Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: one year analysis

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Abstract

***Objectives*—To compare the efficacy, safety, and tolerance of enalapril and nifedipine in hypertensive patients with non-insulin dependent diabetes.**

***Design*—One year double blind follow up of patients randomly allocated to either enalapril or nifedipine with matching placebos for the alternative drug.**

***Setting*—Metabolic Investigation Unit, Hong Kong.**

***Subjects*—102 patients were randomised: 52 to nifedipine and 50 to enalapril. At baseline 44 patients had normoalbuminuria, 36 microalbuminuria, and 22 macroalbuminuria.**

***Main outcome measures*—Blood pressure, albuminuria, and parameters of renal function and glycaemic control.**

***Results*—In patients who completed one year's treatment the median dose required by the nifedipine group (n=49) was 60 mg/day; seven (14%) required additional diuretics. Of 41 patients given enalapril, 37 required the maximum dose (40 mg/day) and 27 (76%) required diuretics. At one year mean arterial blood pressures were similar in both groups. Albuminuria fell by 54% in the enalapril group and 11% in the nifedipine group (p=0·006). Fractional albumin clearance ratio fell by 47% in the enalapril group and increased by 3% in the nifedipine group (p=0·009). Creatinine clearance fell similarly in both groups but plasma creatinine concentration was increased by 20% in the enalapril group versus 8% in the nifedipine group (p=0·001).**

***Conclusion*—Patients taking enalapril often required diuretics to control blood pressure. Enalapril reduced proteinuria significantly more than nifedipine in the microalbuminuric and macroalbuminuric patients but increased plasma creatinine concentrations. Longer follow up is required to clarify the importance of enalapril's antiproteinuric effect.**

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Introduction

Early aggressive antihypertensive treatment has been associated with a reduction in the rate of deterioration in kidney function in patients with insulin dependent diabetes mellitus.[1] Angiotensin II has potent vasoconstrictive effects on the efferent renal arteriole[2]; thus angiotensin converting enzyme inhibitors might reduce filtration pressure and preserve renal function more successfully than alternative antihypertensive drugs. Indeed, animal data suggest that this may be so.[3,4] The antiproteinuric and renal protective effects of long term treatment with angiotensin converting enzyme inhibitors have recently been reported in insulin dependent diabetes.[5] Nevertheless, non-insulin dependent diabetes, which is the more prevalent form of diabetes, particularly among non-whites,[6] contributes importantly to the patient population with end stage renal failure.[7] To date, only a few clinical trials have studied the effects of angiotensin converting enzyme inhibitors in patients with non-insulin dependent diabetes and the results have been inconclusive.[8-16]

We conducted a study to compare the long term effects of the angiotensin converting enzyme inhibitor enalapril with the calcium channel blocker nifedipine in the treatment of non-insulin dependent diabetes associated with hypertension.

TABLE I—*Study protocol for randomised trial of enalapril and nifedipine in hypertensive patients with non-insulin dependent diabetes*

Weeks	−6	−4	0	4	8	12	16	24	36	52
	← Placebo →		← Active treatment →							
24 Hour urine collection	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑↑
Drugs (mg/day):										
Enalapril*				10	20	40				
or										
Nifedipine (modified release)*				40	60	80				
Indapamide							2·5			
or										
Frusemide								40	80	120

*Patients received a matching placebo for the alternative drug.

Patients and methods

STUDY PROTOCOL

The study was approved by the ethics committee of the Chinese University of Hong Kong. Informed consent was obtained from all participants. Table I outlines the study design.

Patients with non-insulin dependent diabetes treated by diet or oral hypoglycaemic drugs, or both, who were either hypertensive or receiving antihypertensive drugs and who were attending the outpatient diabetic clinic at our hospital were invited to participate in the study. All patients were Chinese and aged over 18. Patients were excluded if they were receiving insulin or had a history of non-diabetic renal disease, appreciable renal impairment (plasma creatinine concentration $\geqslant 200$ μmol/l), a plasma potassium concentration $\geqslant 5$ mmol/l, cardiac failure or any concurrent systemic disease, or were receiving treatment for any concomitant disorder.

