Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

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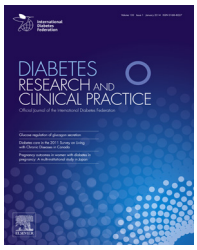

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Effect of low dose pioglitazone on glycemic control and insulin resistance in Type 2 diabetes: A randomized, double blind, clinical trial

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ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form
2 May 2015
Accepted 5 May 2015
Available online 15 May 2015

Keywords:
Pioglitazone
Thiazolidinediones
Type 2 diabetes
Low dose
Insulin resistance

ABSTRACT

This study shows that pioglitazone 7.5 mg/day as an add-on therapy in Southeast Asian patients with Type 2 diabetes is safer and equally efficacious as the 15- and 30-mg doses of pioglitazone. Hence it is prudent to start pioglitazone therapy at a lower dose of 7.5 mg/day.

1. Introduction

Pioglitazone is an insulin sensitising thiazolidinedione which is commonly prescribed as an add-on therapy in patients with Type 2 diabetes. It is used in doses of 15 mg and 30 mg. Pioglitazone in doses of 7.5 mg, though available, are less prescribed. This is because of a lack of efficacy and safety data for the low dose pioglitazone. This study was planned to compare the effects of 7.5-, 15-, and 30-mg of pioglitazone on glycemic parameters, insulin resistance parameters and safety parameters.

2. Subjects and methods

Ninety patients with Type 2 diabetes and HbA1c more than 7% (53 mmol/mol), inspite of metformin and/or sulfonylurea therapy for at least three months, were randomised to three groups ($n = 30$) in 1:1:1 ratio after obtaining written informed

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http://dx.doi.org/10.1016/j.diabres.2015.05.030
0168-8227/

Table 1 – Baseline comparability.

	Pioglitazone 7.5 mg	Pioglitazone 15 mg	Pioglitazone 30 mg	P value
Age (in years)	50.2 ± 9.9	49.5 ± 8.9	53.7 ± 9.7	0.19
Gender (F/M)	14/16	16/14	13/17	0.72
Duration of diabetes (years)	3.3 ± 2.1	3.5 ± 1.7	3.6 ± 1.6	0.74
Weight (in kg)	70.1 ± 9.9	68.0 ± 11.3	69.2 ± 10.5	0.75
BMI	26.4 ± 3.6	27.0 ± 4.4	25.9 ± 3.6	0.59
Waist (in cms)	95.6 ± 7.9	97.9 ± 7.6	98.1 ± 7.6	0.38
Body Fat (%)	29.4 ± 7.4	31.9 ± 8.2	29.6 ± 7.2	0.38
SBP (in mm of Hg)	127.9 ± 11.6	129.1 ± 13.2	130.9 ± 11.6	0.52
DBP(in mm of Hg)	74.5 ± 8.6	77.3 ± 8.9	78.7 ± 6.4	0.12
HbA1 C (%)	8.2 ± 0.9 (66 ± 9.8 mmol/mol)	8.4 ± 0.9 (68 ± 9.8 mmol/mol)	8.5 ± 0.7 (69 ± 7.7 mmol/mol)	0.32
FPG (mg/dl)	162.2 ± 24.9	169.5 ± 31.8	166.2 ± 26.5	0.69
PPG (mg/dl)	236.0 ± 47.8	243.6 ± 64.3	235.1 ± 45.2	0.88
Insulin (μU/ml)	10.7 ± 5.7	10.2 ± 4.8	11.9 ± 4.5	0.37
C-peptide (ng/ml)	3.1 ± 1.5	2.8 ± 0.9	3.5 ± 1.3	0.18
HOMA-IR	4.3 ± 2.4	3.9 ± 2.2	4.3 ± 1.9	0.74
Adiponectin (μg/ml)	6.9 ± 1.5	6.9 ± 1.8	6.8 ± 0.8	0.74
Leptin (ng/ml)	33.5 ± 9.0	35.2 ± 9.8	36.7 ± 9.8	0.43
Hb (gm/dl)	12.9 ± 1.2	12.7 ± 1.5	13.0 ± 1.4	0.59
HCT	40.7 ± 2.9	40.1 ± 3.5	40.3 ± 3.3	0.73
TC (mg/dl)	178.0 ± 37.8	183.4 ± 41.8	185.2 ± 44.9	0.79
TGl (mg/dl)	167.1 ± 46.2	170.5 ± 68.8	168.9 ± 48.5	0.98
LDL (mg/dl)	133.2 ± 42.0	138.1 ± 58.2	131.1 ± 46.4	0.86
HDL (mg/dl)	44.9 ± 9.4	41.7 ± 7.1	43.2 ± 8.6	0.34
S.Cr (mg/dl)	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.37
SGOT (U/L)	24.3 ± 7.6	27.7 ± 13.6	25.6 ± 11.3	0.51
SGPT (U/L)	25.6 ± 9.5	30.1 ± 14.3	28.1 ± 11.9	0.39

