Pioglitazone Metabolic Effect in Metformin-Intolerant Obese Patients Treated with Sibutramine

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Abstract

Objective Metformin is the drug of choice to treat obese type 2 diabetes patients because it reduces either insulin-resistance and body weight. We aimed to comparatively test the efficacy and tolerability of pioglitazone and sibutramine in metformin-intolerant obese type 2 diabetic patients treated with sibutramine.

Materials and Methods Five hundred and seventy-six consecutive Caucasian obese type 2 diabetic patients were evaluated during a 12-months period and fifty-two patients were resulted intolerant to metformin at maximum dosage (3,000 mg/day). All intolerant patients to metformin received a treatment with pioglitazone (45 mg/day) and sibutramine (10 mg/day) and they were compared with fifty-three patients treated with metformin (3,000 mg/day) and sibutramine (10 mg/day) for 6 months in a single-blind controlled trial. We assessed body mass index, waist circumference, glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin, lipid profile, systolic blood pressure, diastolic blood pressure and heart rate at baseline and after 3, and 6 months.

Results No body mass index change was observed at 3, and 6 months in pioglitazone + sibutramine group, while a significant reduction of body mass index and waist circumference was observed after 6 months in metformin + sibutramine group (p<0.05). A significant decrease of glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin and HOMA index was observed after 3, and 6 months in both groups (p<0.05, and p<0.01, respectively). A significant Tg reduction was present after 6 months (p<0.05) in both groups respect to the baseline values. No systolic blood pressure, diastolic blood pressure and heart rate change was obtained after 3, and 6 months in both groups.

Conclusion Pioglitazone and sibutramine combination appears to be a short-term equally efficacious and well-tolerated therapeutic alternative respect to metformin-intolerant obese type 2 diabetic patients treated with sibutramine.

Key words: pioglitazone, sibutramine, metformin, type 2 diabetes mellitus, intolerance

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Introduction

Among the main therapeutic targets to be reached in type 2 diabetic patients are the gluco-metabolic pattern improvement and the body weight reduction (1). Intensive programs aimed at reducing calories (2) intake and at increasing physical activity (3) have clearly shown to improve the metabolic control of obese diabetic patients. However, the behavioural approach is usually slow and not always sufficient to get the optimal targets of weight and metabolic control in obese diabetic patients and a pharmacological treat-
ment has often to be planned in order to significantly and quickly reduce their high cardiovascular disease risk (4). On the other side, a pharmacological treatment for overweight or obese state is sometime necessary, because of the neutral-to-arm effect of the most part of antidiabetic treatments on body weight (5). In fact, the insulin-sensitivity improvement associated to the use of some antidiabetic drugs could lead to a further accumulation of adipose tissue (6), even if mainly located in the subcutaneous tissue and not in the more dangerous visceral one. The only antidiabetic treatment with neutral to positive effect on body weight is metformin, but at full dosage it is not well tolerated by all patients (5). A therapeutic alternative in metformin-intolerant patients could be thiazolidinediones, that are supposed to be the pharmacological agents that more physiologically fight the insulin-resistance associated to obesity, decreasing resi-sitin and increasing adiponectin, both in animal models and in humans (7), however their use is also often associated to body weight increase (7). This side effect, particularly detri-mental for obese diabetics patients, could be theoretically compensated by the concomitant use of weight-reducing drugs, but it has yet to be demonstrated.

In this context, we aimed to comparatively test the effi-cacy and tolerability of pioglitazone in metformin-intolerant obese type 2 diabetic patients treated with sibutramine.

Materials and Methods

Study design

This multicenter double-blind randomized, controlled trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy); the RSA Don Leone Porta (Milano, Italy); the Fondazione Ospedale della Carità (Casalbuttano, Italy); and the “G. Descovich” Atherosclerosis Study Center, “D. Campanacci” Clinical Medicine and Applied Biotechnology Department, University of Bologna (Bologna, Italy).

