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Metabolic effects of long-term angiotensin-converting enzyme inhibition with fosinopril in patients with essential hypertension: relationship to angiotensin-converting enzyme inhibition

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Abstract. Fifty patients with mild to moderate essential hypertension were randomized to receive either 20 mg fosinopril daily for 16 weeks or placebo for 4 weeks followed by 12 weeks of 50 mg atenolol daily. Prior to these 16 weeks there was a placebo wash-out period of 2–6 weeks. Blood pressure measurements, euglycaemic, hyperinsulinaemic glucose clamps, and intravenous glucose tolerance tests (IVGTT) were performed at baseline and after 4 and 16 weeks. Blood lipid status was evaluated at baseline and 16 weeks.

The insulin sensitivity index (M/I) increased by 12% during the prolonged placebo period, and subsequently decreased by 12% during treatment with atenolol in that group. A post-hoc analysis of covariance indicated that the increase in insulin sensitivity during the initial 4 weeks may have been due to carry-over effects from previous antihypertensive treatment. Fosinopril increased glucose disappearance during IVGTT at 4 and 16 weeks (k values 1.46 and 1.33 vs 1.10 at baseline) but had no effect on insulin sensitivity. The change in insulin sensitivity and serum triglycerides during treatment with fosinopril was related to angiotensin-converting enzyme inhibition in serum.

In conclusion, carry-over effects from previous antihypertensive medication were indicated in this study, probably because of an insufficient wash-out period in many patients. Therefore, 4 weeks of placebo wash-out in all patients is advisable in this kind of investigation.

Key words: Hypertension, Fosinopril; essential, insulin sensitivity, carry-over effects, angiotensin converting enzyme inhibition, atenolol

In a series of studies we have investigated the effects of long-term treatment with different antihypertensive compounds on glucose and lipid metabolism. The results indicate that the effects are often large enough to significantly modify the risk of, for example, diabetes or coronary heart disease, even if the clinical consequences only can be investigated by large prospective trials. Details are reported in some recent reviews [1, 2]. Fosinopril is a recent addition to the family of angiotensin-converting enzyme (ACE) inhibitors. It is a highly lipophilic, phosphorus-containing prodrug which, after oral administration, is rapidly metabolised to the active diacid fosinoprilat.

We can find no published studies with a placebo-controlled, parallel group design in which the effects of ACE inhibitors on insulin sensitivity and lipoprotein levels have been investigated in hypertensive subjects. The present study aims to redress this. Fosinopril was compared with placebo for 4 weeks, and subsequently with atenolol for 12 weeks.

Subjects and methods

Study design

The study design comprised parallel groups over two periods (Fig. 1). After a variable time of placebo wash-out treatment (14 days to 6 weeks), patients were stratified by insulin-mediated glucose disposal and then randomized to receive treatment with 20 mg fosinopril once daily for 16 weeks or placebo for 4 weeks and thereafter 50 mg atenolol once daily for 12 weeks. The hyperinsulinaemic and euglycaemic clamp procedure, an intravenous glucose tolerance test (IVGTT) and blood pressure measurement were carried out at baseline, after 4 weeks and after 16 weeks. All other investigations were performed at baseline and after 16 weeks.

Patients

The study protocol was approved by the Human Ethics Committee of the Medical Faculty of Uppsala University and all patients gave their informed consent. Fifty-one patients, 18–72 years old, with essential hypertension were recruited through advertisements in local newspapers. At an initial visit the medical history of each patient was recorded and a physical examination was performed in order to detect any exclusion criteria, i.e. secondary hypertension, clinically important concomitant disease, recent myocardial infarction, stroke or transient ischaemic attack. Concomitant treatment with non-steroid anti-inflammatory drugs and previous treatment with thiazide diure-

