Preliminary Report

Adverse Effect of Pioglitazone in Military Personnel and Their Families: A Preliminary Report

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Background: *Thiazolidinediones (rosiglitazone and pioglitazone) whether administered alone or in combination with metformin, sulfonylurea, or insulin, are often accompanied by an increase in weight and/or plasma volume. Several studies have shown the adverse effect of weight gain and edema with rosiglitazone. But there was less data with pioglitazone, especially in military personnel and their families.*
Material and Method: *The authors prospectively recorded the adverse events in 40 patients with type 2 diabetes mellitus who underwent administration with pioglitazone 15 mg once daily between June 2005 to May 2007.*
Results: *Weight gain was reported in 30/40 of patients (75 %). The mean weight gain was 2.25 $\pm$ 2.23 kg and the median was 2 kg. The slightly lower proportion of patients, 21/40 (52.5 %) developed edema and some of them were associated with weight gain.*
Conclusion: *Pioglitazone was associated with a significant increase in body weight and edema. This finding may lead to increase the risk of myocardial infarction in military personnel and their families, especially those who had underlying disease of congestive heart failure, which was not included in the present study.*

Keywords: *Pioglitazone, Weight gain, Edema, Military personnel*

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Pioglitazone is a peroxisome proliferator-activated receptor-gamma agonist in the thiazolidinedione class. It is widely used to treat patients with type 2 diabetes mellitus and improves glycemic control primarily by increasing hepatic and peripheral insulin sensitivity. In general, thiazolidinediones (TZDs) including rosiglitazone and pioglitazone, whether administered alone or in combination with metformin, sulfonylurea, or insulin, are often accompanied by an increase in weight and/or plasma volume. Thus, mild to moderate edema and congestive heart failure (CHF) might be anticipated side effects of treatment with these drugs[1,2]. However, there was a large observational study of over 16,000 patients with a principal discharge diagnosis of heart failure found a reduced mortality (hazard ratio [HR] 0.87; 95% CI 0.80, 0.94) in those prescribed thiazolidinediones[3].While prospective pioglitazone clinical trial in macrovascular events (PROactive) suggested that more pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study (p = 0.007). However, mortality due to heart failure was similar, 25 of 2,605 (0.96%) for pioglitazone vs. 22 of 2,633 (0.84%) for placebo (p = 0.639). Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone, 40 of 149 (26.8%) vs 37 of 108, (34.3%) with placebo (p = 0.1338)[4]. Besides, weight gain is probably due to several interacting factors. Several studies have shown the adverse effect of weight gain and edema with rosiglitazone[5], and some studies analyzed the rosiglitazone link with myocardial infarction and cardiac deaths[6]. But there was less data with pioglitazone[7,8]. The change in fat distribution may

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explain in part of the improvement in glycemic control despite an overall increase in body weight. However, in the military personnel, these adverse effects may lead to cardiovascular morbidity and mortality, which have not been determined during treatment with pioglitazone.

The objective of the present study was to assess the incidence of weight gain and edema of pioglitazone in military personnel with type 2 diabetes mellitus.

Material and Method

This prospective study was performed in 40 patients with type 2 diabetes mellitus at the Department of Medicine, Phramongkutklao Hospital, Thailand. All patients were either military personnel or their families. Inclusion criteria for pioglitazone administration in the 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 > 1000 mg daily for 3 months or metformin alone > 1500 mg daily for 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, serum creatinine > 1.4 and > 1.5 mg/dL for female and male, severe diabetes or renal complication, $\geq$ 2.5 folds of upper limit normal (ULN) of liver enzymes, history of CHF. Informed consent was obtained from each subject. Duration of observation for adverse effect during treatment with pioglitazone was 24 weeks. The dose of pioglitazone was 15 mg once daily. The research methodology of the present trial was already approved by The Institutional Review Board, The Royal Thai Army Medical Department.

Statistical analysis

Continuous variables were summarized as mean (standard deviation) or median (range) or percent as appropriate. Overall adverse effect and each adverse effect were estimated using binary logistic regression, odds ratio (OR) at 95% confidence intervals (CI).

Results

During a two-year period from June 2005 to May 2007, 40 patients with type 2 diabetes mellitus underwent administration with pioglitazone in combination with other antidiabetic drugs at Phramongkutklao Hospital. Their ages were ranged from 45 to 68 years with the mean age of 57.83 $\pm$ 7.34 years. The distribution of their personal information is presented in Table 1.

