Effects of Enalapril and Nitrendipine on the Excretion of Epidermal Growth Factor and Albumin in Hypertensive NIDDM Patients

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OBJECTIVE — To compare the effect of the antihypertensive drugs nitrendipine and enalapril on the excretion of epidermal growth factor (EGF) and albumin in hypertensive non-insulin-dependent diabetes mellitus (NIDDM) subjects.

RESEARCH DESIGN AND METHODS — After a 4-week washout period, mildly hypertensive (systolic blood pressure [sBP] ≥140 mmHg and/or diastolic blood pressure [dBP] ≥90 mmHg) NIDDM patients with albuminuria (15–200 μg/min) were randomized into an 8-month-long therapy with either nitrendipine (n = 11) or enalapril (n = 10). Blood pressure, EGF, and microalbumin excretion were measured at baseline and throughout the treatment period.

RESULTS — A significant fall in sBP was noticed in the enalapril group and in dBP in the nitrendipine group. In the enalapril group, EGF excretion progressively increased from 188 to 214 nmol/mmol creatinine after 6 weeks and to 274 after 8 months of therapy (P = 0.03). There was a significant fall in albumin excretion while patients were on enalapril, but in the nitrendipine group, neither albuminuria nor EGF excretion changed significantly. There was no correlation of improved EGF excretion with a decrease in albuminuria or BP.

CONCLUSIONS — The angiotensin-converting enzyme inhibitor enalapril has been effective in decreasing albumin and increasing EGF excretion. Measurement of urinary EGF may provide a new valuable index of renal function.

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Received for publication 19 September 1994 and accepted in revised form 11 January 1995.

ACE, angiotensin-converting enzyme; AER, albumin excretion rate; BP, blood pressure; dBP, diastolic blood pressure; EGF, epidermal growth factor; NIDDM, non-insulin-dependent diabetes mellitus; sBP, systolic blood pressure.

Microalbuminuria is frequently found in subjects with hypertension and diabetes. It is a predictor of deteriorating renal function, increased risk of coronary artery disease, and other vascular complications of diabetes (1–5).

Epidermal growth factor (EGF) is another marker of renal function. It is a normal urine constituent of distal tubular origin (6), the excretion of which, in contrast to that of albumin, is sharply decreased in human diabetes, even in the absence of overt nephropathy (7–9). The excretion rate is very low in subjects with severe renal failure of any origin (10). Whether this abnormality reflects local damage or is a renal compensatory mechanism is not known. Also, it is not known whether any specific medication can correct these abnormalities and increase EGF excretion.

Both calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors have been used in an effort to slow down progression of diabetic nephropathy, particularly in the presence of hypertension. While ACE inhibitors may decrease microalbuminuria (11–19), the effects of calcium antagonists are equivocal (14,17–22). The effects of calcium antagonists and ACE inhibitors on the excretion of EGF are unknown. It was assumed that treatment of hypertension could lead to changes in EGF excretion in hypertensive diabetic subjects.

We report the results of an open-label study of the effects of nitrendipine (a calcium antagonist) or enalapril (an ACE inhibitor) on albumin and EGF excretion in hypertensive subjects with non-insulin-dependent diabetes mellitus (NIDDM) attending the University of Calgary Medical Clinic.

RESEARCH DESIGN AND METHODS

— The study was approved by the Conjoint Medical Ethics Committees and Institutional Review Boards and conducted in accordance with the Declaration of Helsinki. The participants signed an informed consent form.

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Table 1—*Characteristics of the patients treated with nitrendipine or enalapril*

	Nitrendipine	Enalapril
n (M/W)	11 (1/10)	10 (2/8)
Age (years)	56 (37–67)	53 (43–68)
Duration of diabetes (years)	8 (2–16)	6 (1–20)
sBP (mmHg)		
Initial	142 (135–156)	149 (122–171)
After 6 weeks	137 (121–156)	138 (109–155)
Individual differences	−6 (−28–16)	−13 (−34–11)
P	NS	0.002*
dBP (mmHg)		
Initial	89 (75–99)	91 (78–103)
After 6 weeks	79 (54–98)	86 (72–103)
Individual differences	−6 (−22–0)	−5 (−14–7)
P	0.0023*	NS
Albuminuria (μg/min)		
Initial	32 (19–107)	49 (20–127)
After 6–8 weeks	23 (13–73)	35 (5–156)
After 3–4 months	41 (5–103)	44 (6–122)
After 6–7 months	42 (5–149)	28 (5–68)
P	NS	0.008*
EGF excretion (nmol/mmol creatinine)		
Initial	250 (107–318)	188 (62–346)
After 6–8 weeks	222 (128–436)	214 (145–318)
After 3–4 months	207 (107–480)	259 (163–329)
After 6–7 months	207 (146–459)	274 (177–365)
P	NS	0.030*

Data are medians (ranges). *Significance of intra-individual differences between baseline values and values at 6–7 months. NS = $P > 0.05$.

The subjects satisfied the National Diabetes Data Group criteria for NIDDM (23). Their characteristics are presented in Table 1. Criteria for entry into the study were systolic blood pressure (sBP) ≥140 mmHg or diastolic blood pressure (dBP) ≥90 mmHg and microalbuminuria (15–200 μg/min) in the absence of other known kidney diseases. Multiple blood pressure (BP) readings were taken following the recommendations from the Canadian Hypertension Society (24). Three microalbumin baseline measurements were obtained for microalbuminuria entry criteria. The subjects were treated with diet alone or with diet plus the oral medications glyburide and/or metformin. There were no differences between the subgroups treated with these different modalities; therefore, their data were combined.