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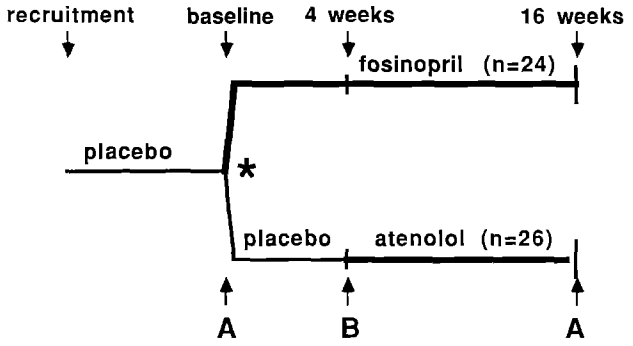

Fig. 1. Layout of trial. **A**: Blood pressure measurement, insulin sensitivity measurement, intravenous glucose tolerance test, lipid status, routine laboratory tests. **B**: Blood pressure measurement, insulin sensitivity measurement, intravenous glucose tolerance test. * Stratification by glucose disposal rate and randomization

Table 1. Clinical baseline characteristics of the treatment groups

	Fosinopril	Placebo/ atenolol	*P*
No. of patients	24	26	–
Sex (M/F)	12/12	12/14	1.0[a]
Age (years)	53.4 (8.0)	51.5 (10)	0.46
No. of smokers	5	6	1.0[a]
Body mass index ($kg \cdot m^{-2}$)	26.4 (2.9)	25.6 (3.3)	0.61
Serum triglycerides (mM)	1.45 (0.89)	1.35 (0.47)	0.79
Diastolic blood pressure (mm Hg)	99.1 (3.8)	99.7 (4.7)	0.90
Fasting serum insulin ($mU \cdot l^{-1}$)	7.58 (4.2)	8.40 (6.1)	0.94
Previous treatment (β-adrenoceptor/ non-β-adrenoceptor blocker)	14/10	22/4	0.059[a]

Values are means (SD)
[a] Fisher's exact test; all others Student's unpaired *t*-test

tics were also disallowed. The patients received atenolol placebo and fosinopril placebo in a single-blind, double-dummy fashion. Because of the design, with a prolonged placebo treatment period in one treatment branch, the placebo run-in period was kept as short as possible in each patient for ethical reasons: each patient was randomized as soon as two blood pressure values qualifying for inclusion (diastolic supine blood pressure 95–115 mmHg) had been recorded (22 patients had a placebo wash-out period of less than 28 days). The baseline characteristics of the two treatment groups are shown in Table 1. Compliance was assessed by interview and a pill count. All procedures were started at 7.30–8.00 a.m. after an overnight fast. The patients were told to take their study medication in the morning before each visit.

Exclusions

Two patients were excluded from the statistical analyses. One patient was diagnosed as diabetic based on baseline fasting glucose values, and one patient was excluded from the analyses of insulin sensitivity because of a technical error during the clamp procedure.

Blood pressure and heart rate

Blood pressure was measured in the right arm with a cuff of appropriate size. Systolic and diastolic blood pressures were defined as Korotkoff phases I and V, respectively. The value was recorded to the nearest even figure, twice in the supine position after resting for 10 min, and twice after the patient had been standing for 2 min.

Insulin sensitivity measurements

Insulin sensitivity was measured by the euglycaemic hyperinsulinaemic clamp procedure as described by DeFronzo et al [3]. Insulin (Actrapid Human, Novo, Copenhagen, Denmark) was infused at a rate of 56 mU/(min × m^2 body surface area). Plasma glucose was assayed in duplicate in a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, Calif., USA). Glucose disposal (M) was calculated as amount of glucose infused per minute and body weight and expressed as M = mg glucose/(minxkg bw). The insulin sensitivity index (M/I) was calculated by dividing glucose disposal by the mean plasma insulin concentration ($mU \cdot l^{-1}$) during the last 60 min of the procedure, and multiplied by 100 to represent glucose disposal at a plasma insulin level of 100 mU/l. The insulin sensitivity index compensates for differences between insulin levels attained during the clamp procedure, and is therefore considered a more accurate index of peripheral insulin sensitivity than the glucose disposal rate.

