Effects of Troglitazone

A new hypoglycemic agent in patients with NIDDM poorly controlled by diet therapy

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OBJECTIVE — To investigate the clinical efficacy of troglitazone, a newly developed oral hypoglycemic agent, in patients with NIDDM.

RESEARCH DESIGN AND METHODS — There were 284 NIDDM patients (20–82 years of age) whose glycemic control while on a diet was judged stable but was judged unsatisfactory (fasting plasma glucose [FPG] ≥8.3 mmol/l) when entered into a multicenter and double-blind study with parallel groups study. They were randomly allocated into two groups, the troglitazone group (the T group: 400 mg/day p.o.) and the placebo group (the P group), and were treated with test drugs for 12 weeks.

RESULTS — We evaluated efficacy in 136 patients of the T group and 126 patients of the P group. There was no significant difference in any of baseline characteristics between the T and P groups. In the T group, FPG and HbA_{1c} decreased significantly after treatment (before versus after, FPG 10.1 ± 1.6 vs. 8.8 ± 1.9 mmol/l, $P < 0.001$; HbA_{1c}: 8.6 ± 1.5 vs. 8.1 ± 1.7%, $P < 0.001$). FPG and HbA_{1c} did not change after treatment in the P group (before versus after, FPG 10.1 ± 1.8 vs. 9.9 ± 2.1 mmol/l; HbA_{1c} 8.5 ± 1.5 vs. 8.6 ± 1.6%). Of 136 patients in the T group, 62 (45.6%) were classified as responders. Serum triglyceride level also decreased in the T group but not in the P group. Body weight increased slightly only in the T group. There were no differences in changes in blood pressure between the two groups. No serious adverse events occurred in either group.

CONCLUSIONS — Troglitazone at 400 mg/day decreased FPG and HbA_{1c} significantly in NIDDM patients who had failed to respond to diet therapy. Troglitazone, developed as a drug to enhance insulin action, can be a useful hypoglycemic agent for the treatment of NIDDM.

Both impaired insulin secretion and decreased insulin sensitivity are major characteristics of NIDDM (1,2). The treatment of diabetes aims to prevent the progress of the disease itself and to prevent the development and deterioration of chronic complications by continuous good glycemic control.

Troglitazone (code name, CS-045), a newly developed oral hypoglycemic agent by Sankyo (Tokyo, Japan), showed a significant antidiabetic effect in various animal models of NIDDM with insulin resistance or slightly impaired insulin secretion (3,4). The putative mechanism of action of this drug is considered to be the potentiation of insulin sensitivity and reduction of hepatic glucose production (4–9).

A dose-finding multicenter clinical trial demonstrated that troglitazone at a daily dose of 400 mg improved glycemic control in NIDDM patients (10,11). In this study, we conducted a multicenter double-blind study to investigate the clinical efficacy and safety of troglitazone for the treatment of NIDDM.

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CPR, C-peptide; FPG, fasting plasma glucose.

RESEARCH DESIGN AND METHODS

— Before starting this study, the protocol was approved by the ethical committee of each institution. The study was carried out according to the Declarations of Helsinki (1964) and Tokyo (1975) and fulfilled the conditions of "Good Clinical Practice."

Inclusion and exclusion criteria

The major inclusion criteria for this study were patients with NIDDM who have been treated with diet alone but whose fasting plasma glucose (FPG) levels were >8.3 mmol/l, which varied <1.7 mmol/l during the 1 month run-in period. Patients treated with hypoglycemic agents, those with severe complications, and those pregnant or of lactating and childbearing potential were excluded from the study. Before initiating the study, patients were fully informed of the details of the study and potential risks and benefits. Informed consents were obtained from all participants.

At the end of the run-in period, patients were randomly allocated to either the troglitazone treatment group (the T group: 200 mg b.i.d.) or placebo treatment group (the P group: b.i.d.) (1:1 ratio).

