The Pharmacokinetics of Pioglitazone in Thai Healthy Subjects

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Background: *Pioglitazone is a thiazolidinedione compound used in the treatment of type 2 diabetes, metabolized mainly by CYP2C8 and CYP3A4. Due to genetic polymorphisms in CYP2C8, interethnic variability in pharmacokinetics should be considered.*
Objective: *To conduct a study on the pharmacokinetics of pioglitazone in Thai subjects.*
Material and Method: *The present study was performed in 24 Thai male healthy subjects. After an overnight fasting, each subject had a single oral dose of 30 mg pioglitazone tablet. Serial blood samples were collected before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 24 and 48 hours after drug administration. Plasma pioglitazone was determined by automated High Performance Liquid Chromatography (HPLC) with UV detection after deproteinized with acetonitrile. The relevant pharmacokinetic parameters including peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), elimination rate constant (Kel), elimination half-life ($T_{1/2}$), area under the plasma concentration-time curve ($AUC_{(0-t)}$, $AUC_{(0-inf)}$), clearance (Cl) and volume of distribution (Vd) were determined.*
Results: *After a single oral dose of 30 mg pioglitazone tablet, the drug was absorbed into systemic circulation with time to maximum concentration (T_{max}) at 2.00 $\pm$ 1.61 (0.5-6) hr, and the plasma level reached the maximum concentration (C_{max}) of 1.14 $\pm$ 0.29 (0.47-1.63) μg/ml. The AUC was 11.47 $\pm$ 4.77 and 16.69 $\pm$ 7.75 μg.hr/ml for AUC_{0-t} and AUC_{0-inf}, respectively. The elimination rate constant (Kel) of pioglitazone obtained was 0.08 $\pm$ 0.04 hr^{-1}, whereas the $t_{1/2}$ was 11.19 $\pm$ 7.38 hrs with the clearance (Cl) of 2.26 $\pm$ 1.22 L/hr. The apparent volume of distribution (Vd) was found to be 30.19 $\pm$ 13.06 L.*
Conclusion: *Pharmacokinetic parameters of 30 mg single oral dose of pioglitazone were characterized in Thai subjects. These parameters showed that pioglitazone had a rapid rate of absorption, small volume of distribution and short elimination half-life.*

Keywords: *Pioglitazone, Pharmacokinetics*

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Pioglitazone hydrochloride is an oral antidiabetic agent belonging to the thiazolidinedione class. Pioglitazone, a derivative of the parent molecule ciglitazone, acts primarily by reducing insulin resistance, improves sensitivity to insulin in muscle and adipose tissues and decreases hapatic gluconeogenesis[1]. It acts as an agonist of the peroxisome proliferators-activated receptor subtype gamma (PPAR-γ)[2].

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Pioglitazone has been evaluated in the treatment of type 2 diabetes mellitus as monotherapy, or in combination with a sulfonylurea, metformin or insulin. The usual dosage of pioglitazone is 30 mg once daily that significantly reduces fasting blood glucose, HbA1c, triglyceride and free fatty acid, and significantly increases HDL-cholesterol. Pioglitazone has also been demonstrated to cause minor increases in blood cholesterol with no effect on LDL-cholesterol[2-3].

Evaluations of 2096 patients taking pioglitazone (30 mg once daily) during clinical trials showed no evidence of hepatotoxic effects. The percentage of

all patients with ALT values > 3 times the upper limit of normal of the reference range was 0.38% with pioglitazone compared to 0.17% for placebo[3]. The most frequently reported adverse events are weight gain, fluid retention and edema, and anemia. Other adverse events that occur more frequently in patients treated with these agents than with placebo include upper respiratory tract infections, sinusitis, headache and myalgia[3].

Pioglitazone is rapidly absorbed, its oral bioavailability exceeds 80%, and it is extensively metabolized by hydroxylation and oxidation to active and inactive metabolites in the liver[4,5]. The main active metabolites are M-III and M-IV[5]. Another metabolite M-II also has pharmacological activity, but its concentrations are low. In vitro studies suggest that the drug is metabolized by several cytochrome P450 (CYP) enzymes, but mainly by CYP2C8 and CYP3A4[4-6]. This may interfere with the metabolism of numerous drugs that play a role of CYP2C8 or CYP3A4 inducer or inhibitor.

