The Effect of Trandolapril and Its Fixed-Dose Combination With Verapamil on Proteinuria in Normotensive Adults With Type 2 Diabetes

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OBJECTIVE — To compare the effect of fixed-dose trandolapril-verapamil (FDTV) with that of trandolapril on proteinuria in normotensive, type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 60 normotensive, type 2 diabetic patients with 24-h proteinuria >300 mg were randomly assigned to two groups for open-label treatment. One group received 2 mg trandolapril/180 mg verapamil FDTV once daily; the other group received 2 mg trandolapril once daily. Study drugs were administered for 6 months in both groups. Creatinine clearance and 24-h urinary protein excretion were measured at the beginning and the end of the study. Patients were evaluated monthly for blood pressure, fasting blood glucose level, heart rate, and adverse events. Statistical analysis was performed using ANOVA.

RESULTS — Both groups experienced a statistically significant (\( P < 0.005 \)) mean decrease in mean proteinuria from baseline: FDTV ([mean ± SD] 1,200 ± 200 to 540 ± 79 mg, \( P < 0.001 \)) and trandolapril (1,105 ± 212 to 750.9 ± 134 mg, \( P < 0.005 \)). A significantly greater reduction from baseline in proteinuria was observed in the FDTV group compared with the trandolapril group. Patients who received trandolapril experienced a statistically significant (\( P < 0.05 \)) decrease in mean creatinine clearance (91.1 ± 3.4 to 75.3 ± 3 ml/min, \( P < 0.05 \)) compared with patients who received FDTV (88.3 ± 3.6 to 82.9 ± 3.5 ml/min, \( P > 0.05 \)). Final fasting blood glucose was significantly lower in the FDTV group (139 ± 19) compared with the trandolapril group (154 ± 22, \( P < 0.001 \)). No significant differences were observed between the two groups in mean baseline or final measurements of blood pressure, mean heart rate, or frequency of adverse events.

CONCLUSIONS — Our results suggest that FDTV is more effective than trandolapril in reducing proteinuria in normotensive, type 2 diabetic patients. This effect on proteinuria is not related with blood pressure reduction.

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The prevalence of diabetic nephropathy is ~30% in patients with type 2 diabetes after 20–30 years. It is the most common cause of end-stage renal disease and increases the mortality rate in those patients (1,2). In diabetic patients, proteinuria levels are related not only to the progression of nephropathy but also to cardiovascular mortality, and in Mexico, proteinuria has a prevalence of 9.3% in type 2 diabetic normotensive patients (3). In turn, reduction of proteinuria or delay in its progression may delay the onset of end-stage renal disease.

Recent clinical studies have shown that several therapeutic strategies are available to delay the progression of diabetic nephropathy: rigorous glycemic control, aggressive antihypertensive control to achieve blood pressure values <130/80 mmHg, and blockade of the renin-angiotensin system (1).

To decrease morbidity and mortality due to diabetic nephropathy, early detection of patients at risk is critical, as is the application of all necessary therapeutic measures. The 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension recommend antihypertensive therapy with a blocker of the renin-angiotensin system in type 2 diabetic patients who have microalbuminuria, irrespective of blood pressure values (4). However, enough evidence exists from clinical trials that both angiotensin II receptor blockers and ACE inhibitors are useful in reducing proteinuria in hypertensive and normotensive patients with type 2 diabetes (4–6).

It has been shown that the combination of an ACE inhibitor and verapamil produces greater decreases in proteinuria and smaller declines in renal function compared with ACE inhibitor therapy alone in hypertensive type 2 diabetic patients with nephropathy. And in those hypertensive type 2 diabetic patients who did not respond to monotherapy with an ACE inhibitor (7,8). However, we could not distinguish whether this response was due to the reduction in blood pressure or a direct nephroprotective effect of the drug combination. The nephroprotective effect of fixed-dose trandolapril-verapamil (FDTV) has been demonstrated in experimental animal studies, in which the

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Abbreviations: FDTV, fixed-dose trandolapril-verapamil; GFR, glomerular filtration rate.

A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.

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FDTV combination prevented the expansion of the mesangial matrix and glomerulosclerosis (8).

This study was conducted to compare the effect of FDTV with that of trandolapril on proteinuria and glomerular filtration rate (GFR) in normotensive, type 2 diabetic patients with nephropathy.