Throughout the run-in period and the treatment period, efforts were made not to change diet instruction and other therapies known to affect glycemia, lipids, and body weight. FPG and HbA_{1c} were measured at week −4, 0, 4, 8, and 12. Fasting serum C-peptide (CPR) level was measured at week 0 and 12, if possible. Subjective and objective symptoms, body weight, and blood pressure were recorded throughout the run-in period and treatment period. Blood counts were measured at week 0, 4, 8, and 12, and liver and renal functions and urinalyses were measured at week 0, 4, and 12. All laboratory findings were measured in each institution. Plasma glucose levels

Table 1—*Demographic characteristics of efficacy evaluated patients*

Item	T group	P group	*P* value
n (men/women)	136 (69/67)	126 (67/59)	NS*
Age (year)	54.6 ± 10.1	57.4 ± 9.3	0.0496
BMI (kg/m^2)	24.1 ± 3.5	24.7 ± 3.4	NS
Duration of diabetes (years)	6.3 ± 4.4	7.5 ± 5.4	NS
Family history (yes/no/unknown)	66/63/7	49/67/10	NS*
Diabetic complications			
Retinopathy (yes/no/unknown)	29/105/2	31/95/0	NS*
Nephropathy (yes/no)	18/118	30/96	0.027*
Neuropathy (yes/no)	20/116	29/97	NS*
Values in the run-in period			
FPG (mmol/l)	10.1 ± 1.6	10.1 ± 1.8	NS
HbA_{1c} (%)	8.61 ± 1.51	8.51 ± 1.46	NS
Fasting CPR (nmol/l)	0.82 ± 0.45	0.85 ± 0.45	NS
Total cholesterol (mmol/l)	5.57 ± 0.87	5.46 ± 0.94	NS
HDL cholesterol (mmol/l)	1.33 ± 0.40	1.31 ± 0.36	NS
Triglyceride (mmol/l)	1.81 ± 1.30	1.62 ± 1.02	NS

Data are means ± SD. *χ^2 test, others; Wilcoxon's 2-sample test. NS; $P \geq 0.05$. $n = 129$ in the T group, 116 in the P group for FPG. $n = 66$ in the T group, 65 in the P group for fasting CPR.

were measured by glucose oxidase method. HbA_{1c} levels were measured by high-performance liquid chromatography method. C-peptide was measured by radioimmunoassay.

If any adverse events or clinically significant laboratory abnormalities were observed, they were categorized in five grades by each investigator considering the patients' status and medical history: obviously related, probably related, possibly related, probably unrelated, and unrelated.

Statistical analysis

The baseline FPG level was calculated as an average of FPG levels at the run-in period. The data at week 0 in the run-in period were used for the baseline of other variables. Changes in fasting CPR, lipids, body weight, and blood pressure were analyzed for cases that have data both at week 0 and week 12. Data were analyzed for an average of FPG levels at week 8 and week 12 as the primary endpoint, with HbA_{1c} at week 12 as the secondary endpoint. Statistical comparisons were made with Wilcoxon's 1-sample test, Wilcoxon's 2-sample test, or χ^2 test. Results are judged significant at $P < 0.05$.

RESULTS— From 76 centers, 284 patients were randomly allocated, 145 to the T group and 139 to the P group. There were 22 patients (9 of the T group, 13 of the P group) excluded from the efficacy analysis, and 39 patients were excluded from the analysis of FPG (16 of the T group, 23 of the P group). All judgments on inclusion and exclusion were made before unblinding the treatment code. Therefore, we evaluated efficacy in 136 patients of the T group and 126 patients of the P group and FPG in 129 patients of the T group and 116 patients of the P group.

Demographic characteristics

Demographic characteristics of the patients evaluated for efficacy are summarized in Table 1. The T and P groups had similar backgrounds in gender, BMI, FPG, HbA_{1c}, fasting CPR, and lipids levels. There were some small differences in age ($P = 0.0496$) and the frequency of diabetic nephropathy ($P = 0.027$) between the two groups.