Subjects began a controlled-energy diet (near 600 kcal daily deficit) based on American Diabetes Association recomm-endations (8) containing 30% of calories as fat (6% saturated), 50% as carbohydrates, 20% proteins, with a maximum cholesterol content of 300 mg/day, and 35 g fiber. Each center’s standard diet advice was given by a dietitian and/or specialist doctor. Dietitians and/or specialist doctors periodically provided instruction on dietary intake recording procedures as part of a behaviour modification program and then later used the subject’s food diaries for counselling. During the study, there were one behaviour modification session on weight-loss strategies (at baseline), one at 3 and 6 months, and two seminars with all patients at 1, and 5 months. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3 to 5 times per week, or by cyctlette. The recommended changes in physical activity throughout the study were not assessed.

Five hundred and seventy-six consecutive Caucasian obese type 2 diabetic patients were evaluated during a 12-months period and fifty-two patients were resulted intolerant to metformin at maximum dosage (3,000 mg/day) (Fig. 1). All intolerant patients to metformin received a treatment with pioglitazone (45 mg/day) and sibutramine (10 mg/day) and they were compared with fifty-three patients. These pa-tients came from the group that were tolerant to metformin and were treated at maximum dosage with metformin (3,000 mg/day) and sibutramine (10 mg/day) for 6 months in a single-blind controlled trial (Fig. 2). Pioglitazone and sibu-tramine were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. At baseline, we weighed participants and gave them a bottle containing a 100-day supply of study medication. Through-out the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. A bottle containing the study medication for the next treatment period was given to participants at the 3-month visit. At the same time, all unused medication was retrieved for inventory. Treatment tolerability was assessed at each study visit using an accurate interview of patients by the investigators. All medications were provided free of charge.

The study protocol was approved at each site by institu-tional review boards and was conducted in accordance with the Declaration of Helsinki. All patients provided written in-formed consent.

Patients

We recruited diabetic patients aged 45-57 years of either sex and were eligible for inclusion in the study if they had type 2 diabetes mellitus, according to the ADA criteria (9). All were required to have been diagnosed as being diabetic for at least 6 months. All patients had a fasting C-peptide level >1.0 ng/mL. They were obese patients (body mass index ≥30 kg/m²) (10). Suitable subjects, identified from re-view of case notes and/or computerized clinic registers were contacted personally or by telephone.

Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function (defined as plasma aminotransferase [aspartate aminotransferase (normal values: 11-39 mU/mL), alanine aminotransferase (normal values: 11-34 mU/mL)] and/or gamma-glutamyltransferase (normal values: 11-53 mU/mL), impaired kidney function [defined as serum creat-inine level (normal values: 0.6-1.3 mg/dL)], or anemia. Pa-tients with unstable cardiovascular conditions (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascu-lar conditions within 6 months of study enrolment were also excluded.

Women who were pregnant, lactating, or of child-bearing potential while not taking adequate contraceptive precautions were also excluded.

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Participants comprised 52 men (49.5%) and 53 women (50.5%). There were no significant differences between centres in sex distribution, age, diabetes duration, and in diabetes treatment.

At entry, 19 subjects (18.1%) were taking antihypertensive drugs [10 subjects, ACE-inhibitors (52.6%); 6 subjects, calcium-antagonists (31.6%); 8 subjects, AT II antagonists (42.1%); and 4 subjects, α1-antagonists (21.1%)] in monotherapy or in combination therapy. No patients were taking lipid-lowering or antiaggregation drugs.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, measurements of body mass index, waist circumference, glycated hemoglobin, fasting plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin, lipid profile, systolic blood pressure, diastolic blood pressure and heart rate. Changes in body mass index, waist
circumference, glycated hemoglobin, lipid profile, systolic blood pressure, diastolic blood pressure and heart rate were the primary efficacy variables. Fasting plasma glucose, postprandial plasma glucose, and HOME index were also used to assess efficacy.

All plasmatic parameters were determined after a 12-hour overnight fast, except that postprandial plasma glucose and postprandial plasma insulin, determined 2 hours after lunch. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by addition of Na2-EDTA, 1 mg/mL, and centrifuged at 3,000 g for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated by HOME index with the formula: fasting plasma insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5, as described by Matthews and coworkers (11).

Glycated haemoglobin level was measured by an HPLC method (DIAMAT, Bio-Rad, USA; normal values 4.2-6.2%), with intra- and interassay CsV of <2% (12). Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and inter assay coefficients of variation of <2% (13). Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay coefficients of variation: 4.6 and 7.3%, respectively) (14).

