Commentary

Should we use thiazide diuretics in hypertensive patients with non-insulin-dependent diabetes mellitus?

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Introduction

Patients with non-insulin-dependent diabetes mellitus (NIDDM) have a high prevalence of hypertension compared to non-diabetic populations. Arterial hypertension is also well established as an important additional risk factor for cardiovascular morbidity and mortality in patients with diabetes mellitus. Treatment of hypertension is strongly recommended, with recently published guidelines suggesting intervention at lower blood pressure levels than those advised for non-diabetic hypertensive individuals.

Increasing attention is therefore being paid to the management of raised blood pressure in diabetic patients. However, the choice of antihypertensive therapy is not straightforward in such patients, and there is no general agreement about which agent is most suitable.

Thiazide diuretics in diabetic patients

Since their introduction into clinical practice in 1957, thiazide diuretics have remained a popular treatment for arterial hypertension. They provide an effective, well-tolerated and inexpensive, once-daily treatment. They have been used in many of the large prospective randomized controlled clinical trials in mild to moderate hypertension, producing a consistent benefit particularly in terms of reducing the excess risk of stroke, heart failure and renal failure. Unfortunately, the majority of these prospective controlled trials have not included individuals with diabetes mellitus, and so decisions regarding the treatment of hypertension in diabetes have been made by extrapolation from studies in non-diabetic subjects. This is unsatisfactory, as risk-factor effects and their reversibility may differ between diabetic and non-diabetic subjects. However, the Hypertension Detection and Follow-up Program, a randomized study which did include diabetic subjects estimated similar reductions in mortality following antihypertensive treatment in the diabetic subgroup compared with the whole study group.

With the arrival of new antihypertensive drugs, thiazide diuretics have become a less popular choice for the treatment of hypertension in diabetic subjects, because they are associated with a number of potentially deleterious metabolic effects, which, it has been suggested, may to some extent offset the benefit gained by blood pressure reduction. These metabolic effects include hypokalaemia, short-term hyperlipidaemia, impaired glucose tolerance and effects on insulin action. Such effects in a group with an already greatly increased risk of vascular disease are clearly very undesirable. However, in general, little information is available on the short- or long-term metabolic effects of thiazide diuretics in diabetes, and many reviewers too readily extrapolate the findings in non-diabetic subjects to the diabetic population.

Recently, interest has focused on the phenomenon of insulin resistance and its possible role in the pathogenesis and clinical course of hypertension. Evidence is accumulating that insulin resistance may be an important underlying metabolic defect in hypertension, contributing not only to the elevation in blood pressure, but also accounting for the constellation of observed abnormalities in carbohydrate, lipid and lipoprotein metabolism so prevalent in hypertensive individuals. As a consequence,
interest has focused on the effects of antihypertensive therapy on insulin sensitivity. Thiazide diuretics, because of their well-characterized effects on glucose tolerance, have received particular attention. The effects of antihypertensive medication on insulin action are of prime clinical relevance in patients with non-insulin-dependent diabetes, in whom metabolic derangement and both hepatic and peripheral insulin resistance are well established and characteristic features.

Further concern has arisen regarding the use of thiazide diuretics in diabetes following reports of an excess mortality in young and old diabetic patients treated with diuretics. The more recent of these studies, from the Joslin Diabetes Centre, reports a 3.8-fold increase in mortality among diuretic-treated hypertensive diabetic subjects, independent of other risk factors. This was a retrospective analysis of patients with advanced microvascular disease who had been enrolled in the Diabetic Retinopathy Study between 1972 and 1975. This multicentre clinical trial was originally designed to assess the efficacy of laser treatment in preventing blindness in patients with proliferative retinopathy. It was not designed to assess risk factors for mortality. These patients were presumably already at a greatly increased risk of cardiovascular mortality, so caution must be exercised in accepting conclusions from such a retrospective analysis. Furthermore, the doses or type of diuretics used were not indicated, but it is likely that high doses were used. However, some concern remains as to whether the use of conventional dose thiazide diuretics in hypertensive patients with diabetes may lead to an increased mortality.

Metabolic effects of thiazide diuretics

The relative lack of impact of antihypertensive treatment with thiazide diuretics and β-blockers on coronary artery disease incidence in large prospective trials, as compared with the effect on stroke, has led to the suggestion that the beneficial blood-pressure-lowering effects have been offset by drug-induced adverse effects on other cardiovascular risk factors. Thiazide diuretics in high dosage produce alterations, albeit minor, in the metabolic profiles of patients. Whether these changes are detrimental in terms of coronary artery disease risk, has yet to be determined.