Efficacy

FPG. FPG level in the run-in period was 10.1 ± 1.6 mmol/l in the T group and 10.1 ± 1.8 mmol/l in the P group, respectively. After treatment, the average of the FPG levels at week 8 and 12 was 8.8 ± 1.9 mmol/l in the T group and 9.9 ± 2.1 mmol/l in the P group, respectively; the decrease in FPG was statistically significantly greater in the T group than in the P group (1.3 vs. 0.2 mmol/l, $P < 0.001$). Figure 1 shows the changes in FPG from the baseline to the end of treatment. In the T group, a significant decrease in FPG was observed already after week 4 ($P < 0.001$), but there was no significant change in FPG in the P group at any period.

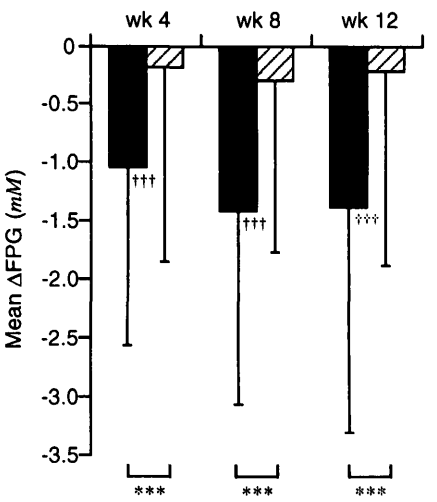

Figure 1—*Mean ± SD decrease of FPG at week 4, 8, and 12 of the treatment period from the run-in period in the troglitazone-treated (T, ■) and placebo-controlled (P, ▨) groups. Differences between the T group and the P group were significant (*** P < 0.001) at all the treatment periods. The fall in FPG levels with the T group was significant (†††P < 0.001) from baseline at week 4, 8, and 12.*

HbA_{1c}. The decreases in HbA_{1c} from the baseline are shown in Fig. 2. HbA_{1c} decreased gradually and progressively in the T group, whereas it remained unchanged in the P group. At weeks 8 and 12, there were significant differences in HbA_{1c} be-

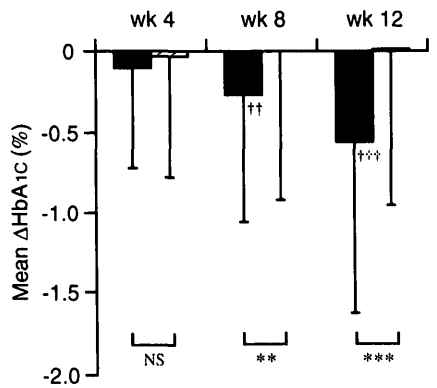

Figure 2—*Mean ± SD decrease of HbA_{1c} at week 4, 8, and 12 of the treatment period from the run-in period. Differences between the T group (■) and the P group (▨) were significant at week 8 (**P < 0.01) and week 12 (***P < 0.001). The fall in HbA_{1c} with the T group was significant at week 8 (††P < 0.01) and week 12 (†††P < 0.001).*

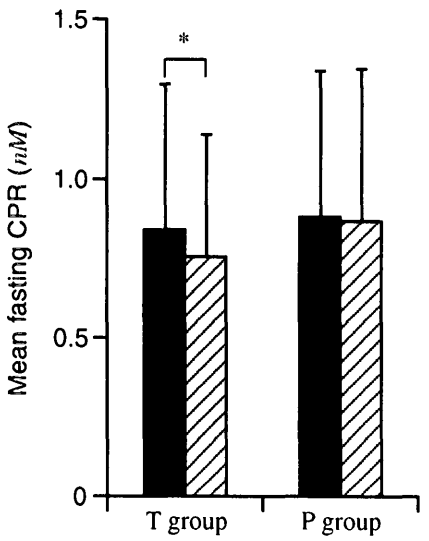

Figure 3—*Mean ± SD of fasting CPR level before (■) and after (▨) treatment of troglitazone (T group, n = 56) or placebo (P group, n = 58). Fasting CPR decreased significantly in the T group (*P < 0.05) but not in the P group.*

tween the two groups (week 8, $P = 0.006$; week 12, $P < 0.001$).