Previous antihypertensive drugs were discontinued and patients received placebo tablets to match enalapril 10 mg once daily and modified release nifedipine 20 mg twice daily. All patients were maintained on diets previously prescribed as part of their routine medical care. At the end of the six week run in period patients who satisfied the inclusion blood pressure criteria and none of the above exclusion criteria were admitted to the study. Inclusion blood pressure criteria were a mean supine systolic blood pressure of 150-220 mm Hg or a diastolic blood pressure (phase V) greater than 100 mm Hg, or both, at three readings during the run in period. Patients were then assigned to receive either

enalapril or modified release nifedipine with matching placebo tablets for the alternative drug according to a random allocation schedule. A schedule of 102 allocation numbers corresponding to similarly numbered drug supplies was provided for this purpose. Both the patients and the staff measuring blood pressure and biochemical indices were blinded to treatment.

Based on the mean value of three measurements of 24 hour urinary albumin excretion during the run in period, 44 patients had normoalbuminuria (< 30 mg/day), 36 microalbuminuria (30-300 mg/day), and 22 macroalbuminuria (> 300 mg/day).[17]

Drug doses were increased over 12 weeks to a maximum of enalapril 40 mg once daily or nifedipine 40 mg twice daily if supine systolic blood pressure remained above 140 mm Hg (table I). Indapamide 2·5 mg/day was added if the blood pressure remained high and, if necessary, this was replaced by frusemide (up to 120 mg/day) to achieve the target supine systolic blood pressure. Follow up visits were scheduled between 8 am and 10 am, at which time the blood pressure was measured, and venous blood was sampled for measurements of renal function, glycated haemoglobin, plasma fructosamine, and fasting plasma glucose concentration, and serum angiotensin converting enzyme activity. Twenty four hour urine samples were collected for estimation of albumin excretion. At the end of one year two 24 hour urine samples were collected within two weeks.

MEASUREMENTS

Blood pressure was measured by a single research nurse using a Hawksley random zero sphygmomanometer after the patient had rested for five minutes in the supine position and also after two minutes of standing. The mean of two readings for each body position was recorded. Mean arterial blood pressure was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure and was shown as a mean of supine and standing values unless otherwise stated. All urine samples were stored at 4°C and analysed within one week of collection for albumin concentration by immunoturbidimetry using a modification of a published technique.[18] Intra-assay and interassay coefficients of variation were 3·3% and 6·7% respectively within the range 1·2-80 mg/l. The lowest detection limit was 1·2 mg/l. Plasma and urine creatinine concentrations were measured by the Jaffe method on an Astra-8 Chemistry Analyser (Beckman Instrument, Palo Alto, California). Glycated haemoglobin concentration (HbA_1) was measured by gel electrophoresis (Ciba Corning Diagnostics, Alto, California) with a reference range of 6·5-8·5%. Plasma glucose concentration was measured by a glucose oxidase method (Diagnostic Chemicals reagent kit) and plasma fructosamine, by published methods.[19] Serum angiotensin converting enzyme activity was measured by a modified spectrophotometric method[20] and the intra-assay and interassay coefficients of variation were less than 5%.

For presentation of skewed data that were analysed as logarithms, the mean was back transformed (antilogged) to give the geometric mean and the 95% confidence intervals obtained for the mean of the log data were also antilogged.

STATISTICS

The study required 51 patients in each treatment group to have a 90% power at the 5% level (two tailed) to show that one drug was at least twice as effective as the other in reducing urinary albumin excretion. The mean (SD) or geometric mean (antilog of SD) values for all variables measured during the last two visits of the run in period were taken as baseline values. Doses of drugs administered are given as median. Fractional albumin clearance ratios were calculated as 24 hour urinary albumin concentration×plasma creatinine concentration/plasma albumin concentration×24 hour urinary creatinine concentration. Plasma creatinine concentration, creatinine clearance, fractional albumin clearance ratio, and urinary albumin excretion and serum angiotensin converting enzyme concentration were log transformed before analysis because of skewed distributions. The mean value from two measurements of urinary albumin excretion, fractional albumin clearance ratio, and creatinine clearance estimated at the end of one year were compared with baseline values and differences were compared between treatment groups. Mean (95% confidence interval) differences between the two treatment groups were examined by Student's two tailed t test. The antilog of a difference between two means was transformed into relative changes expressed as ratios compared with baseline values with 95% confidence intervals. Fisher's exact test was used to compare the rates of conversion from normoalbuminuria to abnormal albuminuria between the treatment groups. Repeated measures analysis of variance was used to test for the effects of treatment and its duration. Only data from patients who completed the one year study were included for these comparisons. Statistical analysis was performed with the packages ABstat (Anderson-Bell, Colorado, United States, 1989) and SPSS. Significance was taken as $p < 0.05$ (two tailed).