Genetic factors are known to contribute to individual differences in bioavailability, drug transport, metabolism and drug action. The genetic polymorphisms in CYP2C8 have effect on the pharmacokinetics of oral antidiabetic drugs[7]. Interethnic differences on drug's pharmacokinetics should be considered. They may contribute to variability to drug response. No clinical pharmacokinetic data has been reported in Thai population. Therefore, the aim of the present study was to determine elucidate the pharmacokinetic parameters of pioglitazone at the usual dose of 30 mg in Thai healthy subjects.

Material and Method

Subjects

Twenty-four Thai healthy male subjects aged 18-45 years were included in the present study. All had normal body build with BMI between 18-25, weighting within ± 10% of ideal body weight. All subjects were in good health as confirmed by physical and clinical laboratory examinations including serology, hematology and biochemical test. The methods and condition of the study were clearly explained to all subjects. Informed consent was signed and obtained from each subject prior to entering the experiment. At least eight weeks before the experiment, the subjects were asked not to donate a unit of blood or participate in another clinical trial. The subjects with cigarette smoking, alcoholic intake and caffeine intake habit were all excluded.

Ethical consideration

The study protocol, informed consent form, patient information sheet and case report form were approved by the Institutional Ethical Review Committee of the Faculty of Medicine, Chulalongkorn University.

Study design

Each subject was prepared in a fasted state approximately eight hours prior to the present study. Test drug-product of pioglitazone 30 mg tablets (Actos®) lot no. 5BTK003 was used for the present study. They received a single oral dose of 30 mg pioglitazone with 200 ml of water. Standard meals were served 2, 4, and 10 hr after drug administration. All subjects were abstained from other drug intake and alcoholic consumption two weeks prior to and throughout the present study. Caffeine containing beverage was not allowed 3 days prior to and throughout the study.

Blood sampling

A forearm vein of each subject was cannulated, and blood samples (7 ml) were drawn into heparinized tubes before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 24 and 48 hours after drug intake. Plasma was separated by centrifugation and stored at -70 C until analysis.

Determination of plasma pioglitazone concentration

Chemical

The standard pioglitazone HCl and internal standard rosiglitazone maleate were kindly donated by Unison Laboratories. Acetonitrile HPLC grade and disodium hydrogen phosphate were obtained from MERCK. In-house deionized water was further purified with a purifying system before use.

Analytical method validation

The analytical method of validation was modified from the method described by Guidance for industry: Bioanalytical method validation (US Department of Health and Human Series FDA, CDER, CVM. May 2001, BP)[8].

Sample preparation

To 500 µl of plasma, 10 µl of internal standard was added and then mixed with 1.8 ml acetonitrile and vortexed for 30 seconds. The samples were centrifuged at 4,000 rpm for 10 minutes at room temperature. The supernatant was transferred and evaporated to

dryness with speed vacuum. Dried samples were reconstituted with 350 μl of mobile phase (50 mM phosphate buffer (pH 4.53) – acetonitrile (55:45; v/v)) and the solution was centrifuged at 4000 rpm for 10 minutes. Aliquot of 100 μl of supernate was injected to the HPLC system.

Instruments and HPLC conditions

Chromatography was carried out at room temperature on Shimadzu-HPLC system-10AD series. A reverse phase column 250 4.6 mm i.d., C18, 5 μm ODS guarded with an inersil ODS-3, 5 μm was used. The mobile phase consisted of 50 mM phosphate buffer (pH 4.53) – acetonitrile (55:45; v/v) flowing through the system at the rate of 1 ml/min. The HPLC column temperature was 40 C. Eluent was monitored by UV detector set at the wavelength of 229 nm, and the sample injection volume was 100 μl.

Statistical analysis

The pharmacokinetic parameters of pioglitazone were characterized including peak concentration in plasma (C_{max}), time to reach peak plasma (T_{max}), area under the plasma concentration-time curve from time 0-48 hr ($AUC_{(0-t)}$) and infinity ($AUC_{(0-inf)}$), elimination rate constant (Kel), elimination half life ($T_{1/2}$), clearance and volume of distribution. The C_{max} and Tmax were taken directly from the individual concentration versus time data. The elimination rate constant (Kel) was determined by log-linear least squared regression of the terminal part of the plasma concentration versus time curve. The $T_{1/2}$ was calculated from the equation $T_{1/2}$ = ln2/Kel. The AUC was calculated by the linear trapezoidal rule. The clearance was calculated from the equation of F. dose/AUC_{0-inf} with the bioavailability (F) > 80% as reported by a previous study[8], and apparent volume of distribution (Vd) was calculated from the equation Cl/Kel.

