Effects of Benfluorex on Insulin Resistance and Lipid Metabolism in Obese Type II Diabetic Patients

RUTGERT BIANCHI, MD
VIVIAN BONGERS
BERT BRAVENBOER, MD
D. WILLEM ERKELENS, MD

OBJECTIVE — To evaluate the change in lipids and insulin sensitivity in 10 obese type II diabetic patients after treatment with benfluorex or placebo for 2 wk.

RESEARCH DESIGN AND METHODS — The study had a double-blind, cross-over design. Insulin sensitivity was measured with the euglycemic hyperinsulinemic glucose clamp technique at two different insulin infusion rates: 0.05 (clamp 1) and 0.10 $U \cdot kg^{-1} \cdot h^{-1}$ (clamp 2).

RESULTS — Subanalysis of the glucose infusion rate under steady-state conditions in the last 30 min of clamp 2 yielded a glucose infusion rate of 5.36 and 3.87 $mmol \cdot kg^{-1} \cdot min^{-1}$ after benfluorex and placebo, respectively ($P = 0.018$).

CONCLUSIONS — Benfluorex increases insulin sensitivity in obese type II diabetic patients.

Type II diabetes (1) is a common but heterogeneous disorder, characterized by an impaired action of insulin on peripheral and hepatic tissue, and a deficient glucose-mediated secretion of insulin (2). Type II diabetes often is associated with combined hyperlipidemia. The co-occurrence of type II diabetes, hyperlipidemia, obesity, and hypertension has been termed Syndrome X, with insulin resistance as the pivotal pathogenic mechanism (3). Benfluorex is a known hypolipidemic agent with possible glucose-lowering effects. Several clinical studies have shown a reduction in lipid levels and an improvement in glucose tolerance after treatment with benfluorex (4). The aim of this study was to investigate whether benfluorex decreases glucose levels by reducing peripheral insulin resistance, using the euglycemic hyperinsulinemic glucose clamp technique.

RESEARCH DESIGN AND METHODS

— We studied 10 obese patients with type II diabetes (Table 1). Patients were 35–60 yr of age, with a BMI >27 kg/m^2, glucagon-stimulated C-peptide increment after 1 mg intravenous glucagon >0.3 nM after 6 min, fasting glucose >7.7 mM, and an HbA_1 of 8.5–15%. Patients with other diseases or previous treatment with biguanides were excluded from the study. All patients gave written informed consent. The study was conducted according to the rules of the Helsinki Convention.

The study had a double-blind, cross-over design. After a run-in period of 2 wk, each patient was allocated randomly to a treatment schedule: placebo or benfluorex 150 mg three times a day for 2 wk, followed by a wash-out period of 2 wk and reciprocal treatment. Before and after each treatment period, we assessed metabolic parameters. After each treatment period, the euglycemic hyperinsulinemic glucose clamp technique was used to measure glucose uptake after an overnight fast. Compliance was determined by counting returned tablets. During the entire study, patients followed a weight-maintaining diet.

Glucose uptake was measured with the euglycemic hyperinsulinemic glucose clamp technique in two 2-h periods with two different insulin infusion rates: 0.05 (clamp 1) and 0.10 $U \cdot kg^{-1} \cdot h^{-1}$ (clamp 2). The targeted mean glucose level was 5.5 mM. This method has been described by DeFronzo et al. (5). Glucose was measured postprandially 2 h after a mixed meal containing 160 Kcal, 38% CHO, 17% protein, 45% fat, and 3.5 g of fiber. Chylomicrons, VLDL, cholesterol, TG,

FROM THE DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL, UTRECHT, THE NETHERLANDS.

ADDRESS CORRESPONDENCE AND REPRINT REQUEST TO RUTGERT BIANCHI, MD, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL UTRECHT, HEIDELBERGLAAN 100, 3584 CX UTRECHT, THE NETHERLANDS.

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TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; CHO, CARBOHYDRATE; VLDL, VERY-LOW-DENSITY LIPOPROTEIN; TG, TRIGLYCERIDE; apoA-I, APOLIPOPROTEIN A-I; apoB-I, APOLIPOPROTEIN B-I; MANOVA, MULTIPLE ANALYSIS OF VARIANCE; BP, BLOOD PRESSURE; HGP, HEPATIC GLUCOSE PRODUCTION.