All previous antihypertensive medications were withdrawn at the commencement of the study, and placebo therapy was instituted for a 4-week baseline period. If a subject experienced persistent elevated BP readings (sBP >170 mmHg, dBP >105 mmHg), they were entered into the titration period provided that all inclusion criteria were met.

The subjects were randomized to one of two groups. Eleven subjects received nitrendipine at an initial dose of 10 mg/day for 4 weeks. If BP did not decrease to <140/90 mmHg, the dose was increased stepwise to 20 mg twice a day. Another group of 10 subjects received enalapril at an initial dose of 5 mg/day, which was increased stepwise, if required, to 10 mg twice a day.

Clinical evaluation and determinations of EGF and albumin excretion rates (AERs) were made at baseline (before the administration of antihypertensive medications) and repeated after 6–8, 12–16, and 28–32 weeks of antihypertensive treatment.

EGF was assayed by specific radioimmunoassay as previously described (9) and expressed in nmol EGF/mmol creatinine. Albumin concentration was measured by a double-antibody ^{125}I radioimmunoassay (Diagnostic, Los Angeles, CA) with a sensitivity of 5 μg/ml. AER was derived using the concentration of albumin, the total time of collection, and the volume of the overnight urine. Glucose control was monitored by monthly measurements of HbA_{1c}, and weight and BP was recorded at each visit.

In view of the small size of the groups and non-normal distribution of some data, the results are shown as medians and ranges (Table 1). Correlations were calculated as the nonparametric Spearman ρ. Significance of intra-individual changes over time was evaluated by a one-sample Student's *t* test. Calculations were done with the help of STATGRAPHICS program (STSC, Rockville, MD).

RESULTS— The results are presented in Table 1. There was a small decrease of BP in both groups that was statistically significant ($P < 0.05$) for the sBP in the enalapril-treated group and for dBP in the nitrendipine-treated patients. These effects on BP were sustained throughout the observation period.

In relation to albumin and EGF excretion, the two groups differed. Patients treated with nitrendipine did not demonstrate significant improvement in either respect. In the nitrendipine group, there was no significant correlation between the excretion of albumin and EGF. In contrast, in the group treated with enalapril, albuminuria decreased in 9 of 10 patients ($P = 0.008$), and EGF excretion increased progressively in the course of therapy in 8 of 10 patients ($P = 0.030$). Again, in the enalapril group, there was no correlation between the decrease in AER and the rise in EGF. There were no

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significant changes in HbA_{1c} or weight in either treatment group throughout the duration of the study.

CONCLUSIONS— Microalbuminuria appears to provide an excellent marker for the presence of early renal changes associated with diabetes and hypertension. An increasing AER is predictive of a deteriorating renal state with increasing likelihood of significant renal damage and elevated BP.

The present research study of a group of patients with NIDDM, mild hypertension, and microalbuminuria has demonstrated a benefit of the ACE inhibitor enalapril in reducing albuminuria, while this effect was not seen with the calcium channel–blocking drug nitrendipine.

ACE inhibitors have been demonstrated to decrease microalbuminuria in both hypertensive and normotensive diabetic subjects with nephropathy. Calcium channel–blocking drugs, however, are not as consistent in reducing microalbuminuria in NIDDM patients. While some studies have demonstrated a fall in microalbuminuria (17,19,25), other studies have not shown any improvement in AER (14,18,22). The difference in these results with the calcium channel–blocking drugs may be related to their structure or to aspects such as protein and salt intake, which could influence the outcome of specific antihypertensive drug trials.

The effectiveness of an antihypertensive drug in reducing AER could be explained by the lowering of BP, but in this study, while both enalapril and nitrendipine were effective in lowering BP, only enalapril decreased the AER. Mogensen (13) has stressed that the effects of ACE inhibitors on proteinuria and BP may be independent, and similar conclusions have been obtained from meta-regression analysis (26).

Minimal research information, however, is available as to the role of EGF excretion as a test of renal function. Diminished excretion of EGF has been described in diabetic patients (7–9), but the pathogenesis of this phenomenon is unknown. Although EGF is produced by many organs and is present in virtually all fluids of the body, its urinary fraction is almost exclusively of local renal origin. EGF is synthesized mainly in the thick ascending loop and distal and collecting tubules as prepro-EGF, which is then locally processed into the EGF monomer and excreted (6).

One or more of several mechanisms may be involved in the decreased secretion of EGF in diabetic subjects. There may be decreased prepro-EGF transcription; decreased processing into the final monomer; diminished luminal EGF secretion; or even normal production but increased local renal consumption. Since the excretion of EGF with urine may well be related to its synthesis and the latter is a highly endergonic process, any decrease in renal perfusion should lead to lower EGF excretion. This may well be the process taking place in the hypertensive subject.

The effect of antihypertensive medications on EGF excretion in diabetes has not previously been described. Enalapril clearly increased EGF excretion, but this effect was not directly associated with the decrease in AER. This may suggest that EGF excretion reflects a renal function that is independent of changes in membrane permeability.

While the precise implications of reduced EGF excretion are unknown, the increase in EGF excretion could be interpreted as an improvement in renal function. It is not known whether these observed changes in EGF excretion are a direct effect of the antihypertensive drugs on its synthesis or perhaps on the processing of EGF precursors. Further understanding of the immunoassay is necessary in terms of whether the antibody recognizes whole EGF, as well as fragments of the molecule. The effect of long-term treatment with antihypertensive drugs on EGF excretion remains to be investigated, but it seems likely that EGF measurements in urine may provide further insights into the benefits, the renal dynamics, and the mechanisms of action of the specific antihypertensive drugs in the hypertensive diabetic subject. The use of the urinary EGF assay deserves careful and detailed evaluation as a potential additional index of renal function.

Acknowledgments— This work was supported by a grant from Miles Canada Inc.

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