RESEARCH DESIGN AND METHODS — A total of 60 normotensive patients with type 2 diabetes (>12 months’ duration and with 24-h proteinuria >300 mg) were evenly randomized into two groups. All study patients were referred from primary care clinics and were not receiving antihypertensive therapy. One group received 2 mg trandolapril/180 mg verapamil FDTV daily; the other group received 2 mg trandolapril daily. Study drugs were administered for 6 months in both groups.

Patients were evaluated monthly during the 6-month period. At each evaluation, blood pressure was recorded in triplicate with a mercurial sphygmomanometer in the sitting position after a 5-min rest and at 3-min intervals. An average of the three measurements was recorded. Heart rate and fasting glyceria (glucose oxidase) also were recorded at each evaluation. At the beginning and end of the study, 24-h albuminuria (nephelometry) was measured; creatinine clearance was also measured at these times. Each patient collected 24-h urine specimens, and the total volume was delivered to the laboratory.

To achieve the best possible compliance, a telegram was sent to each patient 24 h after a missed visit. We dispensed 30 capsules at each visit, and the count of capsules returned by the patient was documented as a measure of compliance with the study drug.

Patients with any of the following diagnoses were excluded from the study: decompensated diabetes (fasting blood glucose level >250 mg/dl); type 1 or secondary diabetes; heart, hepatic, or renal failure; evidence of valvular heart disease; heart block or cardiac arrhythmia; secondary hypertension; acute coronary syndrome or cerebrovascular disease 6 months before initiation of the study; history of abuse of alcohol and/or psychotropic drugs.

Patients were not permitted to use any of the following drugs: any type of antihypertensive, tricyclic antidepressive, and/or monoamine oxidase inhibitor or any other drug for research purposes within the 30 days of initiation of the study.

Postmicturition ultrasonography was performed before initiation of treatment to detect urine retention from a neurogenic bladder, which might have altered the results of proteinuria and creatinine clearance. Patients with >100 ml of residual urine as measured by ultrasonography were excluded from the study.

Data are presented as a means ± SD; statistical analysis was performed with ANOVA. P < 0.05 was considered significant.

The study was conducted with the approval of the Research and Medical Ethics Committee of our hospital, in accordance with the Helsinki Declaration. Participants gave their informed, written consent before inclusion in the study protocol.

RESULTS — The basic features of the patients are described in Table 1.

In patients who received FDTV, proteinuria decreased from 1,200 ± 200 to 540 ± 79 mg (P < 0.001), whereas GFR did not change (88.3 ± 3.6 to 82.9 ± 3.5 ml/min; P > 0.05). In patients who received trandolapril, proteinuria decreased from 1,105 ± 212 to 750.9 ± 134 mg (P < 0.005), and GFR decreased from 91.1 ± 3.4 to 75.3 ± 3 ml/min (P < 0.05). We found a statistically greater reduction (P < 0.005) from baseline in proteinuria in patients who received FDTV compared with patients who received trandolapril. We also found a statistically greater reduction (P < 0.05) in GFR in patients who received trandolapril compared with patients who received FDTV.

No significant differences were found between the two study groups in baseline or final blood pressure, initial glycemia, or heart rate. Although baseline fasting blood glucose level was comparable between groups, a significantly greater reduction in final fasting blood glucose level was observed in patients who received FDTV (Table 2).

Compliance with treatment was >90%, i.e., the number of capsules returned by most patients on each visit was <10% of those dispensed.

Three patients in each group reported dizziness, and two patients had headache. All adverse events were transient and resolved spontaneously, and treatment was not interrupted.

CONCLUSIONS — Our study demonstrated that combination therapy trandolapril-verapamil is more effective than monotherapy with trandolapril for the control of proteinuria in normotensive, type 2 diabetic patients with diabetic nephropathy. Because mean blood pressure changed very little in both study groups, the aforementioned effects would not have been related to reduction in blood pressure. However, no ambulatory registers of blood pressure were obtained; therefore, a nondipping condition or out-