Results were expressed as mean ± standard deviation (SD) in the text and tables and as mean ± standard errors of mean (SEM) in the figures.

Adverse events

The subjects were all requested to report all adverse events at baseline (predose), during and after drug intake. They were inquired for adverse events by the medical staff. Although the reports[2] show that hepatotoxicity caused by pioglitazone is very low, subjects were still screened liver function test immediately after the study. All adverse events encountered during the clinical study were recorded on the Case Report Form.

Results

The analytical method was validated to assure the acceptability of the performance. The HPLC technique for plasma pioglitazone analysis demonstrated high selectivity with clear separation of pioglitazone, internal standard rosiglitazone and endogenous substances. Linear relationship of standard curve of pioglitazone gave high correlation, presented by $r^2 > 0.999$. Percent accuracy of low, medium and high concentrations were within the acceptable limit 85-115%. The intra-day and inter-day precision as presented by % coefficient of variation (%CV) of low, medium and high concentrations were within the acceptable range (%CV < 15%).

The subject data

All subjects were judged healthy based on physical examination, medical history, vital signs and clinical laboratory test. The demographic data of subjects enrolled in the present study are shown in Table 1. Their ages ranged from 21 to 40 years (average 26.71 ± 6.29) with the weight and height ranging from 51.0-78.0 kgs and 161.0-188.0 cms, respectively. Their body mass indexes were within the range of 18-25. The mean of each of the clinical laboratory data of all

Table 1. Demographic data of 24 subjects enrolled in the study

	Mean ± SD	Range
Age (years)	26.71 ± 6.29	21-40
Body weight (kg)	66.24 ± 7.93	51.0-78.0
Height (cm)	172.71 ± 7.60	161.0-188.0
Body mass index (BMI) (kg/m^2)	22.16 ± 1.76	18.60-25.47
Systolic blood pressure (mmHg)	110.42 ± 6.90	100-120
Diastolic blood pressure (mmHg)	69.58 ± 7.51	60-90
Heart rate/min	70.46 ± 7.87	56.0-84.0

Table 2. Clinical laboratory data of 24 subjects enrolled in the study

	Mean ± SD	Normal Value
Hemoglobin (gm/dl)	14.74 ± 1.04	12.0-18.0
Hematocrit (%)	43.52 ± 2.66	37.0-54.0
Glucose (mg/dl)	88.25 ± 5.62	70-110
BUN (mg/dl)	13.17 ± 3.02	10-20
Creatinine (mg/dl)	1.05 ± 0.18	0.5-2.0
SGOT (U/L)	19.79 ± 5.17	0-38
SGPT (U/L)	17.42 ± 8.24	0-38
Alkaline phosphatase (U/L)	69.46 ± 18.24	39-117
Anti HIV	Negative	Negative
HBsAg	Negative	Negative
Urine analysis	Normal	Normal

Table 3. The mean, standard deviation (SD), % coefficient of variation (%CV), maximum and minimum concentration of plasma pioglitazone 30 mg after an oral single dose (n = 24)

Time after Administration (hr)	Mean (μg/ml)	SD	%CV	Maximum (μg/ml)	Minimum (μg/ml)	Max-Min (μg/ml)
0.5	0.8145	0.4181	0.0034	1.6256	0.1261	1.4995
1	0.9591	0.4284	0.0041	1.7010	0.2813	1.4197
1.5	1.1110	0.3784	0.0042	1.7974	0.4085	1.3889
2	1.0948	0.3873	0.0042	1.6910	0.4117	1.2793
2.5	1.0483	0.3464	0.0036	1.5333	0.4281	1.1052
3	0.9966	0.2751	0.0027	1.4302	0.4388	0.9914
3.5	0.9982	0.2559	0.0026	1.3680	0.4160	0.9520
4	0.9899	0.2876	0.0028	1.5751	0.4491	1.1260
5	0.8916	0.2634	0.0023	1.4989	0.2710	1.2279
6	0.8154	0.2743	0.0022	1.3429	0.3077	1.0352
9	0.6550	0.2432	0.0016	1.2731	0.2691	1.0040
12	0.5114	0.2126	0.0011	0.9701	0.1690	0.8011
24	0.2855	0.1014	0.0003	0.5282	0.1654	0.3628
48	0.2012	-	-	0.2012	0.2012	-

subjects is shown in Table 2. All had negative HIV and normal clinical laboratory screening test, including hepatitis test.

