Clinical Efficacy of Pioglitazone: Generic vs. Original Product

Supatta Temboonkiat BSc, MSc*,
Nisamanee Satyapan BSc, MSc*, Yupin Benjasuratwong MD**,
Supen Patarakitvanit BSc, MSc*, Jeeranut Tunkanitlert PhD*,
Thishnapha Vudhironarit BSc, MSc*, Borpit Klangkalya PhD*

** Department of Pharmacology, Phramongkutklao College of Medicine, Bangkok, Thailand*
*** Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand*

Background: *Pioglitazone, an oral antidiabetic agent in the class of thiazolidinediones (TZDs), was widely used in the case of insulin tolerance as it provided more benefit to patients with type 2 diabetes. However, the original product is costly while some generic products are available at the substantial lower cost in Thailand. The objective of the present study was to assess bioequivalence in terms of efficacy between generic and original pioglitazone products.*
Material and Method: *A randomized double blind, crossover controlled trial was performed on 60 patients with type 2 diabetes at the Endocrine Unit, Department of Medicine, Phramongkutklao Hospital, Thailand. All subjects were randomly selected for group A and B (30 volunteers in each group). Duration of observation for efficacy of treatment with pioglitazone (both generic and original products) was totally 24 weeks. The dose of pioglitazone was 15 mg once daily.*
Results: *Finally, 22 males and 37 females remained in the trial. The reduction in means of HbA1c in group A and group B were 0.7% and 0.6% respectively. The least squares means of the HbA1c reduction of the generic and original group were 0.75% and 0.79%, respectively. There was no significant difference in HbA1c reduction between both groups. The average equality of HbA1c in all subjects in both groups was 100.7% (87.9-113.5%) at 90% confidence interval.*
Conclusion: *These findings indicated that both formulations were bioequivalent as their efficacy or therapeutic effects in reduction of HbA1c in the type 2 diabetic subjects were statistically the same.*

Keywords: *Pioglitazone, Test product, Reference product, HbA1c, Clinical efficacy*

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Pioglitazone, a member in the class of thiazolidinediones (TZDs), has been shown to bind with high affinity and activate the nuclear peroxisome proliferator activated receptor-gamma (PPAR-gamma)[1-3]. The PPARs are involved in the modulation of the expression of gene coding for proteins that involved in glucose metabolism and improve glycemic control without effect of endogenous insulin secretion[4]. Pioglitazone reduces insulin resistance by improving insulin sensitivity in muscles with a different mechanism from other classes of antidiabetic drugs and it also decreases hepatic gluconeogenesis. Thus, TZDs including pioglitazone have provided sustained glycemic control that could be confirmed by several studies. These studies illustrated that pioglitazone could significantly reduce HbA1c (glycosylated haemoglobin) level of the patients with type 2 diabetes when used both in monotherapy and in combination with metformin and sulfonylureas[5,6]. Besides TZDs were relatively safe in regard to the adverse events studied[6]. The finding of the significant result from the PROactive Study also demonstrated that pioglitazone reduced the number of patients on insulin and the mean daily insulin dose, while providing better glycemic control than placebo[7]. At present, combination therapy of a TZDs with insulin is no longer contraindicated in Europe and this combination can provide improvements in glycaemic control that are additive to the effects of insulin alone[8]. Formerly, the efficacy of pioglitazone in various doses: 15, 30, 45 mg were evaluated in 273 patients with type 2 diabetes. The finding showed that HbA1c level of the subjects were significantly reduced among all doses of pioglitazone and were statistically