TABLE II—*Clinical characteristics of patients and mean biochemical data from the last two visits of the run in period. Values are means (SD) unless stated otherwise*

	Nifedipine group (n=52)	Enalapril group (n=50)
No of men	21	20
No of women	31	30
Age (years)	56·1 (9·9)	60·1 (9·2)
Duration of diabetes (years)	5·6 (4·6)	5·5 (4·8)
Duration of hypertension (years)	5·3 (4·7)	5·6 (5·3)
No (%) with retinopathy	22 (42)	17 (34)
No (%) with neuropathy	14 (27)	15 (30)
Body mass index (kg/m^2)	24·8 (3·0)	25·2 (2·9)
Supine blood pressure (mm Hg)	166/91 (16/9)	174/92 (17/13)
Erect blood pressure (mm Hg)	167/94 (16/12)	171/94 (19/14)
Mean arterial blood pressure (mm Hg)	117 (9)	120 (12)
Glycated haemoglobin (%)	9·8 (1·7)	10·4 (1·7)
Plasma fructosamine (mmol/l)	2·3 (0·23)	2·3 (0·23)
Fasting plasma glucose (mmol/l)	8·0 (2·1)	8·3 (2·5)
Geometric mean (antilog SD) plasma creatinine (μmol/l)	80·9 (1·4)	83·0 (1·3)
Geometric mean (antilog SD) urinary albumin excretion (mg/day)	69·5 (6·8)	64·7 (6·6)
Geometric mean (antilog SD) creatinine clearance (ml/min)	70·0 (1·6)	65·5 (1·5)
Geometric mean (antilog SD) fractional albumin clearance ratio (×10^{-6})	15·2 (9·6)	15·3 (7·4)

TABLE III—*Severity of proteinuria at baseline and the number of patients who completed one year of treatment in each category*

Category	Urinary albumin excretion (mg/day)	Nifedipine group		Enalapril group	
		Week 0	Week 52	Week 0	Week 52
Normoalbuminuria	< 30	24	24	20	18
Microalbuminuria	30-300	15	15	21	16
Macroalbuminuria	> 300	13	10	9	7

Results

POPULATION CHARACTERISTICS

Of 123 patients recruited, 102 fulfilled all inclusion criteria and were randomised to active treatment. Table II shows the baseline clinical characteristics and mean biochemical data from the last two visits of the run in period. Table III shows the level of albuminuria at baseline and the number of patients who completed one year of treatment in the subgroups. Forty nine of

TABLE IV—*Changes in urinary albumin excretion, fractional albumin clearance, endogenous creatinine clearance, plasma creatinine concentration, and arterial blood pressure in patients after one year of treatment with nifedipine or enalapril*