Intravenous glucose tolerance test

Each patient's response to 0.3 g per kg body weight intravenous glucose was assessed by a 90 – min IVGTT. The glucose disappearance rate was expressed as a k value calculated from the formula $k = \log_e 2 \times 100 / t_{1/2}$ where $t_{1/2}$ is the time required for the glucose concentration to be halved [4]. Plasma glucose was measured by the glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany). Insulin was assayed using a commercial radioimmunoassay kit (Phadeseph Insulin RIA, Pharmacia, Uppsala, Sweden). During the course of the study this was changed to an enzymatic-immunological assay (Enzymmun, Boehringer Mannheim, Germany) performed in an ES300 automatic analyser (Boehringer Mannheim). Checks made at the laboratory indicated that results obtained with the two methods were superimposable. Peak insulin response was defined as the mean of insulin values measured in the samples drawn at 4, 6, and 8 min and the insulin increment is reported as the difference between the peak and mean fasting values. Samples for measurement of serum free fatty acid concentrations were drawn before, and 60 and 90 min after glucose injection.

Lipid and lipoprotein measurement

Cholesterol and triglyceride concentrations in serum were assayed by enzymatic techniques (Boehringer Mannheim). High-density lipoproteins (HDL) were separated by precipitation with magnesium chloride/phosphotungstate. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula: LDL = serum cholesterol – HDL – (0.45 × serum triglycerides). Serum free fatty acids were measured by an enzymatic colorimetric method (Wako Chemical, Neuss, Germany).

Serum ACE activity

Serum ACE activity was measured fluorimetrically using hippuryl-histidyl-leucine as substrate [5].

Table 2. Blood pressure and heart rate values before and during treatment with fosinopril and atenolol

	Fosinopril		Atenolol	
	Baseline	16 weeks	Baseline	16 weeks
Supine				
Systolic BP	158(3.1)	141(4.0)**	160(3.2)	148(4.4)*
Diastolic BP	99.1(0.77)	90.7 (1.7)**	99.7(0.93)	91.7(1.7)**
Heart rate	73.1(2.0)	66.5(1.7)**, ****	74.5(1.8)	57.0(1.0)**, ****
Standing				
Systolic BP	155(2.9)	138(4.1)**	157(3.9)	147(4.6)***
Diastolic BP	104(1.2)	94.1(2.2)**	106(1.5)	96.3(1.6)**
Heart rate	80.2(1.8)	74.1(1.8)***, ****	82.0(2.1)	61.2(1.6)**, ****

* $P < 0.001$ compared with baseline; ** $P < 0.0001$ compared with baseline; *** $P < 0.01$ compared with baseline; **** $P < 0.0001$ between treatments (ANOVA)
Values are least square means (SEM)

Table 3. Changes in insulin sensitivity during treatment with fosinopril and atenolol

	Baseline	Fosinopril		Baseline	Placebo	Atenolol
	0 weeks	4 weeks	16 weeks	0 weeks	4 weeks	16 weeks
Glucose Disposal (mg/(min × kg)	5.86(0.32)	5.98(0.37)	5.83(0.35)	5.83(0.42)	6.35(0.43)*	5.85(0.30)**
Insulin Sensitivity index (mg/(min × kg × mU)	5.95(0.39)	6.16(0.51)	6.23(0.46)	5.86(0.50)	6.57(0.57)*	5.75(0.42)**

Values are least square means (SEM)
* $P < 0.05$ compared with baseline; ** $P < 0.05$ compared with 4 weeks (ANOVA)

Anthropometric measurements

Height was measured to the nearest centimeter, and body weight to the nearest 100 g. The body mass index was calculated as the ratio of the weight in kg to the square of the height in m.