Fasting CPR. The changes in fasting CPR are shown in Fig. 3. Baseline fasting CPR levels were almost the same in these two groups. There was no significant difference in fasting CPR between the two groups. After the treatment, fasting CPR levels fell significantly ($P = 0.049$) in the T group only.

Lipids. The changes in total cholesterol, HDL cholesterol, and triglyceride are shown in Table 2. The levels of total cholesterol and HDL cholesterol did not change and were not different between the two groups. On the other hand, the decrease of triglyceride was significantly greater in the T group than in the P group ($P < 0.001$).

Body weight and blood pressure. As shown in Table 2, the changes in body weight were significantly different between the two groups ($P < 0.001$). A slight but significant increase in body weight was observed in the troglitazone-treated patients ($P = 0.004$), whereas a significant decrease was observed in the placebo-treated patients ($P = 0.004$). The changes in blood pressure were not different between the two groups.

Analysis of the troglitazone group

Comparison between responder and nonresponder. In both the T and P groups, there was a variation in the responses of FPG and HbA_{1c}. We defined a responder as a patient who experienced a FPG reduction of >20% or a HbA_{1c} reduction of >1%. Of 136 patients, 62 (45.6%) in the T group were classified as responders. On the other hand, in the placebo-treated patients, only 17 of 126 patients (13.5%) were classified as responders.

In the T group, there were significant differences in BMI and HbA_{1c} levels at baseline between the responder and nonresponder groups (Table 3). BMI is significantly higher in the responder group than in the nonresponder group ($P = 0.004$). Baseline HbA_{1c} level was higher in the responder group ($P = 0.018$). FPG, fasting CPR, total cholesterol, and triglyceride levels tended to be higher in the responder group, although the differences were not statistically significant.

Effect on triglyceride. As previously described, triglyceride levels significantly decreased after treatment with troglitazone compared with the placebo treatment. In this study, however, baseline levels of triglyceride were scattered, and some patients had hypertriglyceridemia. To clarify the triglyceride-lowering effect of the troglitazone, we divided the T group into two subgroups; the high-triglyceride group (high group; baseline triglyceride level ≥1.7 mmol/l) and the low-triglyceride group (low group; baseline triglyceride level <1.7 mmol/l). Table 4 shows the changes in lipids in these two groups. The decrease of triglyceride was observed only in the high group ($P < 0.001$). The percentage decrease of triglyceride in the high-triglyceride group was 33%.

Safety

Six patients (three of the T group, three of the P group) were excluded from the safety analysis because of serious protocol violations. There were 278 evaluated for safety (142 of the T group, 136 of the P group). Among the safety excluded cases, there were no adverse events.

Adverse events that were suspected to be treatment-related occurred in 10 cases in the T group (7.0%) and 5 cases in the P group (3.7%). Among these cases, treatment was discontinued in five

Table 2—*Changes in lipids, body weight, and blood pressure*

Item	T group	P group	*P* value
Total cholesterol (mmol/l)			
Before	5.57 ± 0.87	5.46 ± 0.94	
After	5.60 ± 1.01	5.44 ± 0.99	
Difference	0.03 ± 0.73	−0.02 ± 0.67	NS
HDL cholesterol (mmol/l)			
Before	1.33 ± 0.40	1.31 ± 0.36	
After	1.36 ± 0.36	1.30 ± 0.37	
Difference	0.02 ± 0.25	−0.02 ± 0.21	NS
Triglyceride (mmol/l)			
Before	1.81 ± 1.30	1.62 ± 1.02	
After	1.42 ± 0.89	1.63 ± 1.13	
Difference	−0.39 ± 1.07	0.01 ± 0.82	<0.001
Body weight (kg)			
Before	61.0 ± 11.0	61.8 ± 10.4	
After	61.6 ± 11.3*	61.4 ± 10.4*	
Difference	0.6 ± 1.6	−0.4 ± 1.2	<0.001
Systolic blood pressure (mmHg)			
Before	131.8 ± 17.5	136.0 ± 17.5	
After	130.3 ± 18.5	132.9 ± 16.8	
Difference	−1.5 ± 16.1	−3.1 ± 15.4	NS
Diastolic blood pressure (mmHg)			
Before	77.2 ± 9.8	79.3 ± 10.2	
After	75.8 ± 10.5†	78.9 ± 8.9	
Difference	−1.4 ± 8.9	−0.4 ± 9.6	NS