	Whole group	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Urinary albumin excretion*:				
Enalapril	0·46 (0·32 to 0·67)	0·88 (0·59 to 1·34)	0·27 (0·15 to 0·46)	0·29 (0·11 to 0·77)
Nifedipine	0·89 (0·66 to 1·2)	0·81 (0·55 to 1·2)	0·85 (0·43 to 0·88)	1·15 (0·85 to 1·54)
p Value	0·006	0·751	0·013	0·006
Fractional albumin clearance ratio*:				
Enalapril	0·53 (0·37 to 0·77)	0·95 (0·58 to 1·72)	0·28 (0·18 to 0·44)	0·38 (0·16 to 0·88)
Nifedipine	1·03 (0·75 to 1·43)	0·96 (0·63 to 1·45)	0·99 (0·43 to 2·3)	1·3 (1 to 1·66)
p Value	0·009	0·773	0·012	0·005
Creatinine clearance*:				
Enalapril	0·85 (0·75 to 0·97)	0·86 (0·72 to 1·03)	0·89 (0·71 to 1·1)	0·76 (0·52 to 1·12)
Nifedipine	0·85 (0·79 to 0·92)	0·85 (0·77 to 0·93)	0·88 (0·75 to 1·04)	0·83 (0·7 to 0·98)
p Value	0·989	0·841	0·989	0·675
Plasma creatinine*:				
Enalapril	1·2 (1·14 to 1·26)	1·15 (1·09 to 1·23)	1·26 (1·17 to 1·36)	1·17 (0·98 to 1·4)
Nifedipine	1·08 (1·05 to 1·12)	1·06 (1·01 to 1·12)	1·06 (1·01 to 1·1)	1·19 (1·08 to 1·3)
p Value	0·001	0·034	<0·001	0·904
Mean arterial pressure†:				
Enalapril	−21·2 (−24·8 to −16·3)	−18·9 (−24·1 to −13·8)	−21·6 (−29·2 to −13·9)	−22·0 (−34·3 to −9·7)
Nifedipine	−20·1 (−24·1 to −18·4)	−17·5 (−20·9 to −14·1)	−25·1 (−31·1 to −19·1)	−24·5 (−29·5 to −19·4)
p Value	0·759	0·633	0·481	0·685

*Mean relative change expressed as ratios compared with baseline values (95% confidence intervals).
†Mean difference (95% confidence intervals).
p Values are for comparisons between changes in the two treatment groups (Student's two tailed *t* test).

TABLE V—*Mean (95% confidence interval) changes in glycaemic indices during 52 weeks' treatment with enalapril or nifedipine*

Glycaemic index	Enalapril group	Nifedipine group	p Value
Glycated haemoglobin (%)	0·63 (−0·2 to 1·47)	0·12 (−0·3 to 0·57)	0·253
Plasma fructosamine (mmol/l)	0·14 (0·0 to 0·27)	0·00 (−0·07 to 0·09)	0·089
Plasma glucose (mmol/l)	0·42 (−0·6 to 1·5)	0·48 (−0·8 to 1·7)	0·93

the 52 patients randomised to nifedipine completed one year of treatment compared with 41 of 50 randomised to enalapril. Of the nine patients taking enalapril who did not complete one year, three were withdrawn because of cough, three were withdrawn because of inadequate control of blood pressure, one died of myocardial infarction, one developed angina, and one defaulted. Of the three patients who received nifedipine, one had inadequate blood pressure control, one had angina, and one had tuberculous lymphadenitis.

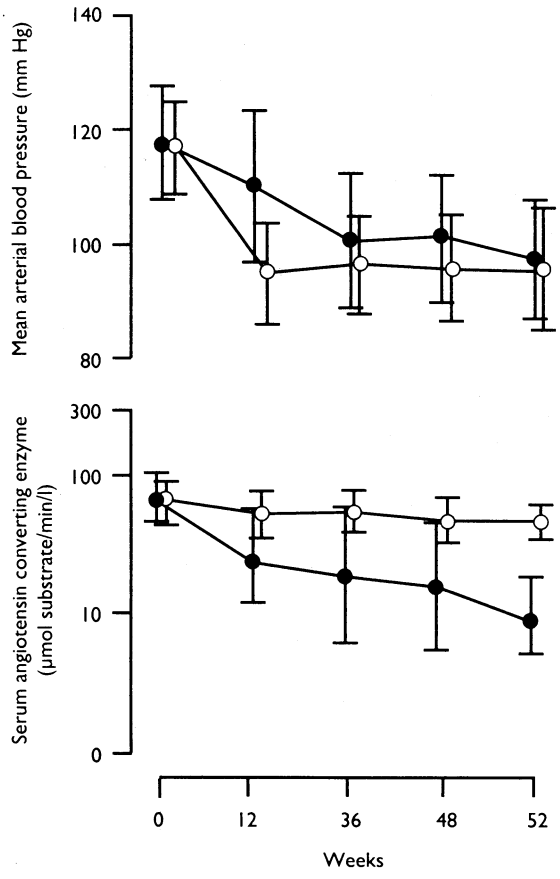

FIG 1—*Blood pressure and serum angiotensin converting enzyme activity during treatment with enalapril (●) or nifedipine (○). Angiotensin converting enzyme activity was plotted on logarithmic scale. Means (geometric means) are shown with SD values drawn as error bars*