**Table 1—Baseline patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trandolapril/verapamil</th>
<th>Trandolapril</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.5 ± 7.6</td>
<td>55 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>9/21</td>
<td>8/22</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8.8 ± 6</td>
<td>8.7 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.7 ± 15</td>
<td>67.8 ± 11.5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8 ± 5.6</td>
<td>28.8 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Basal blood pressure (mmHg)</td>
<td>123 ± 11/76 ± 4</td>
<td>122 ± 10/78 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Basal fasting blood glucose level (mg/dl)</td>
<td>158</td>
<td>164</td>
<td>NS</td>
</tr>
<tr>
<td>Basal heart rate (bpm)</td>
<td>73</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Basal proteinuria (mg/24 hr)</td>
<td>1,200 ± 200</td>
<td>1,105 ± 212</td>
<td>NS</td>
</tr>
<tr>
<td>Basal GFR (ml/min)</td>
<td>88.3 ± 3.6</td>
<td>91.1 ± 3.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are n or means ± SD.
of-office changes not registered but induced by verapamil may affect results.

Further research is required to determine whether FDTV has additional benefits on renal function in normotensive, type 2 diabetic patients. Moreover, because type 2 diabetes is risk equivalent to coronary artery disease, research is also required to determine whether FDTV offers better outcomes than monotherapy with ACE inhibitors in prevention of coronary artery disease.

Several hemodynamic and humoral factors are involved in the pathophysiology of diabetic nephropathy, and most result from angiotensin II activity: increased intraglomerular pressure, vasoconstriction of efferent arteriole, increased glomerular membrane permeability for macromolecules, and mesangial cell proliferation. ACE inhibitors can beneficially block all these effects (9). Overproduction of endothelin-1 by the renal endothelium is a frequent occurrence in type 2 diabetic patients. Endothelin, a potent vasoconstrictor, has fibrotic effects on the kidney and favors mesangial proliferation (10), as those actions are blocked by calcium antagonists (7,10). Then, the benefit of the trandolapril-verapamil combination in those patients may be due to the ability of calcium antagonists to block the effects of endothelin on mesangial proliferation; this requires further investigation. Another possible advantage of the combination consists of the capacity of calcium channel blockers to inhibit the expression of adhesion molecules, which prevents leukocyte infiltration in the kidney independent of the antihypertensive effects of the drugs. This fact ameliorates tissue damage in diabetic rats and has not been observed with other antihypertensive drugs such as hydralazine or hydrochlorothiazide (11). In addition, nondihydropyridinic calcium antagonists, unlike dihydropyridines, promote vasodilatation of the efferent arteriole, which renders them more effective to reduce proteinuria (7,8). These actions of verapamil may account for the greater reduction in proteinuria in the FDTV group, independent of blood pressure effect. Therefore, FDTV may confer to these patients a greater renoprotective effect than monotherapy with an ACE inhibitor at the doses of the drugs studied. Higher doses of an ACE inhibitor might lead to the same outcomes; this possibility requires future study.

In our study, heart rate did not change in patients who took FDTV. We have no explanation for this, because verapamil usually reduces this parameter. Similarly, in one of our previous studies in hypertensive, type 2 diabetic patients, FDTV did not reduce heart rate (7).

Although the final albumin levels in all of our study patients were <50% of the initial values in the FDTV group, further reductions would likely be beneficial. This might be accomplished with longer antihypertensive treatment as well as improved glycemic control. Some reports have established that glycemic control plays a major role in the development of albuminuria when arterial pressure has been reduced (12). The fasting blood glucose level in the FDTV group was significantly better than in the trandolapril group and may have influenced the results. In other studies comparing the FDTV with another antihypertensive drug therapy in type 2 diabetic patients, glycemic control in subjects receiving the trandolapril-verapamil combination was observed to be better (13). Indeed, the higher proteinuria level in the trandolapril group may be due, in part, to the poor glycemic control in those patients.

Patients with type 2 diabetes are at high risk for ischemic heart disease, especially in the presence of albuminuria, which is an indicator of endothelial dysfunction. Both hyperglycemia and albuminuria should be treated aggressively because both conditions are associated with increased risk of macrovascular disease and microvascular complications (14).

Our results suggest that FDTV is more effective than trandolapril alone in reducing proteinuria in normotensive, type 2 diabetic patients. FDTV seems to be a safe and effective option for management of patients with type 2 diabetes, when they did not respond to monotherapy, or in diabetic normotensive patients with proteinuria >1 g/dl.

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References