Total cholesterol and triglycerides levels were determined using fully enzymatic techniques (15, 16) on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay coefficients of variation were 1.0 and 2.1 for total cholesterol measurement, and 0.9 and 2.4 for triglycerides measurement, respectively. HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid (17) intra- and inter assay coefficients of variation were 1.0 and 1.9, respectively; LDL-C level was calculated by the Friedewald formula (18).

Blood pressure measurements were obtained from each patient (right arm) in the seated position, by using a standard mercury (Erkameter 3000, ERKA, Bad Tolz, Germany) sphygmomanometer (Korotkoff I and V) with a cuff of appropriate size. Measurements were always taken by the same investigator in the morning before daily drug intake (i.e. - 24 hours after dosing) and after the subject had rested 10 minutes in a quiet room.

Body mass index, glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin, lipid profile, systolic blood pressure, diastolic blood pressure and heart rate were evaluated at baseline and after 3, and 6 months.

In order to evaluate the tolerability assessments, all adverse events were recorded.

Statistical analysis

An intent-to-treat analysis was conducted in patients who had received at least one dose of study medication and had a subsequent efficacy observation. Patients were included in the safety analysis if they had received one dose of trial medication after randomization and had a subsequent safety observation. The null hypothesis that the expected mean body mass index, waist circumference, glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin, total cholesterol, LDL-C, HDL-C, triglycerides, systolic blood pressure, diastolic blood pressure and heart rate change from baseline to the end of 6 months of single-blind treatment did not differ significantly between pioglitazone and metformin treatments was tested using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models (19). The statistical significance of the independent effects of treatments on the other parameters was determined by ANCOVA. A one-sample t test was used to compare values obtained before and after treatments administration; and two-sample t tests were used for between-group comparison. The Bonferroni correction for multiple comparison also was carried out. Statistical analysis of data was performed by means of the SPSS statistical software package for Window (version 11.0; Chicago, Illinois, USA); data are presented as mean ± standard deviation. For all statistical analysis, p <0.05 was considered statistically significant.

Results

Anthropometric parameters

No body mass index and waist circumference change was observed at 3, and 6 months in pioglitazone + sibutramine group. A significant reduction of body mass index and waist circumference was observed after 6 months in metformin + sibutramine group (p<0.05, respectively). There was no significant difference between the two groups (Table 1).

Glycemic control

A significant decrease of glycated hemoglobin, fasting plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin and HOME index was observed after 3, and 6 months in both groups (p<0.05, and p<0.01, respectively). No significant difference was obtained between the two groups (Table 1).

Lipid profile

No significant total cholesterol, LDL-C, and HDL-C change was observed at 3, and 6 months, while a significant triglycerides reduction was present after 6 months (p<0.05) in both groups respect to the baseline values. There was not difference in triglycerides value between the two groups (Table 1).
## Table 1. Parameter Changes at 3, and 6 Months in both Groups during the Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metformin + sibutramine</th>
<th>Pioglitazone + sibutramine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>27/26</td>
<td>25/27</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>51 ± 6</td>
<td>50 ± 5</td>
</tr>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td>32.3 ± 1.2</td>
<td>32.5 ± 1.5</td>
</tr>
<tr>
<td><strong>WC (cm)</strong></td>
<td>105.6 ± 5.3</td>
<td>105.9 ± 5.8</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.4 ± 0.5</td>
<td>7.5 ± 0.6</td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td>138 ± 12</td>
<td>148 ± 15</td>
</tr>
<tr>
<td><strong>FPI (µU/mL)</strong></td>
<td>29.5 ± 6.1</td>
<td>30.6 ± 6.4</td>
</tr>
<tr>
<td><strong>TC (mg/dL)</strong></td>
<td>186 ± 11</td>
<td>183 ± 12</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td>113 ± 15</td>
<td>109 ± 12</td>
</tr>
<tr>
<td><strong>HDL-C (mg/dL)</strong></td>
<td>41 ± 5</td>
<td>43 ± 4</td>
</tr>
<tr>
<td><strong>Tg (mg/dL)</strong></td>
<td>161 ± 25</td>
<td>158 ± 24</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>134 ± 4</td>
<td>135 ± 4</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>86 ± 3</td>
<td>85 ± 3</td>
</tr>
<tr>
<td><strong>HR (b/min)</strong></td>
<td>76 ± 4</td>
<td>75 ± 5</td>
</tr>
</tbody>
</table>

Data are means ± SD

* p < 0.05 vs Baseline; ** p < 0.01 vs Baseline

BMI: body mass index; WC: waist circumference; HbA1c: glycated haemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; FPI: fasting plasma insulin; PPI: postprandial plasma insulin; HOMA index: homeostasis model assessment index; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

### Blood pressure

No systolic blood pressure and diastolic blood pressure change was obtained after 3, and 6 months in both groups (Table 1). No significant heart rate variation was obtained during the study in both groups (Table 1).