Data are means ± SD. Wilcoxon's 2-sample test was used for *P* values; NS, $P \geq 0.05$. In each group, the statistical analysis was determined by Wilcoxon's 1-sample test; *$P < 0.01$, †$P < 0.05$ vs. before treatment.

Table 3—*Demographic characteristics of the responder and nonresponder group in the troglitazone treatment group*

Item	Responder	Nonresponder	*P* value*
n	62	74	
Age (years)	55.2 ± 11.3	54.2 ± 9.1	NS
BMI (kg/m^2)	25.0 ± 3.3	23.4 ± 3.4	0.004
Duration of diabetes (years)	6.4 ± 4.6	6.3 ± 4.1	NS
Baseline values			
FPG (mmol/l)	10.3 ± 1.7	9.9 ± 1.5	NS
HbA_{1c} (%)	8.92 ± 1.53	8.35 ± 1.45	0.018
Fasting CPR (mmol/l)	0.94 ± 0.55	0.73 ± 0.32	NS
Total cholesterol (mmol/l)	5.72 ± 0.86	5.43 ± 0.87	NS
HDL cholesterol (mmol/l)	1.33 ± 0.40	1.33 ± 0.40	NS
Triglyceride (mmol/l)	1.87 ± 1.25	1.76 ± 1.35	NS

Data are means ± SD. *Wilcoxon's 2-sample test was used for *P* values; NS, $P \geq 0.05$. $n = 58$ in the responder group, 71 in the nonresponder group for FPG. $n = 29$ in the responder group, 37 in the nonresponder group for fasting CPR.

patients in the T group and four in the P group. There were no severe adverse events in either group. All events were relieved or disappeared soon. Dizziness (four of the T group, one of the P group) and edema (three of the T group) were more frequent in the T group than in the P group.

The incidence of possible hypoglycemic symptoms was 1.4% (2 of 142) in the T group and 0.7% (1 of 136) in the P group. These symptoms were mild and relieved by ingesting sugar or food.

With regard to laboratory abnormalities that were judged to be treatment-related, 27 occasions in 13 patients (9.2%) in the T group and 17 occasions in 7 patients (5.1%) in the P group were recorded. No significant difference was observed in the incidence between the two groups. Decreases in red blood cell count (four of the T group), decreases in hemoglobin (five of the T group), decreases in hematocrit (three of the T group), and increases in lactic dehydrogenase (six of the T group, one of the P group) were observed.

CONCLUSIONS— In this study, a significant decrease in FPG and HbA_{1c} levels was evident in patients receiving troglitazone. In contrast, no significant change in FPG and HbA_{1c} levels was observed in the placebo group. These results are consistent with those of the phase-two clinical studies (11) and indicate that the drug is effective in improving glycemic control in NIDDM.

The drug was not effective in all patients receiving troglitazone. Of the patients in the troglitazone group, ~50% (62 out of 136 patients) were responders. Between responder and nonresponder groups, there were significant differences in BMI and HbA_{1c} levels in the run-in period. Insulin resistance is a characteristic feature of obesity in both humans and animals. This drug appears to be more effective in obese patients. Suter et al. (12) reported a pilot clinical study of this drug in 11 obese patients with NIDDM. In their study, 8 out of 11 patients were responders. Oral glucose tolerance test and glucose clamp tests showed that the fall in plasma glucose was related to the suppression of hepatic glucose output.