Statistics

For data processing the statistical program package SAS version 6.04 for personal computers was used. The analyses have taken into account the design of the study, the scales, and the distribution of the variables. All tests used were two-sided. When necessary, variables were logarithmically transformed to allow the use of parametric tests for hypothesis testing. Testing for differences between treatment groups and between treatments and placebo was performed with a model for analysis of variance (ANOVA) with factors for treatment, study period, and patient, the interaction terms between treatment and study period representing treatment effects. Testing for baseline differences in nominal variables between groups was done by Fisher's exact test. Results are generally reported as mean and standard error of the mean (SEM) or 95% confidence interval (CI), except in Table 1, where standard deviation is reported. Statistical significance was accepted as P-values of less than 0.05. Stratification was done according to an expected median value for glucose disposal.

Results

Blood pressure

Both treatments lowered blood pressure significantly (Table 2).

Insulin sensitivity

Insulin sensitivity values are reported in Table 3. There were no significant differences between fosinopril and placebo or fosinopril and atenolol. The M and M/I values were unchanged after 4 weeks [+2.0% (CI–6.8 to +11) and +3.5% (CI–8.4 to +15), respectively] and 16 weeks [–0.51% (CI–9.3 to +8.5) and +4.7% (CI–7.1 to +17), respectively] of fosinopril treatment as was the case in the placebo/atenolol-treated group when measured over the whole study period [+0.34% (CI–8.3 to +9.1) and –1.9% (CI–14 to +9.2), respectively]. However, after the 4 weeks of placebo treament in that group both M and M/I values increased significantly [+8.9% (CI +0.3 to +18) and +12% (CI +0.17 to +23), respectively]. This may be due to influence from previous antihypertensive treatment (see below). After commencement of active treatment with atenolol the M and M/I values decreased significantly by 7.9% and 12%, respectively. Based on the variances, a power calculation was made. This showed the power of of the study to be 87% and 66% for detecting a 20% difference in effect between treatments for M and M/I values, respectively.

Relationship between ACE inhibition and insulin sensitivity

The change in values for M, M/I, and serum triglycerides correlated with serum ACE inhibition during treatment with fosinopril ($r = 0.53$, $P = 0.0091$, $r = 0.48$, $P = 0.022$; and $r = -0.54$, $P = 0.0075$ respectively; Fig. 2.)

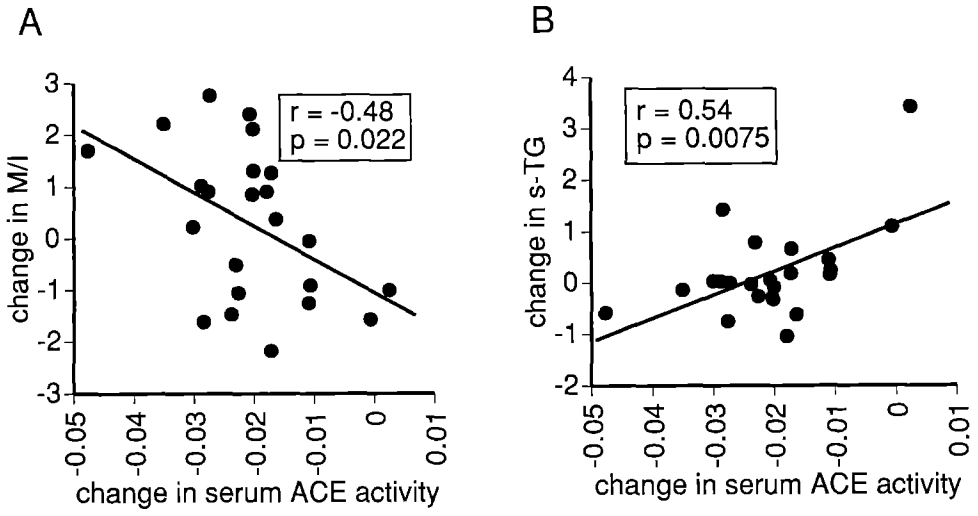

Fig. 2 A,B. Correlation between serum angiotensin-converting enzyme (ACE) inhibition and change in insulin sensitivity index (M/I; mg glucose × min^{-1} × kg bw^{-1} $(mU/l)^{-1}$, **A**) and serum triglycerides (S-TG; mmol × l^{-1}, **B**) in 24 patients with essential hypertension during long-term treatment with fosinopril