BLOOD PRESSURE, BODY WEIGHT, AND GLYCAEMIC CONTROL

At one year, 90% (37/41) of the patients receiving enalapril required the maximum dose of enalapril (40 mg/day) and 76% (31/41) required the addition of diuretic treatment (20 took indapamide and 11 frusemide). The median dose of nifedipine was 60 mg/day and 14% of patients (7/49) required additional diuretics (four indapamide and three frusemide). Although at one year the reduction in and the achieved levels of mean arterial pressures were similar in both treatment groups (table IV), blood pressure was significantly higher overall in the enalapril group than in the nifedipine group ($p<0·001$ for drug difference, $p<0·001$ for time trend, and $p=0·001$ for time and drug interaction). The relative change in serum angiotensin converting enzyme activity was significantly greater in patients receiving enalapril (0·12 (95% confidence interval 0·1 to 0·15)) than in those receiving nifedipine (0·71(0·63 to 0·81), $p<0·001$; fig 1).

Body mass index fell by 0·28 (−0·58 to 0·01) kg/m² over 12 months in the enalapril group and 0·25 (−0·48 to −0·02) kg/m² in the nifedipine group (p=0·841). The haemoglobin concentration fell by 7·5 (−11·5 to −3·6) g/l in the enalapril group compared with a reduction of 2·4 (−0·5 to 0·6) g/l in the nifedipine group (p=0·035). At week 4, before the addition of diuretics, the plasma glucose concentration had fallen by 0·98 (−1·7 to −0·31) mmol/l in the patients receiving enalapril compared with 0·09 (−0·57 to 0·38) mmol/l in those receiving nifedipine (p=0·033). However, glycaemic indices were similar in the two treatment groups at one year and overall changes were not significantly different between the groups (table V).

ALBUMINURIA AND RENAL FUNCTION

Table IV summarises changes in mean arterial blood pressure, urinary albumin excretion, fractional albumin clearance ratio, creatinine clearance, and plasma creatinine concentration in the two treatment groups. Treatment with enalapril reduced proteinuria, and the fractional albumin clearance ratio significantly more than treatment with nifedipine, in all patients and also in the microalbuminuric and macroalbuminuric groups separately. In normoalbuminuric patients, urinary albumin excretion remained less than 30 mg/day in all of the 18 patients given enalapril whereas two of the 23 patients receiving nifedipine developed abnormal albuminuria (p=0·621). Figure 2 shows changes in urinary albumin excretion in individual patients during one year of treatment. Creatinine clearance fell to a similar extent in both

TABLE VI—*The effects of additional diuretic on renal function and blood pressure in patients receiving enalapril*

	No diuretics (n=10)	Diuretics (n=31)
Mean (95% confidence interval) arterial pressure (mm Hg)	−20·1 (−28·9 to −11·1)	−20·6 (−25·5 to −15·8)
Urinary albumin excretion rate*	0·65 (0·38 to 1·09)	0·42 (0·27 to 0·65)
Fractional albumin clearance ratio ($\times 10^6$)*	0·77 (0·34 to 1·71)	0·47 (0·31 to 0·71)
Plasma creatinine (μmol/l)*	1·08 (0·98 to 1·18)	1·24 (1·18 to 1·31)†
Creatinine clearance (ml/min)*	0·90 (0·67 to 1·2)	0·84 (0·72 to 0·97)

*Mean relative change expressed as ratios compared with baseline values (95% confidence intervals).
†p=0·011.

groups of patients but plasma creatinine concentration was increased to a greater extent by treatment with enalapril (table IV).

The effects of adding diuretics (indapamide or frusemide) were analysed (table VI). There was no difference in changes in urinary albumin excretion between patients who received enalapril alone and those requiring the addition of a diuretic. The rise in plasma creatinine concentration was significantly greater in patients receiving combined enalapril and diuretic compared with that in those treated with enalapril alone.