Correspondence to:
Satyapan N, Department of Pharmacology, Phramongkutklao College of Medicine, Bangkok 10400, Thailand.
Phone & Fax: 0-2354-7752
E-mail: nsatyapan@yahoo.com

different from placebo ($p < 0.05$)[9]. Moreover, pioglitazone has been associated with improvements in the long-term cardiovascular morbidity and mortality of patients with type 2 diabetes[10-12]. This indicated that pioglitazone provided more benefits to the type 2 diabetic patients with pre-existing macrovascular complications, without a history of congestive heart failure. As a consequence of various benefits previously mentioned, remarkable growth in use of the agents has been noted. Some analysises indicated that treatment with pioglitazone was associated with lower costs than rosiglitazone. Therefore, in the United Kingdom, adjunctive pioglitazone may represent a cost-effective treatment choice for patients with type 2 diabetes who have insufficient glycaemic control while receiving the maximal tolerated dose of metformin monotherapy[13]. The study seemed to support the tremendous treatment with pioglitazone in Thailand, as well. But in fact, pioglitazone hydrochloride was originally synthesized by Takeda Chemical Industries Ltd, Japan, so imported, original product is costly. If generic product of pioglitazone can be manufactured locally at the substantial lower cost with similar efficacy, it will save a lot of budget for the Thai government. The objective of the present study was to assess clinical efficacy between generic and original products of pioglitazone 15 mg tablet.

Material and Method

Pioglitazone Preparations

The test or generic product was Senzulin® (Lot No.C6PI00130/2 manufactured by Siam Bheasach Co. Ltd.) containing 15 mg of pioglitazone per tablet while the reference or original product was Actos® (Lot No. 0116 manufactured by Takeda Co. Ltd, Japan) containing 15 mg of pioglitazone per tablet. Formulations of both drugs were similar in the physicochemical properties.

Subjects and Study design

A randomized double blind, crossover controlled trial was performed in 60 patients with type 2 diabetes at the Endocrine Unit, Department of Medicine, Phramongkutklao Hospital, Thailand.

Inclusion criteria for pioglitazone administration in the present study were; aged between 40 to 70 years, body mass index (BMI) between 18.5-30 kg/m^2, being treated with sulfonylurea half maximum dose and metformin > 1,000 mg daily at least 3 months or metformin alone > 1,500 mg daily at least 3 months, fasting plasma glucose (FPG) between 140-270 mg/dL, HbA1c between 7-10%.

Exclusion criteria were; pregnancy or nursing mother, being treated with insulin or α-glucosidase inhibitors or other drugs that affected the blood glucose *i.e.* glucocorticoid or some herbal medicines, serum creatinine > 1.4 mg/dL (female) and > 1.5 mg/dL (male), > 2.5 folds of upper limit normal of liver enzymes, severe diabetes or renal complications, haemoglobinopathy, history of thiazolidinedione allergy or congestive heart failure, receiving oral contraceptives or some hormones.

Duration of observation for efficacy of treatment with pioglitazone was totally 24 weeks. The dose of pioglitazone was 15 mg once daily.

During the run-in period, the volunteer patients who passed the screening test, had to continue their previous medication as well as control the diet and do the gentle exercises as recommended by the endocrinologist for 4 weeks. Then the subjects were randomly selected with the ratio of 1:1 to receive the add on of either test or reference product of pioglitazone for 12 weeks and switched to another product for the next 12 weeks. The serum HbA1c of each group of the subjects were recorded at 12 and 24 weeks, respectively.

Informed consent was obtained from each subject. The research methodology of the present trial was already approved by the Institutional Review Board, the Royal Thai Army Medical Department.

Statistical analysis

The data was analyzed by using the analysis of variance for two way crossover design for testing the inter- and intra-subject variability of HbA1c. Differences of mean HbA1c in each group were analyzed by the paired t-test.

Results

Of 60 patients with type 2 diabetes who were recruited in the present study, they were 22 males and 38 females. During treatment, one female dropped out at week 19 for abdominal surgery. Thus, 22 males and 37 females finally remained in the trial. All of these subjects were divided into 2 groups: group A (started with test product, followed by reference product) and group B (started with reference product, followed by test product) which consisted of 29 and 30 subjects, respectively. The baseline characteristics of subjects in each group were not statistically different as shown in Table 1.

After 12 weeks of pioglitazone administration, the average HbA1c in both groups was compared with

baseline HbA1c as illustrated in Fig. 1. The reduction in mean of HbA1c in group A and group B were 0.7% and 0.6% respectively. There were significant differences in the reduction of HbA1c from the baseline HbA1c in all subjects ($n = 59$, $p < 0.05$), despite of insignificant difference in reduction of HbA1c between each group ($p = 0.3$).