Table 1— *Clinical characteristics of type II diabetic patients*

	Treatment group	
	Benfluorex/placebo sequence	Placebo/benfluorex sequence
n	5*	5
Age (yr)	43.8 ± 1.0	46.0 ± 3.4
Weight (kg)	104.8 ± 6.6	92.7 ± 6.4
BMI (kg/m^2)	33.8 ± 1.2	34.5 ± 2.7
HbA_1 (%)	12.4 ± 1.6	9.1 ± 0.6
Fasting glucose (mM)	13.3 ± 1.9	12.0 ± 1.5
Postprandial glucose (mM)	16.4 ± 1.9	15.0 ± 1.1
Fasting C-peptide (nM)	1.5 ± 0.4	1.2 ± 0.4

Data are means ± SE. Comparison between both sequences, NS.
*For postprandial glucose, $n = 4$.

apoA-I, apoB-I, cortisol, C-peptide, and insulin were measured with our standard laboratory methods.

Statistical analysis

We tested the homogeneity of the subgroups with MANOVA for quantitative variables and the χ^2 test for qualitative variables. MANOVA was used to analyze treatment effects.

RESULTS — The study group comprised five men and five women (Table 1). We observed no significant changes in BMI and BP during treatment. Patient compliance was 87%. No differences were evident between treatment groups. Table 2 shows the biochemical variables. Total glucose uptake in the two clamp periods was compared separately for treatment with benfluorex and placebo. Not all patients reached euglycemia during clamp 1 because of high fasting glucose levels. The plateaus of glycemia under the first clamp were 5.5–12 mM for placebo vs. 5.5–9 mM for benfluorex; 70% of the patients in the benfluorex group and 40% in the placebo group reached a euglycemic plateau. Figures 1*A* and 1*B* present the glucose uptake data, and Fig. 1*C* shows the subanalysis of the last 30 min. No side effects were observed by verbal report or laboratory investigations. One patient complained of transient nausea after benfluorex.

CONCLUSIONS — We observed an increased glucose uptake during low and high insulin clamping after treatment with benfluorex. Fasting and postprandial glucose were lower after benfluorex than after placebo, whereas fasting insulin levels were not different. Taken together, these observations suggest an increased disposal of glucose attributable to a reduction in insulin resistance. The small differences between postprandial and fasting glucose values can be explained by high fasting glucose levels attributable to relative insulin resistance and a light breakfast, consisting merely of slow- reabsorbing CHO and fiber.

Banerji and Lebovitz (6), using ^3H-labeled glucose, calculated the concentration of insulin that suppressed basal glucose production by 50% to be 30.5 μU/L in obese type II diabetic patients. The insulin levels reached in our experiments during steady state for the last 30 min of clamp 2 were 153.7 ± 8.2 and 157.7 ± 7.6 μU/L for the benfluorex and placebo groups, respectively. This suggests HGP was completely suppressed.

Reaching euglycemia was not always possible during clamp 1: 30% of the patients in the benfluorex group did not reach a euglycemic plateau, compared with 60% of the patients in the placebo group. Although these data sug-

Table 2— *Parameters of glucose and lipid metabolism*

		Placebo treatment		Benfluorex treatment		
	n	Before	After	Before	After	*P* Value
Fasting glucose (mM)	8	11.9 ± 0.9	13.3 ± 1.0	13.1 ± 1.1	10.2 ± 0.9	<0.001*
Postprandial glucose (mM)	7	14.8 ± 1.9	14.8 ± 1.5	13.9 ± 1.3	12.3 ± 1.4	0.013*
Insulin (μU/L)	10	25.9 ± 4.6	25.1 ± 5.1	26.5 ± 6.5	22.0 ± 5.2	0.435
C-peptide (nM)	10	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.2	1.3 ± 0.2	0.908
HbA_1(%)	9	10.1 ± 1.0	10.5 ± 1.1	10.4 ± 0.9	10.1 ± 0.9	0.166
Cholesterol (mM)	10	6.1 ± 0.6	5.6 ± 0.4	6.0 ± 0.4	5.4 ± 0.4	0.042*
TG	10	4.0 ± 0.8	3.0 ± 0.7	3.6 ± 0.7	2.3 ± 0.4	0.636
apoA-1 (g/L)	9	1.22 ± 0.08	1.21 ± 0.07	1.22 ± 0.05	1.16 ± 0.05	0.650
apoB (g/L)	9	0.91 ± 0.09	0.77 ± 0.08	0.89 ± 0.09	0.74 ± 0.06	0.938

Data are means ± SE.
*Placebo treatment compared with benfluorex treatment.

