Efficacy and Safety of Generic and Original Pioglitazone in Type 2 Diabetes Mellitus: A Multicenter, a Double-Blinded, Randomized-Controlled Study

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Objective: To compare the efficacy and safety of generic (Utmos®) and original (Actos®) 30 mg Pioglitazone tablets.
Study design: A multicenter, parallel randomized, double-blinded, controlled study.
Material and Method: Type 2 diabetic patients, with glycosylated hemoglobin (HbA1c) > 7.0%, who received Metformin not less than 1,000 mg/day over three months were recruited. Patients were randomized to receive either generic or original Pioglitazone 30 mg/day for 24 weeks.
Results: Eighty-five patients were enrolled, forty-four patients received generic Pioglitazone and forty-one received original Pioglitazone. There were no significant differences in baseline characteristics between generic and original Pioglitazone group. There were significantly reduced HbA1c, fasting plasma glucose (FPG) and significantly increased HDL-cholesterol from baseline (p < 0.0001) without statistically differences between the two groups. Headache and edema were found in both groups at comparable rates (p > 0.05).
Conclusion: Generic Pioglitazone (Utmos®) is effective in controlling blood glucose and has similar effects on lipid profile as the original one. Both generic (Utmos®) and original (Actos®) 30 mg Pioglitazone tablets were not different in the efficacy and safety profiles.

Keywords: Pioglitazone, Thiazolidinedione, Generic, Diabetes mellitus, Type 2

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Type 2 diabetes, which accounts for 94% of those with diabetes(1), is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response(2). Diet and exercise are the first line treatment for type 2 diabetes. However, most patients will require the addition of medications over the course of their diabetes. Only 30.7% of patients in Thailand achieved HbA1c of less than 7%(3).

A newer group of medication that decreases insulin resistance and increases insulin sensitivity is Thiazolidinediones (TZDs): Rosiglitazone and
Pioglitazone. TZDs have demonstrated a 0.5-1.4% decrease in HbA1c. They increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin (“insulin sensitizers”) and decrease insulin resistance which caused type 2 diabetes. The most common adverse effects are weight gain and fluid retention. Pioglitazone improves lipid profile; decrease triglycerides (TG), increase high-density lipoprotein cholesterol (HDL-C), decrease low-density lipoprotein (LDL) particle concentration, LDL particle size and reduces the need to add insulin to existing therapy. In high-risk patients with type 2 diabetes and previous MI, Pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and acute coronary syndrome.

The Thailand Diabetes Registry Project found that sixty-nine percent of patients received combination therapy and TZDs were commonly used. With recent economic status, generic pioglitzone will help increase patients’ access to this essential drug. The bioequivalence study of 30 mg Pioglitazone indicated that generic (Utmos®) and original (Actos®) Pioglitazone were bioequivalent in Thai healthy volunteers. The objective of the present study were to compare the efficacy and safety of generic (Utmos®) and original (Actos®) 30 mg Pioglitazone tablets in type 2 diabetic patients. The primary objective was to compare the change of HbA1c and FPG between generic and original 30 mg Pioglitazone tablets. The secondary objective was to compare changes of lipid profile (total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C)) and safety (occurrence of side effects) between the two groups.

Material and Method
The present study was a multicenter, double-blinded, parallel randomized-controlled study. The unachieved glycemic control type 2 diabetic patients, ages 30 to 70 years, with glycated hemoglobin (HbA1c) ≥ 7.0% who received Metformin not less than 1,000 mg/day over three months were recruited from 7 Hospitals. Subjects were excluded if they were pregnant, breast-feeding or planning to get pregnant during the study; current users of TZDs; hypersensitivity to TZD; infected with HIV; or partake in other on going clinical trial; if they had AST, ALT more than 2.5 times the upper limit of normal; serum creatinine more than 1.8 mg/dl or 160 mmol/L; glomerulonephritis; coronary heart disease (CHD) or congestive heart failure (CHF); or recent history of drug and alcohol abuse.

The study was approved by the Ethics Committee of each participating hospital. Signed informed consent was obtained from all participants. Patients were randomized (1:1) to receive generic or original Pioglitazone 30 mg/day for 24 weeks. Randomization was stratified by center (computerized random numbers). Each center received generic and original Pioglitazone that were packed in opaque blister pack, sealed in aluminium moisture-barrier bag and labeled with random numbers. Patients attended the clinics for five study-visits: screening visit, randomized visit and subsequently at 4, 12 and 24 weeks after the randomized visit. Physical examination; body weight, waist circumference, blood pressure and pulse; were measured at every visit. HbA1c were analyzed at screening visit, 12 and 24 weeks at a central laboratory, Rajavithi hospital. Fasting plasma glucose (FPG), lipid profile and liver function were analyzed at screening visit and subsequently at 4, 12 and 24 weeks after the randomized visit. Repeated measures ANOVA were designed for analyzing changes in HbA1c, FPG and lipid profile between baseline and each visit and between groups. T-test, Pearson Chi-square test and analysis of variance (f-test) were used to compare means of the various measurements between the two groups and within each group. A p-value less than 0.05 was considered as statistically significance. Data were analyzed by statistical program Minitab version 13. The sample size to give 95% confident interval and 90% power was calculated by repeated measures model.