After 24 weeks of drug administration, the mean HbA1c of each group were compared with the mean HbA1c at week 12 as shown in Table 2. There were no significant differences of the mean HbA1c at week 12 and 24 within each group ($p = 0.3$ and 0.6) as well as of the mean HbA1c at week 24 between both groups ($p = 0.8$).

By using the ANOVA to analyze the HbA1c of all subjects, it was shown that the subjects who received the test drug as well as the reference drug in both groups had the least squares means of the HbA1c

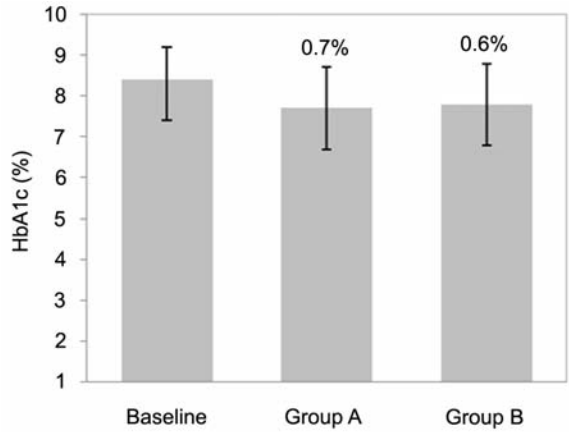

Fig. 1 HbA1c in both groups compared with baseline HbA1c at week 12

Table 1. Baseline characteristics of the subjects

Parameters	Group A (n = 29)	Group B (n = 30)	p-value
Age	57.9 ± 7.1	57.3 ± 6.4	0.150
HbA1c	8.4 ± 0.8	8.3 ± 0.9	0.745

Table 2. HbA1c of both groups after 12 weeks and 24 weeks

After	Group A	Group B	p-value
12 weeks	7.79 ± 1.29	7.85 ± 0.80	0.3
24 weeks	7.57 ± 1.11	7.92 ± 1.84	0.8
p-value	0.3	0.6	

reduction of 0.75% and 0.79% respectively. At 90% confidence interval, mean HbA1c in both groups were ranged from 87.9-113.5%, with an average equality of 100.7%. Such interval was in the range of the required interval of bioequivalence (80-125%). Therefore, it clearly indicated that the test drug was bioequivalent to the reference drug.

Discussion

Actually, pioglitazone was metabolized by the liver, obtained three active metabolites (M-II, M-III and M-IV) that had hypoglycemic action similar to its parent drug[5]. Besides, Chatsiricharoenkul S et al also mentioned that the overall pharmacokinetic parameters from both generic and original formulations in their study were not similar to data previously published in other countries due to metabolism of pioglitazone in Thai people was probably different from foreign people[14]. Therefore, the quantitative analysis of pioglitazone from blood sample by using HPLC might not directly represent the overall efficacy of the unchanged pioglitazone and its active metabolites in a Thai population. Thus, clinical trial was particularly assigned to determine the therapeutic effect of both formulations in subjects with type 2 diabetes. The purpose of the randomized crossover design without the washing period in the present trial was to minimize the intra-subject variations and to prevent the accidental hyperglycemia which would be harmful to the subjects.

Sample size was calculated in accordance with a previous study[5] with type 1 error of 0.05 and type 2 error of 0.20 which required 26 patients in each group. Consequently, the authors enrolled a total of 60 subjects, 30 in each group in order to reserve for some dropping out. So the study design and sample size of the present study were considered most appropriate for the study concerned with therapeutic effect of pioglitazone with its active metabolites.

Conclusion

Mean HbA1c of the subjects recorded at 12 weeks and 24 weeks, before and after switching from the test to reference drug or vice versa were not significant difference ($p = 0.3$, 0.8, 0.3 and 0.6). At 90% confidence interval, the ratio of HbA1c in both groups were in the range of 80-125% as required by the study of drug bioequivalence[15]. After the drug administration for 12 weeks, the reduction of HbA1c of all subjects were significantly different from their baseline HbA1c ($p < 0.005$). All of these findings indicated that both

formulations were bioequivalent as their clinical efficacy or therapeutic effects in reduction of HbA1c in the type 2 diabetic subjects were statistically the same.