Pharmacokinetic parameters

The mean, SD, coefficient of variation (%CV), maximum and minimum plasma pioglitazone concentrations at each sampling time up to 48 hours following a single oral dose of 30 mg pioglitazone are presented in Table 3. The graphic profile curve of mean plasma pioglitazone concentration vs time is illustrated in Fig. 1.

After a single oral administration of 30 mg pioglitazone, an average peak plasma concentration (C_{max}) was 1.14 ± 0.29 mg/ml, while the time to reach peak plasma concentration was 2.00 ± 1.61 hrs (0.5-6 hrs). The $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, which describe the extent of drug absorption, were 16.69 ± 7.75 and 11.47 ± 4.77 mg.hr/ml, respectively. The mean elimination rate constant (Kel) determined by the terminal part of the plasma concentration versus time curve was 0.08 ± 0.04 hr^{-1}. The mean elimination half life ($T_{1/2}$) calculated from 0.693/Kel was 11.19 ± 7.38 hrs. The clearance and apparent volume of distribution (Vd) were 2.26 ± 1.22 L/hr and 30.19 ± 13.06 L, respectively. All the relevant pharmacokinetic parameters are shown in Table 4.

Adverse events

Adverse events were monitored during and

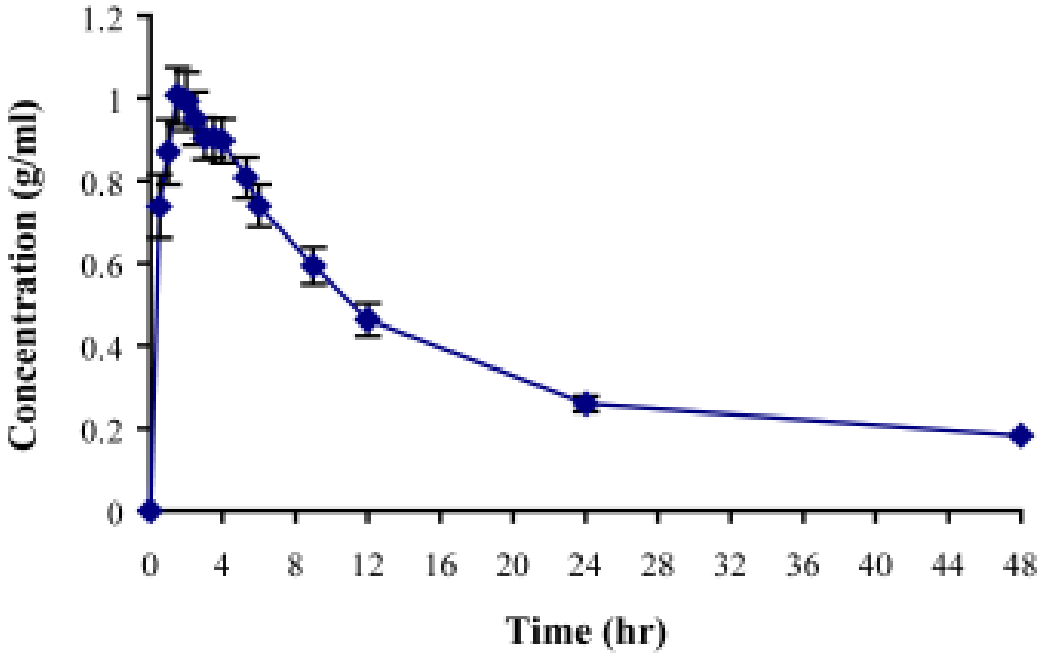

Fig. 1 Mean plasma pioglitazone concentration-time curve after a 30 mg single oral dose (n = 24)

Table 4. Pharmacokinetic parameters (mean ± SD) of pioglitazone after an oral dministration of pioglitazone 30 mg in 24 healthy male volunteers

Parameters	Mean ± SD	Range
C_{max} (μg/ml)	1.14 ± 0.29	0.47-1.63
t_{max} (hr)	2.00 ± 1.61	0.50-6.00
$AUC_{0\rightarrow t}$ (μg.hr/ml)	11.47 ± 4.77	3.48-20.66
$AUC_{0\rightarrow\infty}$ (μg.hr/ml)	16.69 ± 7.75	5.56-39.22
$t_{1/2}$ (hr)	11.19 ± 7.38	3.55-38.22
K_{el} (hr^{-1})	0.08 ± 0.04	0.02-0.20
CL (L/hr)	2.26 ± 1.22	0.76-5.40
Vd (L)	30.19 ± 13.06	13.05-67.92

after drug administration. All subjects completed the study without any detectable adverse events.