Table 4. Results from the intravenous glucose tolerance test during treatment with fosinopril and atenolol

	Baseline	Fosinopril		Baseline	Placebo	Atenolol
	0 weeks	4 weeks	16 weeks	0 weeks	4 weeks	16 weeks
Glucose disappearance constant (k)	1.10 (0.08)	1.46 (0.16)**	1.33 (0.14)*	1.20 (0.06)	1.40 (0.09)	1.37 (0.08)
Insulin peak (mU)	49.1 (8.2)	54.9 (9.1)	48.7 (8.8)	53.1 (8.6)	52.8 (7.0)	48.4 (9.0)***
Insulin increment (mU)	41.5 (7.5)	48.0 (8.6)	40.5 (8.1)	44.7 (7.8)	44.4 (6.4)	40.3 (8.2)***

Figures are least square means (SEM).
* $P < 0.05$ compared with baseline; ** $P < 0.01$ compared with baseline; *** $P < 0.06$ compared with 4 weeks (ANOVA)

Glucose tolerance

The fasting insulin and glucose values did not change in either treatment group. Results from the IVGTT are shown in Table 4. The k value increased significantly during treatment with fosinopril but not with atenolol.

Serum lipids and lipoproteins

Fosinopril treatment did not affect the serum lipid levels. Treatment with atenolol resulted in lower serum free fatty acids during fasting [0.44(0.03) vs 0.60(0.05) mmol · l^{-1} before treatment, $P < 0.05$, ANOVA], and at 90 min during IVGTT [0.15(0.01) vs 0.21(0.02) before treatment, $P < 0.05$, ANOVA]. Atenolol increased the total cholesterol level [5.69(0.21) vs 5.32(0.19) mmol · l^{-1} before treatment, $P < 0.01$, ANOVA], the LDL level [3.71(0.20) vs 3.35(0.17) mmol · l^{-1} before treatment, $P < 0.01$, ANOVA] and the LDL/HDL ratio (3.11 vs 2.70 before treatment, $P < 0.001$, ANOVA). The therapies differed significantly in their effects on the latter.

Influence of the wash-out period and previous therapy on insulin sensitivity

In an attempt to determine whether previous therapy had any influence on the insulin sensitivity values at baseline, we performed a post-hoc covariance analysis where previous therapy (expressed as β-adrenoceptor or non β-adrenoceptor blocker therapy), length of the placebo wash-out period, treatment group, and corresponding interaction terms were entered into the model along with the baseline value of the outcome variable (M or M/I). The change in the M value over the first 4 weeks was significantly affected by previous antihypertensive therapy ($P = 0.005$), the interaction between previous therapy and treatment group ($P = 0.027$), and the interaction between previous therapy and the length of the wash-out period ($P = 0.031$).

Discussion

When this study was designed it was assumed that the effect of fosinopril on insulin sensitivity would be similar to that observed for captopril [6]. The size of the study groups was calculated to be large enough to demonstrate such an effect over a 4-week period tested against the effect in a parallel group. As patients with moderate hypertension were included in the study, the length of the total permitted placebo treatment period was 7 weeks with hypertensive blood pressure values. This meant an unusually short wash-out/run-in period of 2–4 weeks in almost half of the patients. The prolonged placebo treatment was associated with a significant increase in insulin sensitivity which was offset by the ensuing treatment with atenolol, and at the end of the study insulin sensitivity had returned to baseline values. Therefore, it may be that insulin resistance induced by previous treatment with β-adrenoceptor-blocking agents was still present at baseline. Based on the use of atenolol in previous studies in which placebo run-in periods of 4–6 weeks have been used

[7, 8], the apparent lack of effect of atenolol on insulin sensitivity over the whole study period may represent a combination of an initial phase consisting of recovery from previous antihypertensive therapy and a second phase in which insulin sensitivity returns to the lower level attained during antihypertensive therapy with β-adrenoceptor blocking drugs. In an attempt to investigate this further we carried out a post-hoc covariance analysis. This did indeed indicate that previous therapy had significant influence on the change in glucose uptake during the initial 4 weeks of the study.

