\beta$-blockers.
†Incidence rates are per 1,000 patient-years.

References


**KEY WORDS** • adrenergic receptor blockade • catecholamines • diuretic therapy • human studies • statistical studies
Diuretic agents and beta-blockers in the treatment of hypertension.
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Hypertension. 1989;13:I62
doi: 10.1161/01.HYP.13.5_Suppl.I62

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