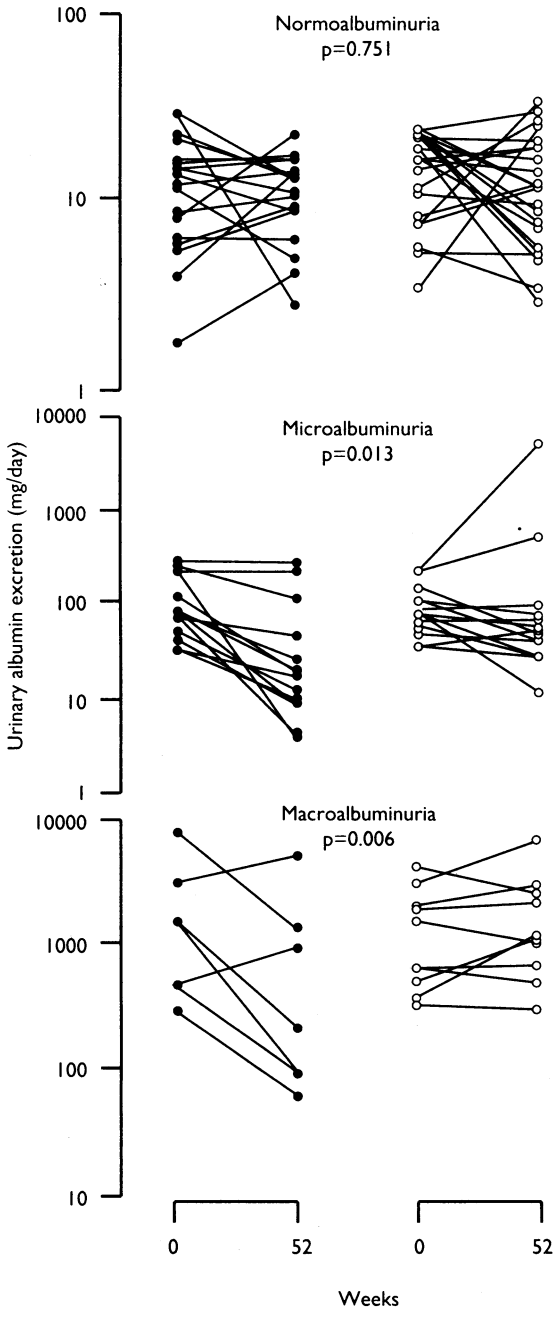

FIG 2—*Urinary albumin excretion, expressed on logarithmic scales, at weeks 0 and 52 in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria. p Values are shown for differences in changes in urinary albumin excretion between patients treated with enalapril (●) and nifedipine (○)*

Discussion

Considerable attention has been directed to the potential renal protective effects of angiotensin converting enzyme inhibitors in insulin dependent diabetes, and recent data suggest that these drugs may slow the rate of decline in glomerular filtration rate more effectively than β adrenoceptor blocking drugs.[5] Although non-insulin dependent diabetes is the more prevalent form of diabetes, particularly among non-whites,[6] and accounts for a considerable proportion of patients with end stage renal disease,[7] few trials have been reported comparing angiotensin converting enzyme inhibitors with alternative antihypertensive drugs in such patients.[8-16] Some of the longer term studies suggest there is little difference between antihypertensive drugs with regard to their effects on urinary protein excretion[8-15] whereas Ferder *et al* reported that enalapril had a superior antiproteinuric action to nifedipine in hypertensive patients.[16] We studied a homogeneous population of 102 Chinese patients with hypertension and non-insulin dependent diabetes to compare the effects of an angiotensin converting enzyme inhibitor, enalapril, with a calcium channel blocker, nifedipine, on blood pressure, renal function, and glycaemic control.

The antihypertensive effects of treatment with enalapril and nifedipine were similar at one year, but the fall in blood pressure was slower with the angiotensin converting enzyme inhibitor, as has been reported previously in elderly white patients with essential hypertension.[21] Furthermore, more patients receiving enalapril required a diuretic to achieve the goal systolic blood pressure (140 mm Hg in the supine position) than patients receiving nifedipine. These apparent differences in antihypertensive effectiveness might reflect the fact that full comparative dose response (drug and blood pressure) curves were not assessed, that the full antihypertensive action of enalapril may require more than 12 weeks to develop under the conditions of the study, and that racial factors might modify the antihypertensive efficacy of the drugs chosen—as is the case for β adrenoceptor blockers and diuretics in black, compared with white, patients.[22]