Thiazide diuretics reduce plasma potassium via an increased delivery of fluid and bicarbonate to the distal nephron, resulting in increased potassium and hydrogen ion excretion and thus the development of alkalosis and hypokalaemia. A fall in plasma potassium occurs within the first 2–4 weeks of treatment with a thiazide diuretic, after which the levels tend to return towards basal values. This effect of thiazides on plasma potassium is dose-dependent. During the Multiple Risk Factor Intervention Trial, an increase in the number of cardiac deaths in a subgroup of patients with minor electrocardiographic abnormalities was attributed to thiazide diuretic therapy, with hypokalaemia inducing cardiac arrhythmias as the proposed mechanism. Although diuretic-induced alterations in potassium and magnesium may predispose certain patients to arrhythmias and sudden death, it must be emphasized that the majority of clinical trials do not clearly demonstrate any increase in the incidence of myocardial infarction or sudden death in thiazide-treated patients compared to those given placebo or other treatments. Whether or not thiazide-induced hypokalaemia is an important arrhythmogenic risk in hypertensive subjects, hypokalaemia is easily avoided by the use of low-dose thiazide diuretics.

Thiazide diuretics in high doses (i.e. bendrofluazide 10 mg, hydrochlorothiazide 40 mg, cyclopenthiazide 500 µg) have also been shown to cause deterioration in glucose tolerance in non-diabetic and diabetic patients. Several mechanisms have been suggested to explain thiazide-induced glucose intolerance. Hypokalaemia, reduced insulin secretion or insulin resistance may all play a part. Hypokalaemia correlates strongly with the degree of hyperglycaemia and also with the reduction in insulin secretion. However, potassium replacement only partly ameliorates the change in fasting glucose induced by hydrochlorothiazide. Also, in a study in insulin-dependent diabetes, although patients on frusemide and hydrochlorothiazide had similar degrees of hypokalaemia, only hydrochlorothiazide resulted in an elevated haemoglobin A1c, indicating that potassium depletion is an aggravating rather than a primary factor causing impaired glucose tolerance.

Recently the role of insulin resistance has received increasing attention and a much quoted study by Pollare et al. is of interest. Using the euglycaemic glucose clamp technique, they evaluated the effects of hydrochlorothiazide, at a relatively high dose of 40 mg daily, on insulin sensitivity. This dose impaired insulin sensitivity with an 11% reduction in insulin-stimulated glucose uptake. This change in insulin action did not correlate with the small decrease in serum potassium level (0.3 mmol/l). Despite this, the possibility remains that thiazide-induced decreases in insulin sensitivity do not depend on hypokalaemia per se but on the degree of potassium deficiency in skeletal muscle, the chief target of insulin action. Another factor may be the effect of thiazide diuretics on hepatic glucose production. We have demonstrated increases in endogenous (hepatic) glucose production rates in diabetic and
non-diabetic subjects following treatment with conventional dose (500 µg) cyclopenthiazide and conventional dose (5.0 mg) bendrofluazide. The effects of thiazide diuretics on lipid levels has not been widely studied in diabetic patients but studies in non-diabetic subjects indicate that the modest elevations seen in total and LDL-cholesterol levels are short-lived effects with no long-term clinical trials demonstrating a persistent increase in lipid levels. This is particularly true when low doses of thiazide diuretics are used.

**Low-dose thiazide diuretics**

The precise antihypertensive mechanism of thiazide diuretics is unknown, but it may be related to their ability to produce a sodium-depleted state, a reduction in plasma volume and direct peripheral vasodilatation. In diabetic subjects, thiazide diuretics appear to lower blood pressure by removing excess sodium and by the restoration of noradrenaline pressor sensitivity towards normal. Diabetic subjects with hypertension are known to have an increased total body exchangeable sodium, making thiazide diuretics a logical choice to reduce blood pressure.

Dosage levels evolved empirically with the assumption that larger doses would result in correspondingly greater reductions in blood pressure. This erroneous assumption resulted in early reports of a high incidence of side-effects, and led investigators in the majority of large-scale trials in mild hypertension to use unnecessarily high doses of thiazide diuretics in their treatment protocols.

It is now becoming clear that the need for large doses of thiazide diuretics in hypertensive patients is unwarranted. Early studies demonstrated a flat antihypertensive dose-response curve with use of these agents. Not only are low-dose thiazide diuretics as effective as higher, more conventional doses, but many of their adverse effects are dose-dependent and can be minimized by using lower doses. The effectiveness of low-dose thiazide diuretics in the absence of adverse metabolic effects has been emphasized recently for bendrofluazide, cyclopenthiazide and hydrochlorothiazide in both non-diabetic and diabetic hypertensive subjects. The question of dose-related effects is of importance to diabetic patients, as the disturbance of glucose homeostasis is proportionally diminished when lower doses of thiazides are used. Employing a lower than usual dose of hydrochlorothiazide (25 mg) with supplemental potassium chloride in diabetic hypertensives appears to have little impact on glycaemic control or serum potassium. Cyclopenthiazide 125 µg is as effective as 500 µg in reducing diastolic blood pressure in mildly hypertensive type 2 diabetic patients, with less adverse effects on glucose control and serum concentrations of triglycerides, potassium and urate. In fact, evidence is emerging that in diabetic as in non-diabetic subjects, lower than conventional doses of thiazide diuretics while effectively reducing blood pressure may have much less impact on the metabolic profile.

