Adverse Metabolic Effects Of Antihypertensive Drugs
Implications for Treatment

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\textbf{Summary}

Adverse metabolic effects have been associated with drugs used in the therapy of hypertension, especially diuretics and \textbeta-blockers. These effects include electrolyte, glucose/insulin, lipid and uric acid disturbances. This may explain, at least in part, why early trials examining the impact of antihypertensive pharmacotherapy with diuretics and \textbeta-blockers showed beneficial effects on coronary artery disease that fell disappointingly short of the predicted effect.

Among therapeutic drugs, diuretics cause disturbances in electrolyte homeostasis, e.g. hypokalaemia, hypomagnesaemia, and hyponatraemia. In contrast, ACE inhibitors cause hyperkalaemia under certain circumstances. Both diuretics and \textbeta-blockers, especially nonselective \textbeta-blockers that lack intrinsic sympathomimetic capabilities, have been associated with disturbances in glucose/insulin metabolism and can cause deleterious alterations in the profile of circulating plasma lipids. Hyperuricaemia, associated with diuretic use, appears to be a problem only in those patients who are predisposed to high circulating levels of uric acid.
The benefits of accepted therapeutic regimens must be carefully weighed against risks on a regular basis. Nowhere is this statement more true than in the field of hypertension. Treatment of hypertension is directed toward decreasing morbidity and mortality, not just lowering blood pressure. In this regard, therapeutics have generally improved outcome, but not sufficiently in all respects.

Although traditional diuretic-based, stepped-care procedures have markedly reduced complications of hypertension, such as stroke, congestive heart failure, and premature death, prevention of coronary deaths has proven less successful. How therapy affects the interrelationship between hypertension and other cardiovascular risk factors is especially important in the majority of patients who have only mild elevations in blood pressure. Accordingly, some patients with hypertension still face a considerable risk of cardiovascular disease, despite modern drug treatment.

1. Metabolic Abnormalities and Cardiovascular Risk

Early trials examining the impact of antihypertensive pharmacotherapy with diuretics and \( \beta \)-blockers showed significant decreases in the incidence of stroke. However, effects on coronary heart disease have been disappointingly smaller than predicted. A meta-analysis of 14 unconfounded hypertension-treatment trials reported a lower than expected 14% decrease in coronary artery disease in treated patients. In comparison, the decrease in cerebrovascular events was in the 33 to 40% range.

Nevertheless, it is generally accepted that treatment with hypertensive agents is beneficial overall. The original Veterans Administration Cooperative Study demonstrated that cerebrovascular events in actively treated middle-aged men, most of whom had moderate to severe hypertension, were reduced to less than one-third of the incidence in the placebo group. The incidence of accelerated hypertension-induced congestive heart failure and renal damage was virtually eliminated after treatment was instituted. These findings were essentially duplicated in subsequent studies such as the Hypertension Detection and Follow-up Program and the Australian National Blood Pressure Trial. The latter two trials demonstrated that antihypertensive therapy was beneficial in patients with mild hypertension, in women, and in both old and young patients. The Systolic Hypertension in the Elderly (SHEP) Co-operative Study Group also found benefit in the treatment of isolated systolic hypertension in the elderly.

Many intriguing possibilities have been proposed to explain the discrepancies between stroke and coronary artery disease prevention in patients with hypertension receiving antihypertensive drug therapy. Reasons include study designs (i.e., performing relatively small-sized studies over too short a duration) and an inappropriate drug dosage. Focusing on the latter explanation, two contrasting possibilities on the magnitude of necessary treatment exist. On the one hand, poor outcome may be the result of a need for more aggressive therapy to lower blood pressure to a more effective range. On the other, some patients with existing coronary artery disease may be harmed by too extensive a drop in blood pressure, the well-known ‘J-Curve’ hypothesis.

In addition to the above possibilities, a popular theory is that metabolic disturbances already present in hypertensive patients are made worse by using certain antihypertensive drugs. Hypertensive patients often possess additional cardiovascular risk factors, such as glucose intolerance and insulin resistance, dyslipidaemias, and obesity. Accordingly, the benefit of reducing blood pressure with antihypertensive medications could theoretically be offset by worsening of other risk factors, such as derangements in the glucose/insulin system and increases in circulating levels of deleterious plasma lipids, such as cholesterol and triglycerides. In a Swedish study, involving 1915 treated hypertensive patients who were receiving all classes of drugs, a high level of cardiovascular risk factors was found. Drug-treated hypertensive patients of both gender showed inadequate blood pressure control, a high prevalence of diabetes mellitus, and lipid abnormalities.