consent in a double blind, randomised trial which was approved by the Post Graduate Institute of Medical Education and Research ethics committee, Chandigarh, India. The three groups received pioglitazone 7.5 mg/day, 15 mg/day and 30 mg/day respectively as add-on therapy to metformin and/or sulfonylureas. Patients in each group received placebos of the other two doses of pioglitazone, in all receiving three tablets as add-on. All the patients were encouraged to follow dietary restriction and lifestyle modification. The patients were assessed at the end of every 4th week for 12 weeks.

Clinical and biochemical parameters were tested at regular intervals. Body fat was measured by body fat analyser using bioelectrical impedance technique (TBF-300A, Tanita Corp., Tokyo, Japan). HbA1c, Fasting plasma glucose (FPG), Postprandial Plasma glucose (PPG), Fasting plasma Insulin (FPI), C-peptide, Adiponectin, Leptin, were measured at baseline and at the end of the study. Apart from this, FPG and PPG were also measured at the end of 4th and 8th week. Insulin resistance was quantified by homeostasis model of assessment-insulin resistance (HOMA-IR) which was calculated as: [FPG (mmol/l) × FPI (μIU/ml)]/22.5 [1].

Continuous data are presented as mean ± standard deviation (SD). Baseline parameters and laboratory efficacy and safety parameters were compared using appropriate parametric and nonparametric tests. A *P* value of less than 0.05 was considered as significant.

3. Results

The baseline characteristics of patients in the three groups were comparable (Table 1). All three groups showed a significant reduction in HbA1c. The mean reduction in HbA1c in the three groups was 0.5 ± 0.1% (5.5 ± 1.1 mmol/mol), 0.6 ± 0.2% (6.6 ± 2.2 mmol/mol) and 0.7 ± 0.1% (7.7 ± 1.1 mmol/mol) in pioglitazone 7.5 mg, 15 mg and 30 mg groups (Table 2). However, there was no statistically significant difference in between the three groups in terms of HbA1c reduction ($p = 0.68$). Furthermore we could not find any dose dependency in HbA1c reduction by the three dose groups ($r = 0.09$; $p = 0.42$). Ten patients (33.3%) each in pioglitazone 7.5 mg and 15 mg groups achieved an HbA1c of <7% (53 mmol/mol) at the end of the study whereas 12 patients (40%) did so in pioglitazone 30 mg group. There was a significant decrease in FPG levels in the three groups, at the end of the study period (Table 2). Similarly, there was a significant reduction in PPG in all three groups at the end of 12 weeks. Dose dependency could not be demonstrated for both FPG reduction ($r = 0.144$; $p = 0.175$) and PPG reduction ($r = 0.06$; $p = 0.58$). There was a significant insulin sensitising effect of all three doses of pioglitazone as evidenced by a significant reduction in FPI, c-peptide levels and HOMA-IR (Table 2). There was also a significant reduction in adiponectin levels.

The 15- and 30-mg pioglitazone showed significant increase in weight, BMI and Body fat which was not seen in the low dose pioglitazone group (Table 3). There was a significant reduction in triglyceride and increase in HDL-C levels in all three groups. There was no significant change in any of the other laboratory parameters

4. Discussion

This study has established the efficacy of the 7.5 mg dose of pioglitazone as an add-on therapy in Southeast Asian patients with Type 2 diabetes. The low-dose pioglitazone was even