Discussion

Pioglitazone is eliminated by extensive metabolism in the liver, and CYP2C8 and CYP3A4 are the most important CYP isoforms involved in the biotransformation of parent pioglitazone and secondary metabolism of M-IV and M-II[4]. The result of a previous study demonstrated that gemfibozil, a strong inhibitor of CYP2C9 and CYP2C8, elevates the plasma concentration of pioglitazone, whereas the itraconazole, a potent inhibitor of CYP3A4, has no effect on the pharmacokinetics of pioglitazone[9]. These findings suggest that pioglitazone is metabolized mainly by CYP2C8 in vivo. Another study has reported that genetic polymorphisms in CYP2C9 and CYP2C8 have effect on the pharmacokinetics of oral antidiabetic drugs[7]. Inter-ethnic differences on drug's pharmacokinetics need to further study. The present study aimed to characterize the pharmacokinetic parameters of single oral 30 mg pioglitazone in 24 Thai male subjects.

It is already well known that C_{max} and T_{max} show the evidence involving the rate of drug absorption and $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ are the prominent parameters indicating whole drug existing in the body or the extent of drug absorption into systemic circulation. The present results showed that after a single oral administration pioglitazone was rapidly absorbed, reaching peak plasma concentration within 2.00 ± 1.61 hrs with the C_{max} of 1.14 ± 0.29 μg/ml. The AUC_{0-inf} and AUC_{0-t} was 16.69 ± 7.75 and 11.47 ± 4.77 μg.hr/ml, respectively. The rate and extent of absorption, indicated presented by C_{max}, T_{max} and AUC of a single oral dose 30 mg pioglitazone, as reported by other studies is shown in Table 5[1,10]. From a Japanese report[11], pioglitazone was rapidly absorbed within one hour,

Table 5. Comparison of pharmacokinetic parameters of pioglitazone in Thai, Chinese and Japanese healthy subjects

	Chinese[11] (n = 10)	Japanese[12] (n = 14)	Thai (n = 24)
C_{max} (μg/ml)	1.36 (1.10-1.62)	1.46 ± 0.35	1.14 ± 0.29
T_{max} (hr)	-	1.9 ± 0.5	2.00 ± 1.61
$AUC_{0\rightarrow\infty}$ (μg.hr/ml)	11.1 (8.3-13.8)	13.9 ± 3.1	16.69 ± 7.75
$T_{1/2}$ (hr)	6.5	7.9 ± 1.7	11.19 ± 7.38

achieved peak concentrations at 2-3 hr, and unchanged pioglitazone was eliminated from serum between 24 hr and 36 hr. The C_{max} of unchanged pioglitazone was 1.46 ± 0.35 g/ml, and the $AUC_{0\text{-}96\ h}$ of unchanged pioglitazone was 13.9 ± 3.1 g.h/ml. Pioglitazone demonstrates dose dependent pharmacokinetics, and food did not significantly affect the pharmacokinetic profile of pioglitazone[1].

The comparative data of C_{max}, T_{max} and AUC (Table 5) demonstrated that time to reach peak plasma concentration after drug administration is comparable between a Thai study and Chinese or Japanese studies which have a slightly lower level of peak concentration. However, the extent of drug absorbed into systemic circulation as found from the present study seems to be higher. In a previous bioavailability study[4], pioglitazone was shown to have an absolute bioavailability of > 80%. It was highly bound to plasma proteins (approximately 97%), with a low tissue distribution as indicated by a small volume of distribution of 0.2-0.3 L/Kg. Pioglitazone was hepatically metabolized mainly by CYP2C8 and CYP3A4 to six metabolites (M-I~M-VI)[11] which were active and inactive. The main active metabolites were M-III and M-IV[5]. The majority are excreted as inactive metabolites in the feces[8]. The elimination half-life of the parent compound pioglitazone has been reported in the range of 6.5-9 hr with an estimated clearance of 1.7-4.2 L/hr. The present study found the elimination half life of pioglitazone in Thai subjects at 11.19 ± 7.38 hr with the mean elimination rate constant of 0.08 + 0.04 hr^{-1}. The average clearance and Vd calculated from the data were 2.26 ± 1.22 L/hr and 30.19 ± 13.06 L or 0.46 ± 0.19 L/kg, respectively. The results showed pioglitazone having a low volume of distribution as in other reports and had an average elimination half-life longer than Chinese and Japanese. The clearance calculated from the present study was within the range of clearance reported by a previous study[10,11].

