Recent Advances in Pharmacological Management of Hypertension in Diabetic Patients with Nephropathy
Effects of Antihypertensive Drugs on Kidney Function and Insulin Sensitivity

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Summary

Hypertension is often seen in Type 1 and Type 2 diabetic patients, particularly in those with nephropathy, and the progression of diabetic nephropathy is closely related to blood pressure elevation. Thus, the effects of antihypertensive drugs on kidney function and insulin sensitivity in diabetic patients are of great clinical importance.

Successful antihypertensive treatment has been shown to slow the progression of diabetic nephropathy. Several results from short term studies have suggested that angiotensin converting enzyme (ACE) inhibitors may be advantageous over other conventional antihypertensive agents in reducing albuminuria in both hypertensive and normotensive diabetics with microalbuminuria or persistent proteinuria. However, the decline in glomerular filtration rate during ACE inhibitor treatment is comparable to that during effective treatment with conventional antihypertensive drugs in hypertensive Type 1 diabetic patients with overt nephropathy. Whether ACE inhibitors...
possess a specific effect in preventing the development of diabetic nephropathy remains to be seen in properly designed long term studies. Although calcium antagonists may preserve kidney function or possess a renoprotective effect in hypertensive Type 2 diabetics with nephropathy, firm evidence supporting this contention seems to be lacking and also requires long term evaluation.

Increasing attention is being directed toward the effect of antihypertensive drugs on insulin sensitivity in diabetic patients: ACE inhibitors and α₁-adrenoceptor blocking agents have been shown to improve this sensitivity. Despite the widespread involvement of calcium in hormone secretion and action, calcium antagonists appear to have little effects on the glucoregulatory and calcium-regulatory hormones within the drug dosages used in clinical practice.

Several clinical variables, such as the presence or absence of hypertension, overt nephropathy and microalbuminuria, or a combination of variables should be accounted for when evaluating critically the cumulative data on the effects of antihypertensive drugs on kidney function and albuminuria in the variety of diabetic patient groups. Understanding the pharmacokinetic and pharmacodynamic characteristics of antihypertensive drugs will be of clinical importance in diabetic patients with advanced nephropathy (glomerular filtration rate of < 30 ml/min) and/or other complications, such as impaired gastric motility or gastroparesis, and will thereby lead to a more rational management of hypertension in those patients.

Diabetes mellitus and hypertension are common chronic conditions which frequently coexist (Christlieb et al. 1981; Felicetta & Sowers 1988; Klein et al. 1984; Lipson 1984; Sowers et al. 1988; Sowers & Zemel 1990). Hypertension contributes to morbidity and mortality, such as coronary artery disease and end-stage renal disease (ESRD), in diabetic patients (Working Group on Hypertension in Diabetes 1987a,b). Hypertension is often associated with diabetic nephropathy (Baba et al. 1985; Parving et al. 1983b; Reddi & Camerini-Davalos 1990), and the progression of nephropathy appears closely related to blood pressure elevation (Christensen & Mogensen 1985a; Feldt-Rasmussen et al. 1986; Mogensen 1976; Reddi & Camerini-Davalos 1990). Once clinical or overt nephropathy, which is characterised by persistent proteinuria (total urinary protein excretion of > 0.5 g/day or urinary albumin excretion of > 300 mg/day) is established in diabetic patients, attempts to modify the relentless decline in glomerular filtration rate (GFR) to ESRD have been essentially unsuccessful (Andersen et al. 1983). Improved glycaemic control has not been shown to produce obvious beneficial effects (Viberti et al. 1983). However, the treatment of hypertension has emerged as an effective means of slowing the progression rate of nephropathy (Baba et al. 1990b; Mogensen 1976, 1982; Parving et al. 1983c). Antihypertensive treatment thus is now considered to be an important therapeutic intervention in diabetic patients with nephropathy (Christlieb 1990; Mogensen 1990; Parving 1991; Stein & Black 1991).

During the last several years, some substantial advances have been made in understanding the pathophysiological aspects of diabetic nephropathy and the treatment of hypertension in diabetic patients (Christlieb 1990; Mogensen 1990; Parving 1991; Reddi & Camerini-Davalos 1990; Stein & Black 1991; Trost 1989). The results of some selected trials and the management of hypertension in diabetic patients will be the main focus of this review, which will also evaluate kidney function and insulin sensitivity, parameters which may be altered by antihypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors and calcium antagonists.

1. Pathogenetic Features of Hypertension in Diabetic Patients

Hypertension and diabetes coexist more frequently than hypertension would be expected from its relative random prevalence in the general population, although estimates of the prevalence of hypertension have been a controversial issue for