The effects of thiazide diuretics on insulin sensitivity are also pertinent. Hydrochlorothiazide in conventional dosage appears to decrease insulin-mediated glucose disposal in non-diabetic hypertensive subjects, indicating an increase in peripheral insulin resistance. By contrast, we have shown recently that low-dose thiazide diuretic (bendrofluazide 1.25 mg) is an effective antihypertensive in non-diabetic subjects, and does not have any adverse effects on peripheral and hepatic insulin action over a 3-month period. We have since examined the effects of low-dose thiazide diuretics on insulin action in NIDDM in the context of a double-blind randomized crossover study comparing the effects of low (1.25 mg) and conventional (5.0 mg) dose bendrofluazide on both hepatic and peripheral insulin sensitivity. Conventional dose (5.0 mg) bendrofluazide led to significant worsening of hepatic and peripheral insulin resistance after 12 weeks of therapy. Fasting glucose and HbA<sub>1c</sub> were both increased and serum potassium fell. In contrast, low-dose bendrofluazide (1.25 mg daily), which had similar antihypertensive effects, showed no such deleterious effects on glycaemic control or insulin action. It appears then that low-dose thiazide diuretics are effective in diabetic hypertensive subjects in the absence of any adverse metabolic effects, at least in the short term. Unfortunately, bendrofluazide 1.25 mg is not currently commercially available, bendrofluazide 2.5 mg being the lowest dose in use.

**Choice of treatment for hypertension in NIDDM**

The optimal choice of antihypertensive treatment in non-insulin-dependent diabetic subjects is currently debated. Should we continue to use thiazide diuretics or switch to newer agents such as ACE inhibitors and calcium antagonists, based on the view that they have fewer metabolic adverse effects? In contrast to conventional-dose thiazide diuretics, ACE inhibitors appear to be free of adverse metabolic effects, and may improve insulin sensitivity. Captopril improves insulin sensitivity in hypertensive NIDDM patients in the short term but there are conflicting results regarding longer term effects. In two recent studies, perindopril and enalapril had no long-term effects on insulin sensitivity. Torlone et al. (1993)
showed an improvement in insulin sensitivity following long-term captopril therapy, whereas others have failed to detect any changes. 61, 62 Improvements in insulin sensitivity may be dependent on the presence of a sulphydryl group. 63

It is now clear that the rate of decline in renal function in diabetic patients with overt nephropathy can be reduced by antihypertensive treatment. Thiazide diuretics are as effective in reducing blood pressure as any other class of antihypertensive drug. However, ACE inhibitors may have a beneficial effect, over and above their blood-pressure-lowering ability, on the progression of diabetic nephropathy 64 and many, but not all, comparative studies have suggested that treatment with ACE inhibitors brings about larger reductions in urinary protein excretion than treatment with thiazide diuretics. 65-67 In practice, however, treatment with either a thiazide or loop diuretic is invariably required in nephropathic patients to reduce fluid overload and adequately control blood pressure.

Critics of thiazide diuretics should also remember that in general, many diabetic patients (30-60%) require more than one antihypertensive agent to meet therapeutic goals. Thiazide diuretics can be used with any other antihypertensive drug, and in combination with ACE inhibitors present a particularly effective and rational approach to hypertension. 68 More work needs to be done to assess the effects of this type of combination therapy on both glycaemic control and insulin sensitivity in diabetic patients.

When pharmacological treatment is necessary for our non-insulin-dependent diabetic patients with hypertension (the vast majority of whom are not nephropathic) which drug should we choose? As there are no long-term clinical trials comparing diuretics or beta-blockers with newer agents in diabetic subjects, we are left with a high degree of uncertainty when attempting to decide on optimal treatment. One factor felt to be important is the effect of antihypertensive treatment on glycaemic control and insulin action. As there is now good evidence that low-dose thiazide diuretics are effective in the absence of any detrimental effect on glycaemic control and insulin sensitivity, a strong argument can be made for their continued use and we would endorse the view expressed in a recent consensus statement that thiazide diuretics should continue to be used as antihypertensive therapy for patients with diabetes. 69 In support of the continued use of thiazide diuretics in preference to the much more costly newer agents, we can state that thiazide diuretics are inexpensive, safe, well-tolerated, free from adverse metabolic effects in low doses and have been proven to be effective in reducing cardiac and cerebrovascular events (at least in non-diabetic subjects and in the elderly where one might have expected risk factor reversibility to be difficult). 60, 67, 70 ACE inhibitors and calcium channel blockers have not been tested in long-term prospective clinical trials and so, as yet, we cannot be entirely confident that they reduce mortality and morbidity as well as, or better than, older agents.

Conclusion

For a final answer to which is the optimal choice in the treatment of our hypertensive non-insulin-dependent diabetic patients, we must await the results of large prospective randomized controlled studies. The United Kingdom Prospective Diabetes Study is one such study which will be reporting soon. 71 Unfortunately, the use of low-dose thiazide diuretic is not part of the treatment protocol, which compares atenolol with captopril. We await with interest the design, implementation and results of further studies. In the meantime we continue to advocate the continued use of thiazide diuretics in the treatment of hypertension in patients with uncomplicated non-insulin-dependent diabetes, provided that the lowest possible doses are used.

References

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