### Discussion

Both type 2 diabetes and obesity are associated with severe insulin resistance and compensatory hyperinsulinemia (20). In type 2 diabetes, insulin-resistance is a substantially inherited metabolic defect, whereas obesity and its consequent insulin-resistance may be due to either excessive caloric intake or an inherited disturbance in thermogenesis or intermediary metabolism (21). In both cases, the main pathophysiological approach to the therapy is the reduction of insulin-resistance through intensive life-style modification and specific pharmacotherapy (22). The more widely known, tested and used insulin-sensitizing agent is the biguanide metformin: its use is generally safe, but when administered at full-dosage its tolerability decreases thus reducing the patient compliance to the therapy (23).

In our study, aimed at comparing the efficacy of an intensive insulin-sensitization in type 2 diabetic obese patients treated with sibutramine, we observed that pioglitazone and metformin treatments were similarly associated to an improvement in metabolic parameters without significant modification on blood pressure. In particular, after 6 month of treatment, both patient groups experienced a significant reduction of fasting plasma glucose (-16.1%), postprandial plasma glucose (-17.1%), glycated hemoglobin (-14.1%), fasting plasma insulin (-40.4%), postprandial plasma insulin (-31.5%), HOMA index (-50%), and triglycerides (-17.7%). The only parameter that significantly improved in metformin but not pioglitazone treated patients was body mass index (-4.0kg/m² vs -1.5kg/m²).

Pioglitazone was chosen as alternative to metformin, because it has comparable (if not slightly stronger) insulin-sensitizing activity (24), a preventive effect on cardiovascular disease (25) and a nearly neutral effect on body weight (26).

Several concerns have been recently raised on the cardiovascular safety of thiazolidinediones use in diabetic patients (27). However, it seems that they regard more strictly rosiglitazone than pioglitazone (28). Moreover, in this study as in our several ones carried out with pioglitazone (29-31) the simple application of exclusion criteria suggested by the international literature and guidelines (32) justify its observed high tolerability.

In our study we did not observe any change in blood pressure under sibutramine treatment. Some Authors suggest that the use of sibutramine could be dangerous for patients at high cardiovascular disease risk, because of the possibility...
that it could rise blood pressure and induce arrhythmias in some patients (33), maybe due to a paradoxical effect on the autonomic system (34). However, in the most part of cases, patients who lose 5% or more of initial body weight have a reduction in blood pressure, which correlates with the degree of weight loss (35). Therefore, in previous studies carried out by our research unit (36, 37) and in previous reports of other groups (38, 39), sibutramine use was not related to a significant increase in systolic nor diastolic blood pressure during 12 months of treatment with sibutramine, nor to changes in heart rate, when patients have blood pressure adequately controlled by efficacious antihypertensive treatments. Moreover, insulin-sensitization obtained by pioglitazone and metformin per se could balance the eventual sibutramine hypertensive effect (40, 41). On the other side sibutramine could as well exert indirect insulin-sensitizing effect by weight-loss induction (37), thus potentiating the antidiabetic drug effect.

Of course, our study has some relevant limitation as it regards the short duration and the relatively small patient sample. However, the selection of metformin-intolerant patient is not easy, since metformin is usually well-tolerated (5), and the question addressed in this study on the tolerability of insulin-sensitizing drug associated to sibutramine treatment was really specific. In fact, the main clinical implication of our results is that we demonstrated that the association of a weight-reducing drug, such as sibutramine is tolerable and efficacious in compensating the eventual body weight increase associated to thiazolidinediones assumption.

In conclusion, from our study carried out on a small sample of metformin-intolerant obese type 2 diabetic patients treated with sibutramine, pioglitazone appears to be a short-term equally efficacious and well-tolerated therapeutic alternative.

References

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