The triglyceride-lowering effect has been observed in several preclinical studies in obese animal models of NIDDM (4,6) and in the late phase-two clinical study (11). In accordance with the previous studies, serum triglyceride level decreased after treatment with troglitazone. The mean triglyceride level of the troglitazone group was 1.8 mmol/l. When the T group patients were divided into two groups according to the baseline level of serum triglyceride, the decrease of triglyceride was observed only in the group with a high triglyceride level at baseline.

Troglitazone decreased blood pressure in obese Zucker rats (13) and fructose-induced insulin resistance rats (14). On the other hand, troglitazone did not show blood pressure–lowering effects in spontaneously hypertensive rats in spite of improved insulin resistance (15). Nolan et al. (16) demonstrated that troglitazone lowered blood pressure in obese subjects with impaired glucose tolerance. Ogihara et al. (17) also demonstrated that troglitazone showed hypotensive effect in essential hypertensive patients with NIDDM. In this study, we could not see the blood pressure–lowering effect of troglitazone. These differences may be explained by the difference of patients characteristics. There are lots of arguments about whether insulin resistance is one of the causes for hypertension. The effect of troglitazone on hypertension still remains unresolved.

Body weight increased signifi-

Table 4—*Changes in lipids in the T group stratified by the starting triglyceride level*

Item	High group	Low group	*P* value
Triglyceride (mmol/l)			
Before	3.00 ± 1.44	1.08 ± 0.33	—
After	2.00 ± 0.95*	1.05 ± 0.56	—
Difference	1.00 ± 1.40	−0.03 ± 0.46	$P < 0.001$
Total cholesterol (mmol/l)			
Before	5.85 ± 0.84	5.40 ± 0.87	—
After	5.93 ± 0.96	5.38 ± 1.00	—
Difference	0.08 ± 0.77	−0.02 ± 0.62	NS
HDL cholesterol (mmol/l)			
Before	1.22 ± 0.44	1.40 ± 0.36	—
After	1.23 ± 0.29	1.43 ± 0.40	—
Difference	0.01 ± 0.33	0.04 ± 0.21	NS

Data are means ± SD. The high group (baseline triglyceride level ≥1.7 mmol/l) consisted of 49 patients, and the low group (baseline triglyceride level <1.7 mmol/l) consisted of 76 patients. Maximum triglyceride value was 8.8 mmol/l in the high group and 1.7 mmol/l in the low group, respectively. Minimum triglyceride value was 1.7 mmol/l in the high group and 0.5 mmol/l in the low group, respectively. Wilcoxon's 2-sample test was used for *P* value. NS, $P \geq 0.05$. In each group, the statistical analysis was determined by Wilcoxon's 1-sample test. *$P < 0.001$ vs. before treatment.

cantly in patients receiving troglitazone, although the increase was minimal. This suggests that the improvement of glycemic control was not due to body weight reduction in the T group.

Adverse reactions were observed in both groups with no significant difference in frequency. Dizziness and edema were more common with troglitazone than with placebo. Edema was also reported from the previous late phase-two study (11). In the present study, edema appeared in three patients, but it was temporary and disappeared in all patients without cessation of the treatment. Possible hypoglycemic symptoms were observed in a few cases in both groups.

Abnormal laboratory findings were detected in 13 (9.2%) patients receiving troglitazone and 7 (5.1%) receiving placebo, but there was no significant difference in frequency between the groups. As shown in the previous clinical studies, decreased erythrocyte count and elevated lactic dehydrogenase were more common with troglitazone than with placebo.

In conclusion, we have shown the effectiveness and safety of troglitazone for the treatment of NIDDM patients in a double-blind placebo-controlled method. Troglitazone at 400 mg/day decreased FPG and HbA_{1c} in patients with NIDDM who had failed to respond to diet therapy.

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