There was no detectable effect of fosinopril on insulin sensitivity, either compared to placebo during the initial 4 weeks or compared to the baseline value. However, it is possible that the comparison between the fosinopril and placebo effect during the initial four weeks is misleading, since the fosinopril group contained fewer previously β-adrenoceptor blocker-treated patients than the placebo/atenolol group (Table 1).

The positive correlation observed between serum ACE inhibition and the effect on insulin sensitivity in those treated with fosinopril may represent metabolically favourable haemodynamic changes during treatment with that compound. A link between skeletal muscle blood flow and insulin sensitivity has been described in normal humans [9, 10], obesity [9], non-insulin-dependent diabetes mellitus [11], and essential hypertension (P.-E. Andersson, personal communication). Also, antihypertensive compounds which have been associated with increased insulin sensitivity have generally been vasodilators [6, 12, 13]. The lack of an effect in the whole treatment group may be due to counterregulatory blood pressure-maintaining mechanisms with detrimental effects on insulin sensitivity. On the other hand, a moderate dose of an ACE inhibitor may cause a non-uniform vasodilation in skeletal muscle, enough to lower peripheral resistance and blood pressure, but also introducing a "steal" phenomenon, which could impair peripheral insulin sensitivity, whereas a higher concentration of inhibitor may produce a uniform, metabolically more favourable peripheral vasodilation.

In another recent study in healthy volunteers, insulin sensitivity as measured by the "minimal model" technique was found to be unchanged during treatment with 20 mg fosinopril once daily [14]. It is possible, however, that a higher dose of fosinopril may have a more positive effect on insulin sensitivity, in view of the above mentioned positive correlation between serum ACE inhibition and insulin sensitivity. Therefore, it may be of relevance that the recommended doses of captopril, a drug that previously has been shown to increase insulin sensitivity in essential hypertension [6] are considered to be in the upper, flat part of the dose-response relationship [15], which may explain the difference in effect. However, some recent studies have failed to detect any positive effect of ACE inhibitors on insulin resistance in hypertension [14, 16, 17], although others have [18]. Furthermore, very recent research in healthy volunteers presents conflicting data on whether angiotensin II acutely increases insulin sensitivity as measured by the glucose clamp technique [19, 20]. Bradykinin may also have the ability to increase muscle glucose uptake, and haemodynamic factors, as mentioned earlier, may also be of importance. The net effect of ACE inhibition on insulin sensitivity is therefore difficult to assess. It is clear, however, that positive effects on insulin sensitivity are not typical of ACE inhibitors at the doses used in clinical practice.

Fosinopril treatment was found here to increase glucose disposal in response to IVGTT, demonstrated as an increase in the k value. An increase in glucose tolerance has previously been observed with several ACE inhibitors [6, 14, 16, 17], but not in all studies [21–24]. A proposed reason for this putative effect is an ACE inhibitor-induced resistance to the potassium-lowering effect of insulin [16]. In this study we did not measure serum potassium levels during IVGTT or the glucose clamp procedure. In summary, the design used in this study proved less than perfect for this kind of metabolic investigation, making the results difficult to interpret. Nevertheless, we consider fosinopril to have minor effects on insulin sensitivity with a small positive effect on glucose tolerance. The insulin sensitivity during treatment with fosinopril may be influenced by dosage, a hypothesis that remains to be tested. Because this study uncovered circumstantial evidence implying a carry-over effect on insulin sensitivity from previous antihypertensive treatment, we consider a 4-week drug-free period before baseline examination mandatory in similar metabolic studies, although this is not always the case [25].

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