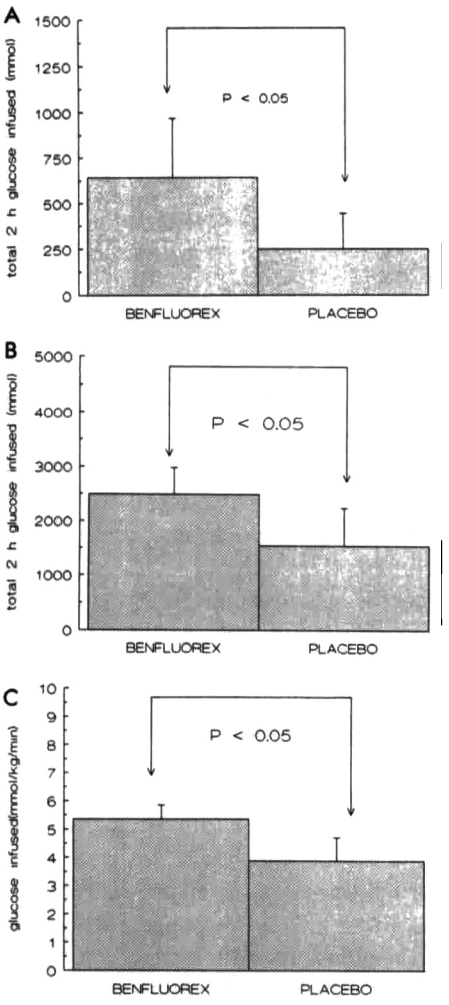

Figure 1—*A: The total amount of glucose (mean ± SE) infused during clamp 1 (insulin infusion rate 0.05 $U \cdot kg^{-1} \cdot h^{-1}$) for all patients treated with benfluorex or placebo. After benfluorex, significantly more glucose was infused (643.4 ± 323.8 mmol) than after placebo (250.1 ± 193.3 mmol, $P < 0.05$). B: The total amount of glucose (mean ± SE) infused during clamp 2 (insulin infusion rate 0.10 $U \cdot kg^{-1} \cdot h^{-1}$) for all patients treated with benfluorex or placebo. After benfluorex, significantly more glucose was infused (2490.7 ± 490.5 mmol) than after placebo (1544.3 ± 693.9 mmol, $P < 0.05$). C: The glucose infusion rate (mean ± SE) during steady state in the last 30 min of clamp 2 (insulin infusion rate 0.10 $U \cdot kg^{-1} \cdot h^{-1}$) for all patients treated with benfluorex or placebo. Neither group had significant differences in mean plasma glucose or insulin levels in this period, although the glucose infusion rate was significantly higher after benfluorex (5.36 ± 0.49 $mmol \cdot kg^{-1} \cdot min^{-1}$) than after placebo (3.87 ± 0.83 $mmol \cdot kg^{-1} \cdot min^{-1}$, $P < 0.05$).*

gest improved glucose uptake during benfluorex treatment, we cannot draw definite conclusions regarding the effects on insulin sensitivity. Obtaining euglycemia was possible in all patients during clamp 2, with a stable glucose level of 5.5 mM during the last 30 min of the clamp. Glucose infusion rates were significantly higher during these last 30 min after benfluorex than after placebo, whereas plasma insulin levels and plasma glucose concentrations were comparable. Assuming HGP was completely suppressed, these results indicate a reduction of peripheral insulin resistance.

In none of the other studies on benfluorex and metabolic control was peripheral insulin resistance assessed with the hyperinsulinemic euglycemic clamp technique. Pasquali et al. (7) studied 16 overweight type II diabetic patients treated with benfluorex for 3 mo. Fasting and postprandial glucose and HbA_{1c} levels improved regardless of weight changes. They found no changes in fasting or meal-stimulated insulin levels. Pestell et al. (8) and Scheen et al. (9) studied the effects of short-term treatment of the structurally related compounds fenfluramine and D-fenfluramine in obese type II diabetic patients. They observed a significant increase in insulin action with the hyperinsulinemic euglycemic clamp technique, independent of significant weight reduction.

In our study we observed a reduction in TG in both the benfluorex and placebo groups. The most likely explanation is the more consequent dieting of our patients, although dietary intake, as assessed by repeated inquiries, was not significantly different between either treatment group. In addition, weight was stable in both groups during the study (98.8 ± 4.7 and 98.4 ± 4.7 kg during benfluorex treatment; 98.2 ± 4.7 and 98.3 ± 4.6 kg during placebo treatment, $P = 0.466$). We observed a significant treatment effect on cholesterol. The higher level of cholesterol before treatment in the benfluorex/placebo group than in the placebo/benfluorex group, with the subsequent greater reduction in cholesterol levels, could account for this.

We conclude that benfluorex increases the glucose disposal rate without changing peripheral insulin levels in obese type II diabetic patients.

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