Distribution of patients treated with pioglitazone in combination with other antidiabetic drugs is illustrated in Fig. 1. Most of them (87.5 %) received pioglitazone in combination with sulfonylurea and metformin.

Besides type 2 diabetes mellitus, all subjects also had other concomitant diseases, which were being treated with other groups of drugs as presented in Table 2.

Weight gain and edema

It is shown in Table 3 that 30/40 of patients **(**75 %) had weight gain and there was a significant

Table 1. Distribution of personal information of patients (n = 40)

Type of patients	No.	%
Military personnels	12	30.00
Family	28	70.00
Male	14	35.00
Female	26	65.00
Age (years)		
40-50	8	20.00
51-60	14	35.00
61-70	18	45.00

Table 2. Other groups of drugs used by subjects (n = 40)

Groups of drugs for concomitant diseases	No.	%
Antihypertensives	10	25.0
Antihyperlipidemic drugs	3	7.5
Antihypertensives + antihyperlipidemic drugs	24	60.0
Antihypertensives + antihyperlipidemic drugs + antianginal drugs	1	2.5
Antihypertensives + antihyperlipidemic drugs + respiratory drugs	1	2.5
Antihypertensives + respiratory drugs	1	2.5
Total	40	100.0

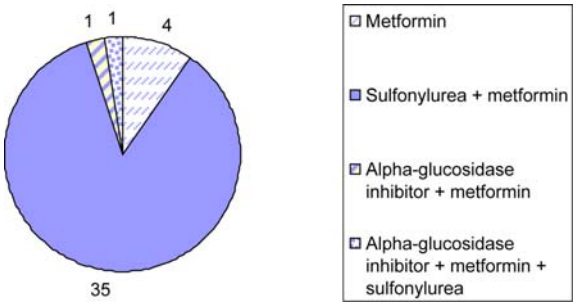

Fig. 1 Other antidiabetic drugs used by subjects (n = 40)

difference between body weight of patients before (week 0) and after (week 24) treated with pioglitazone. The change of subjects' body weight ranged from 8 to -2 kg The mean weight gain was 2.25 ± 2.23 kg and the median was 2 kg. There was no statistic relation between weight gain and age.

It was found that 21/40 of them (52.5%) developed edema. The number of patients being treated with diuretics who had edema and no edema were 5 and 4, respectively. The relation between edema and other factors is presented in Table 4.

Discussion

The weight gain associated with the use of TZDs is probably due to several interacting factors[9]. In general, improvement in glycemic control with decreased glycosuria and caloric retention may result in increased weight. Several studies have shown that the weight gain with TZDs may be associated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat; although subcutaneous fat area increases, visceral fat area and the ratio of visceral to subcutaneous fat decrease[10,11]. This change in fat distribution may explain in part the improvement in glycemic control despite an overall increase in body weight[12]. In the present study, an increase in appetite had also been seen with pioglitazone treatment even though some other studies stated that it was not clear if weight gain associated with pioglitazone can be attributed to this effect[13]. Fluid retention, of course, is another potential cause of increased body weight, which was also found in the present study. There was significant association of body weight gain and edema as one kilogram of weight gain may induce 1.115 fold of edema.

The reasons for fluid retention and peripheral edema with TZDs use are not clearly understood and are likely to be multifactorial. The increase in plasma volume related to TZDs has already been cited and may result from a reduction in renal excretion of sodium and an increase in sodium and free water retention. TZDs may interact synergistically with insulin to cause arterial vasodilatation, leading to sodium reabsorption with a subsequent increase in extracellular volume, and thereby resulting in pedal edema. While in the present study, there was no statistical relation between edema and diuretic treatment. This finding may be due to concomitant diseases; hypertension and hyperlipidemia in such patients, which were not well-controlled. Increased sympathetic nervous system activity, altered interstitial ion transport, alterations in endothelial permeability, and peroxisome proliferator-activated receptor-gamma-mediated expression of vascular permeability growth factor representing other possible mechanisms for edema with pioglitazone[14].