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Potential conflicts of interest

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ประสิทธิภาพทางคลินิกของยาไพโอกลิทาโซน-เปรียบเทียบผลิตภัณฑ์สามัญกับผลิตภัณฑ์ต้นแบบ

สุภัททา เต็มบุญเกียรติ, นิสามณี สัตยาบัน, ยุพิน เบ็ญจสุรัตน์วงศ์, สุเพ็ญ ภัทรกิจวานิช, จีรานุช ตันคณิตเลิศ, ธิษณาภา วุฒิรณฤทธิ์, บพิตร กลางกัลยา

ภูมิหลัง: *ไพโอกลิทาโซนเป็นยาลดระดับน้ำตาลในเลือดที่มีประโยชน์เสริมหลายอย่าง และใช้กันอย่างกว้างขวางในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะดื้อต่ออินซูลิน แต่ยาต้นแบบมีราคาสูงมาก และปัจจุบันบริษัทยาในประเทศมีความสามารถผลิตยาไพโอกลิทาโซนสามัญได้ การศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาประสิทธิภาพของยาสามัญเปรียบเทียบกับยาต้นแบบ*

วัสดุและวิธีการ: *เป็นการศึกษาทางคลินิกแบบข้ามเชิงสุ่ม ปกปิดข้อมูลสองด้าน ศึกษาในอาสาสมัครที่เป็นผู้ป่วยเบาหวานชนิดที่ 2 ที่แผนกโรคต่อมไร้ท่อ โรงพยาบาลพระมงกุฎเกล้าจำนวน 60 คน โดยสุ่มแบ่งอาสาสมัครเป็น 2 กลุ่มๆ ละ 30 คน ให้ได้รับยาเม็ดไพโอกลิทาโซนขนาด 15 มิลลิกรัม ผลิตภัณฑ์สามัญ หรือต้นแบบ รับประทานวันละ 1 เม็ด เป็นเวลา 12 สัปดาห์ และเจาะเลือดวัดค่าน้ำตาลสะสม (ฮีโมโกลบินเอวันซี) แล้วจึงเปลี่ยนสลับให้รับยาอีกผลิตภัณฑ์หนึ่ง เมื่อครบเวลา 12 สัปดาห์ ให้เจาะเลือดวัดค่าน้ำตาลสะสมอีกครั้งหนึ่ง และนำมาเปรียบเทียบกัน*

ผลการศึกษา: *พบว่าอาสาสมัครที่ได้รับยาจนจบการศึกษามีทั้งหมด 59 คน (ชาย 22 คน หญิง 37 คน) มีค่าเฉลี่ยของน้ำตาลสะสมในอาสาสมัครทั้งสองกลุ่มภายหลังได้รับยาลดลงกว่าก่อนได้รับยา 0.7% และ 0.6% ตามลำดับ และในรายที่ได้รับยาสามัญ หรือยาต้นแบบ มีค่าเฉลี่ยน้ำตาลสะสมลดลงจากค่าเฉลี่ยน้ำตาลสะสมก่อนรับยา 0.75% และ 0.79% ตามลำดับ เมื่อเปรียบเทียบค่าเฉลี่ยน้ำตาลสะสมที่ลดลงในอาสาสมัครทั้งสองกลุ่ม พบว่าไม่มีความแตกต่างกัน และค่าเฉลี่ยความเท่าเทียมกันของค่าน้ำตาลสะสมของอาสาสมัครทั้งสองกลุ่ม ภายหลังได้รับยาสามัญและยาต้นแบบมีค่าเท่ากับ 100.7% (87.9-113.5%) ที่ระดับความเชื่อมั่น 90%*

สรุป: *ผลิตภัณฑ์สามัญและผลิตภัณฑ์ต้นแบบมีชีวสมมูลต่อกันและมีประสิทธิภาพเหมือนกัน สามารถใช้แทนกันได้*