Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 1552 – 1557
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Sibutramine effect on metabolic control of obese patients with type 2 diabetes mellitus treated with pioglitazone

Giuseppe Derosa[a,*], Angela D'Angelo[a], Sibilla A.T. Salvadeo[a], Ilaria Ferrari[a], Alessia Gravina[a], Elena Fogari[a], Pamela Maffioli[a], Arrigo F.G. Cicero[b]

[a]*Department of Internal Medicine and Therapeutics, University of Pavia, 19-27100 Pavia, Italy*
[b]*Aging and Kidney disease Department, "G. Descovich" Atherosclerosis Study Center, Internal medicine, University of Bologna, 40138 Bologna, Italy*

Received 28 December 2007; accepted 11 June 2008

Abstract

Thiazolidinediones are supposed to be the pharmacologic agents that more physiologically fight the insulin resistance, but a possible adverse effect may be a weight increase. The aim of the study was to test the efficacy and tolerability of sibutramine on the metabolic effect of pioglitazone in obese patients with type 2 diabetes mellitus. All enrolled patients were required to have been diagnosed as being diabetic for at least 6 months and did not have glycemic control with diet and oral hypoglycemic agents such as sulfonylureas or metformin, both to the maximum tolerated dose. After a run-in period in which the eligible patients took a fixed dose of pioglitazone (30 mg/d), the patients were randomized to receive also sibutramine (10 mg/d) or placebo for 6 months. We assessed body mass index, hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), lipid profile, lipoprotein parameters, and lipoprotein (a) at baseline and after 3 and 6 months. No body mass index change was observed after 3 and 6 months in the pioglitazone + placebo (pp) group. Significant decrease was present in the pioglitazone + sibutramine (ps) group after 3 ($P < .05$) and 6 months ($P < .01$) compared with the baseline values, and this variation was significant ($P < .05$) between groups. A significant HbA_{1c} decrease was observed after 3 ($P < .05$) and 6 months ($P < .01$) in both groups with respect to the baseline values. There was no difference in HbA_{1c} value between the 2 groups. No FPG, PPG, FPI, PPI, and homeostasis model assessment index change was observed at 3 months, whereas a significant decrease was present after 6 months ($P < .05$), in both groups with respect to the baseline values. There was no difference in FPG, PPG, FPI, PPI, and homeostasis model assessment index value between the pp and ps groups. No significant low-density lipoprotein cholesterol change was observed at 3 months, whereas a significant decrease was present after 6 months ($P < .05$), in both groups with respect to the baseline values. There was no difference in low-density lipoprotein cholesterol value between the pp and ps groups. No triglyceride variation was present at 3 and 6 months in the pp group and at 3 months in the ps group, whereas a significant decrease was observed at 6 months ($P < .05$) in the ps group with respect to the baseline values. There was no difference in triglyceride value between both groups. No high-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) changes were present in both groups with respect to the baseline values. Sibutramine appears to be a tolerable and efficacious drug when added to pioglitazone for the global management of obese diabetic patients.

1. Introduction

The prevalence of obesity has been increasing dramatically in the last decades in the whole world, not only in industrialized countries, but also in developing areas [1]. Major direct complications of obesity are insulin resistance and type 2 diabetes mellitus, whose prevalence is also rapidly increasing worldwide, reaching a prevalence in adults of approximately 5% to 6% in Central Europe and in the United States and more than 50% in specific, genetically prone populations [2].

Intensive programs aimed at reducing calorie [3] intake and at increasing physical activity [4] have clearly been shown to reduce progression from obesity to diabetes and to improve the metabolic control of obese diabetic patients. However, the behavioral approach is usually slow and not always sufficient to get the optimal target of weight and metabolic control in obese diabetic patients; and a pharmacologic treatment has to be planned to significantly and quickly reduce their high cardiovascular

* Corresponding author. Tel.: +39 0382 526217; fax: +39 0382 526259.
E-mail address: giuseppe.derosa@unipv.it (G. Derosa).

0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.06.010

disease risk [5]. Moreover, beyond metformin and the recently marketed exenatide, for the most part, antidiabetic agents have a neutral or harmful effect on body weight [6]. In fact, the insulin sensitivity improvement associated with the use of some antidiabetic drugs could lead to a further accumulation of adipose tissue [7], even if mainly located in the subcutaneous tissue and not in the more dangerous visceral one. This effect has been clearly demonstrated with efficacious insulin-sensitizing drugs acting on peroxisome proliferator–activated receptor–γ, such as thiazolidinediones [8].

In this context, we tested the efficacy and tolerability of sibutramine, a monoamine-reuptake inhibitor with body weight–reducing properties, on the metabolic effect of pioglitazone, a peroxisome proliferator–activated receptor–γ activator, in obese patients with type 2 diabetes mellitus.

2. Materials and methods

2.1. Study design

This multicenter, double-blind, randomized, controlled trial was conducted in the Department of Internal Medicine and Therapeutics at University of Pavia and in the "G. Descovich" Atherosclerosis Study Center, Internal Medicine, Aging and Kidney Disease Department at University of Bologna.

Subjects began a controlled-energy diet (nearly 600 kcal daily deficit) based on American Diabetes Association recommendations [9] containing 30% of calories as fat (6% saturated), 50% as carbohydrates, 20% as proteins, with a maximum cholesterol content of 300 mg/d, and 35 g fiber. Each center's standard diet advice was given by a dietitian and/or a diabetologist. Dieticians and/or diabetologists periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counseling. During the study, there were 1 behavior modification session on weight-loss strategies (at baseline), 1 session at 3 and 6 months, and 2 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 exercise bicycle. The recommended changes in physical activity throughout the study were not assessed.

After a 3-month run-in period in which the eligible patients took a fixed dose of pioglitazone (30 mg/d, once a day), the patients were randomized to receive also sibutramine (10 mg/d, once a day) or placebo for 6 months (Fig. 1). Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Sibutramine or placebo was supplied as matching opaque white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout 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 new study medication for the next treatment period was given to participants every 3 months. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

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

2.2. Patients

We recruited diabetic patients of either sex who were eligible for inclusion in the study if they had type 2 diabetes mellitus according to the American Diabetes Association criteria [10]. All were required to have been diagnosed as being diabetic for at least 6 months and did not have glycemic control with diet and oral hypoglycemic agents such as sulfonylureas or metformin, both to the maximum

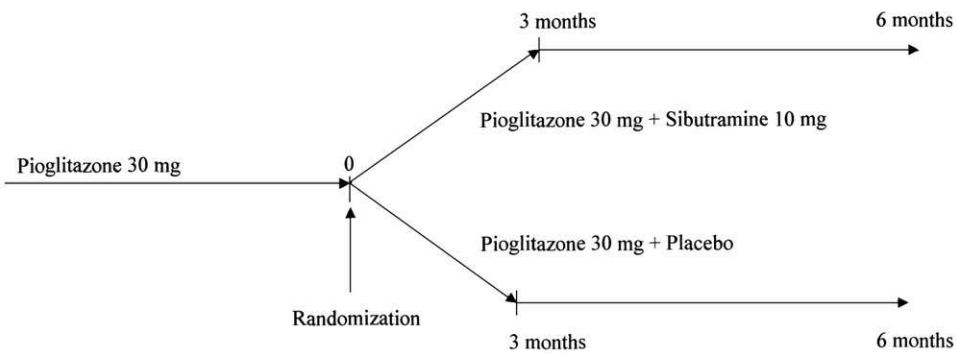

Fig. 1. Study design.