Results
Eighty-five patients were enrolled, forty-four patients received generic Pioglitazone and forty-one received original Pioglitazone. Patients were recruited from April 2008 to March 2009 and attended clinic visits at the time of randomization (baseline) and at week 4th, 12th and 24th. Baseline characteristics of participants in both groups were similar as shown in Table 1.

HbA1c, FPG, lipid profile and body weight during 24-week of treatment with generic and original 30 mg Pioglitazone tablets are shown in Table 2, Fig. 1 and Fig. 2. HbA1c reduction from baseline at week 12th and 24th in generic group were 0.76 and 0.91% (p < 0.0001) and in original group were 0.88 and 0.98%, respectively (p < 0.0001). FPG reduction from baseline at week 4th, 12th and 24th in generic group were 20.00, 24.93 and 23.93 mg/dl (p < 0.0001) and in original group were 21.75, 27.85 and 24.87 mg/dl, respectively.
There were no significant differences in HbA1c and fasting plasma glucose (FPG) reduction between generic and original Pioglitazone group (p = ns).

Total cholesterol and LDL-cholesterol were not significantly changes and no differences between the original and the generic Pioglitazone. Triglycerides were decreased from baseline at week 4th, 12th and 24th 39.18, 29.43 and 39.25 mg/dl in generic group and 30.88, 22.02 and 24.05 mg/dl in original group, respectively (p < 0.01). HDL-cholesterol at week 4th, 12th and 24th were significantly increased from baseline 4.57, 5.69 and 6.73 mg/dl in generic group and 6.14, 7.19 and 5.58 mg/dl in original group, respectively (p < 0.0001).

Body weight at week 4th, 12th and 24th was increased from baseline 0.42, 1.26 and 1.86 kg in generic group and 0.73, 1.12 and 1.33 kg in original group, respectively (p < 0.05).

Discussion

Type 2 diabetes, the most common form of diabetes, is characterized by insulin deficiency and resistance. Pioglitazone is an antihyperglycaemic agent that can increase insulin sensitivity and decrease insulin resistance. Because of its action on the major pathoetiology of type 2 diabetes, Pioglitazone is one of the antidiabetic agents commonly prescribed worldwide. The objective of the present study was to compare the efficacy and safety of generic (Utmos®) and original (Actos®) 30 mg Pioglitazone tablets in type 2 diabetes mellitus.
Results of the present study demonstrated that generic (Utmos®) and original (Actos®) 30 mg Pioglitazone tablets were not different in the efficacy and safety profiles. There were no statistically significant differences in HbA$_1c$ and fasting plasma glucose (FPG). HbA$_1c$ reductions from baseline at 24 weeks were 0.91% in generic and 0.98% in original group (p < 0.0001). FPG reductions from baseline in 24 weeks were 23.9 mg/dl in generic and 24.9 mg/dl in original (p < 0.0001). Starting with similar baseline HbA$_1c$ of participants in both groups 7.72% in generic and 7.85% in original, HbA$_1c$ were reduced to 6.81%
in generic and 6.87% in original. In 24 weeks, generic achieved HbA1c goal (HbA1c < 7% ADA guideline) in 31 case (70.45%) and original group in 22 case (53.66%). Combinations of Pioglitazone and metformin used in this study have benefit for achieving HbA1c goal without increasing risk of hypoglycemia.

Lipid profiles were changed in the same pattern and no significantly differences between groups. Triglyceride levels at week 24th were decreased from baseline by 39.3 mg/dl in generic group and 24.1 mg/dl in original group (p < 0.01). LDL-C levels at week 24th were increased from baseline by 5.97 mg/dl in generic group and 1.26 mg/dl in original group (p = ns). HDL-C levels at week 24th were increased from baseline by 6.73 mg/dl in generic group and 5.58 mg/dl in original group (p < 0.0001). The results showed that Pioglitazone have benefit for decreasing triglyceride and increasing HDL-cholesterol as a result of specific nuclear receptor activation (peroxisome-proliferator activated receptor-gamma and alpha [PPAR-gamma and PPAR-alpha]).