Table 3. Change in body weight at week 24 of pioglitazone treatment (n = 40)

Change in body weight	No. of patients	%
Gain weight	30	75.0
No change	5	12.5
Loose weight	5	12.5
Total	40	100.0

Table 4. Edema in each type of patients

	Total	Edema		p-value	OR (95% CI)
		Edema	No edema		
Diuretics					
Yes	9	5.0 (55.56)	4 (44.44)	0.835	1.172 (0.264, 5.208)
No	31	16.0 (51.61)	15 (48.39)		
Age	57.83 ± 7.34	59.0 ± 6.72	56.53 ± 7.95	0.285	1.049 (0.961, 1.145)
Weight gain	2.25 ± 2.23	2.5 ± 2.52	1.98 ± 1.88	0.461	1.115 (0.835, 1.487)

A recent study suggested that there was little clear evidence that either rosiglitazone or pioglitazone caused major improvements in cardiovascular outcomes. The difference might be that rosiglitazone had no effect or may even increase cardiovascular outcomes, whereas, in high-risk subjects, pioglitazone had a marginal ability to decrease cardiovascular outcomes[15].

However, in patients without established heart disease, both pioglitazone and rosiglitazone should be prescribed according to the package insert guidelines for each drug. It should be recognized that weight gain and/or edema will be encountered more often in patients on concomitant insulin treatment but this factor was not included in the present study.

Conclusion

Pioglitazone was associated with a significant increase in body weight and edema. This finding may lead to increase the risk of myocardial infarction in military personnel and their families, especially those who had underlying disease of CHF which was not included in the present study. However, the adverse events and the risk of myocardial infarction may or may not be the same as those that occurred in other groups of population . Thus, further study should be performed in a larger group of subjects to confirm the adverse event of pioglitazone in the Military. Despite this preliminary report, physicians should consider the potential for adverse cardiovascular effects of treatment with pioglitazone as well as with rosiglitazone for type 2 diabetes.

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อาการไม่พึงประสงค์ของยาไพโอกลิตาโซนในบุคลากรของกองทัพบกและครอบครัว: รายงานเบื้องต้น

ธิษณาภา วุฒิรณฤทธิ์, ยุพิน เบญจสุรัตน์วงศ์, สุเพ็ญ ภัทรกิจวานิช, สุภัททา เต็มบุญเกียรติ, นิสามณี สัตยาบัน

ภูมิหลัง: *ยากลุ่มไธอะโซลิดีนไดโอน (โรซิกลิตาโซนและไพโอกลิตาโซน) ซึ่งอาจใช้อย่างเดียวหรือให้ร่วมกับเมทฟอร์มิน ซัลโฟนิลยูเรีย หรือ อินซูลิน พบว่าทำให้น้ำหนักเพิ่ม และ/หรือ มีปริมาณน้ำในร่างกายเพิ่มขึ้นได้บ่อย โดยที่ส่วนใหญ่เป็นการศึกษาการใช้โรซิกลิตาโซน ส่วนการศึกษาการใช้ไพโอกลิตาโซนยังมีน้อยโดยเฉพาะอย่างยิ่งในบุคลากรของกองทัพบกและครอบครัว*

วัสดุและวิธีการ: *ศึกษาโดยการสังเกตอาการไม่พึงประสงค์ในผู้ป่วยเบาหวานชนิดที่ 2 ที่เป็นบุคลากรของกองทัพบกและครอบครัว จำนวน 40 รายซึ่งได้รับการรักษาด้วยยาไพโอกลิตาโซนขนาด 15 มิลลิกรัม วันละครั้ง ระหว่างเดือนมิถุนายน พ.ศ. 2548 ถึง พฤษภาคม พ.ศ. 2550*

ผลการศึกษา: *ผู้ป่วยที่น้ำหนักเพิ่มคิดเป็นร้อยละ 75 (30/40 ราย) โดยมีน้ำหนักเพิ่มเฉลี่ย 2.25 $\pm$ 2.23 กิโลกรัม และมีค่ากลางของน้ำหนักที่เพิ่ม 2 กิโลกรัม ผู้ป่วยที่มีอาการบวมคิดเป็นร้อยละ 52.5 (21/40 ราย) โดยในจำนวนนี้มีบางรายเกี่ยวข้องกับการที่น้ำหนักเพิ่มด้วย*

สรุป: *ไพโอกลิตาโซนทำให้น้ำหนักเพิ่มและเกิดบวมอย่างมีนัยสำคัญ ซึ่งอาจทำให้เสี่ยงต่อการเกิดกล้ามเนื้อหัวใจตายได้ในบุคลากรของกองทัพบกและครอบครัว โดยเฉพาะผู้ที่เป็นโรคหัวใจล้มเหลวร่วมด้วย ซึ่งไม่ได้รวมอยู่ในการศึกษานี้*