ALBUMINURIA

Despite a higher overall level of blood pressure, patients receiving enalapril showed the greater fall in urinary albumin excretion. A significant antiproteinuric action of enalapril, compared with nifedipine, was observed in patients who initially exhibited macroalbuminuria or microalbuminuria. The rates of conversion from normoalbuminuria to microalbuminuria were not different between the two study groups after one year. As diuretics were required by most patients receiving enalapril it is possible that the diuretics, rather than the angiotensin converting enzyme inhibitor, accounted for the fall in urinary albumin excretion, especially since indapamide has recently been shown to have an antiproteinuric action in hypertensive non-insulin dependent diabetic patients.[23] Further analysis of our data, however, showed similar antiproteinuric effects of enalapril whether or not a diuretic was added. Our data, therefore, agree with the findings of Ferder *et al*, who reported that fixed dose enalapril (40 mg/day) for one year in 18 hypertensive non-insulin dependent diabetic patients reduced urine excretion significantly whereas fixed dose nifedipine (40 mg/day) failed to alter urinary protein output in 12 patients.[16]

Endogenous creatinine clearance fell to a similar extent in the two treatment groups. By contrast, plasma creatinine rose to a greater extent in patients treated with enalapril. This discrepancy may be largely due to the greater coefficient of variation inherent in

the measurement of endogenous creatinine clearance, as it is dependent not only on determination of plasma creatinine concentrations but also on measurements of urinary creatinine concentration and urine volume.[24] Further analysis of our data showed that plasma creatinine concentrations rose more in patients taking enalapril who received concomitant diuretics than in patients taking only enalapril. The higher plasma creatinine concentration in the enalapril group might therefore reflect the greater number of patients requiring a diuretic. In severe cardiac failure the combination of a diuretic and angiotensin converting enzyme inhibitor often induces a rise in plasma creatinine concentration[25-27] which, on prolonged treatment, usually falls again.[25] Björck *et al* also reported an early fall in glomerular filtration rate in patients with insulin dependent diabetes after the introduction of enalapril but stabilisation occurred after six months.[5] Whether such a biphasic pattern in glomerular filtration rate occurs in our patients, remains to be seen.

EFFECT ON GLYCAEMIC CONTROL AND HAEMOGLOBIN

Hypoglycaemia consequent on initiation of treatment with angiotensin converting enzyme inhibitors has been reported in both insulin dependent and non-insulin dependent diabetic patients.[28-30] Furthermore, the angiotensin converting enzyme inhibitors have been shown to improve insulin sensitivity,[31] perhaps as a result of the accumulation of bradykinin, which has an insulin-like action.[32] Early in our study, the mean fasting plasma glucose concentration fell significantly in patients receiving enalapril, but not in those receiving nifedipine. Subsequent indices of glycaemic control were similar in the two groups, presumably because the addition of diuretics, which are known to worsen glucose tolerance,[30] countered any beneficial effect of the angiotensin converting enzyme inhibitor.

We observed a small but significant fall in haemoglobin concentration during treatment with enalapril. Angiotensin converting enzyme inhibitors have also been noted to reduce haemoglobin concentration in patients with insulin dependent diabetes,[5] congestive heart failure, chronic renal failure, and kidney transplants.[33] This effect may be partly due to a fall in angiotensin II concentration, which is known to stimulate erythropoietin under certain circumstances.[33,34]

Chinese hypertensive patients with non-insulin dependent diabetes treated with enalapril often required additional diuretic therapy to control blood pressure. Despite similar blood pressure responses in the two groups at the end of one year, enalapril reduced proteinuria more effectively than nifedipine. The reduction in proteinuria occurred in patients with both microalbuminuria and macroalbuminuria. Plasma creatinine concentration increased in both groups but to a greater extent in the enalapril group, particularly in those requiring diuretics. Withdrawal from the study was more common with enalapril, mostly because of cough or inadequate control of blood pressure. A longer period of treatment is required to establish the significance of the reduction of proteinuria with enalapril and to determine whether this will be translated into a beneficial effect on glomerular filtration rate. Our study will continue for a further two years. Until more information is available it is premature, in our view, to suggest that any one group of antihypertensive drugs is superior to any other in the treatment of non-insulin dependent diabetes associated with hypertension.

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