Body weights were increased in both groups but not significantly different between groups. At week 24th body weight was increased from baseline by 1.86 kg in generic group and 1.33 kg in original group (p < 0.05). Body weights of subjects in this study were increased in lower rate than previous reports (0.9-5.5 kg). This may be the result of combination with metformin that attenuated the effect of Pioglitazone on body weight.

The present study revealed 19 adverse events. Headache was 3 (6.8%) and 1 (2.4%) and edema was 8 (18.2%) and 7 (17.1%) in generic and original group, respectively. There were no significant differences between groups. Congestive heart failure (CHF) was not found in both groups in this study. Nevertheless, TZDs must be used with caution in CHF and/or ankle edema patients. Headache was not severe and not related to blood pressure change. Pioglitazone was well tolerated and no patient withdrawn from this study.

Fasting Plasma Insulin was changed in the same pattern and no significant differences between generic and original group. Fasting Plasma Insulin was decreased by 2.84 μU/ml in generic group and
1.58 μU/ml in original group. Because Pioglitazone decreases peripheral insulin resistance, insulin requirement was decreased. This is a long-term benefit that helps preserve beta-cells function.

In conclusion, generic Pioglitazone 30 mg (Utmos®) is effective as original Pioglitazone 30 mg (Actos®) when combined with metformin in 24-week comparative study. There were no differences in metabolic control and safety findings.

References
การศึกษาประสิทธิภาพและความปลอดภัยของยาพิโอกลิตาโซนต้นแบบและยาสามัญในผู้ป่วยโรคเบาหวานชนิดที่ 2

เพชรรอดอารีย์, ชัยชาญ ดีโรจนวงศ์, ธวัชชัย พีรพัฒน์ดิษฐ์, สมพงษ์ สุวรรณวลัยกร, อภัสนี บุญญาวรกุล, ธัญญา เชฏฐากุล, ธงชัย ประฏิภาณวัตร, นันทกร ทองแดง, ยุพิน เบ็ญจสุรัตน์วงศ์, อัมพร ใจรินทร์, อภิชิต ประชิรัตน์วงศ์, ณัฐพงศ์ โฆษชุณหนันท์, นันทกร ทองแตง, อำไพ เข็มค้า, ธงชัย ประฏิภาณวัตร, ณัฐพงศ์ โฆษชุณหนันท์

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิภาพและความปลอดภัยของยาพิโอกลิตาโซนต้นแบบและยาสามัญในผู้ป่วยโรคเบาหวานชนิดที่ 2

รูปแบบการศึกษา: วิจัยเชิงทดลองแบบสหสถาบัน double-blinded, randomized-controlled study

วัสดุและวิธีการ: ศึกษาในผู้ป่วยเบาหวานชนิดที่ 2 ที่กำลังรักษาด้วยยา Metformin ขนาด 1,000 มก. หรือไม่ต่ำกว่า 3 เดือน แต่ไม่สามารถควบคุมระดับน้ำตาลได้ตามเป้าหมาย คือมีระดับ HbA1c ≥ 7.0% ผู้ป่วยถูกสุ่มให้ได้รับยาพิโอกลิตาโซนสามัญ (Utmos®) หรือต้นแบบ (Actos®) วันละ 30 มก. ต่อเนื่องเป็นเวลา 24 วัน

ผลการศึกษา: ผู้ป่วยเข้าร่วมการศึกษาจำนวน 85 คน ได้รับยาพิโอกลิตาโซนสามัญจำนวน 44 คน และได้รับยาต้นแบบจำนวน 41 คน ในทั้งหมดมีความแตกต่างทางสถิติระหว่างกลุ่มที่ได้รับยาพิโอกลิตาโซนสามัญและต้นแบบที่สังเกตุได้มีประสิทธิภาพในการลดระดับ HbA1c, ระดับน้ำตาลในเลือดหลังอัตนะ (FPG) และมีประสิทธิภาพในการเพิ่ม HDL อย่างมีนัยสำคัญทางสถิติ (p < 0.0001) เมื่อเปรียบเทียบจากเวลาเริ่มต้นการศึกษา อาการปวดศีรษะและบวมพบในทั้งสองกลุ่ม (p > 0.05)

สรุป: ยาพิโอกลิตาโซนสามัญ (Utmos®) สามารถควบคุมระดับน้ำตาลและระดับไขมันในเลือดได้อย่างมีประสิทธิภาพเช่นเดียวกับยาต้นแบบ ยาพิโอกลิตาโซนสามัญ (Utmos®) และต้นแบบ (Actos®) มีประสิทธิภาพและความปลอดภัยไม่แตกต่างกัน