The major active metabolites have considerably longer terminal half-life than the parent compound (approximately 26-28 hr)[4]. More data is needed about the pharmacokinetic parameters of the major active metabolites in Thai subjects.

Conclusion

Pharmacokinetic parameters of 30 mg single oral doses of pioglitazone were characterized in Thai subjects. Some of these parameters from the present study were different from those in previous reports. These data should be useful for clinical use in Thai diabetic patients who have to receive pioglitazone.

Acknowledgements

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เภสัชจลนศาสตร์ของพิโอกลิตาโซนในอาสาสมัครไทยสุขภาพดี

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***ที่มา**: พิโอกลิตาโซนเป็นสารประกอบประเภท thiazolidinedione ใช้ในการรักษาโรคเบาหวานชนิด 2 ถูกเมตาบอไลซ์โดย CYP2C8 และ CYP3A4 เนื่องจากการทำงานของ CYP2C8 มีความแปรปรวนทางพันธุกรรม จึงน่าจะมีผลทำให้เภสัชจลนศาสตร์ของยาตัวนี้แตกต่างกันในระหว่างชนชาติ*

***วัตถุประสงค์**: เพื่อศึกษาเภสัชจลนศาสตร์ของพิโอกลิตาโซนในอาสาสมัครคนไทย*

***วัสดุและวิธีการ**: ทำการศึกษาในอาสาสมัครชายไทยสุขภาพดีจำนวน 24 ราย ภายหลังจากการงดรับประทานอาหารหลังเที่ยงคืน ให้อาสาสมัครรับประทานยาเม็ดพิโอกลิตาโซนขนาด 30 มิลลิกรัม เจาะเลือดอาสาสมัครก่อนการรับประทานยาพิโอกลิตาโซนและภายหลังการรับประทานยาที่เวลา 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 24 และ 48 ชั่วโมง ตามลำดับ หาระดับยาพิโอกลิตาโซนในเลือดโดยวิธี High Performance Liquid Chromatography (HPLC) และใช้ UV detector เป็นเครื่องตรวจวัด ทำการคำนวณหาค่าเภสัชจลนศาสตร์ ได้แก่ ความเข้มข้นของยาสูงสุด (C_{max}) ระยะเวลาที่ความเข้มข้นสูงสุด (T_{max}) อัตราการขจัดยาออกจากร่างกาย (Kel) ค่าครึ่งชีวิต ($t_{1/2}$) พื้นที่ภาพใต้กราฟ ($AUC_{(0-t)}$, และ AUC_{0-inf}) อัตราการขจัดยา และปริมาตรการกระจายตัวของยา*

***ผลการศึกษา**: ภายหลังการรับประทานยาเม็ดพิโอกลิตาโซน ขนาด 30 มิลลิกรัม ยาจะถูกดูดซึมเข้าสู่กระแสเลือดโดยระดับยาในเลือดสูงสุด (t_{max}) ใช้เวลาเฉลี่ย 2.00 $\pm$ 1.61 ชั่วโมง (0.5-6) ค่าระดับความเข้มข้นของยาในเลือดสูงสุดเฉลี่ย (C_{max}) 1.14 $\pm$ 0.29 (0.47-1.63) ไมโครกรัมต่อมิลลิลิตร ปริมาณที่ยาถูกดูดซึมแสดงเป็นค่าพื้นที่ภาพใต้กราฟ (AUC) มีค่าเฉลี่ย 11.47 $\pm$ 4.77 และ 16.69 $\pm$ 7.75 ไมโครกรัม.ชั่วโมง/มิลลิลิตร เป็นค่า $AUC_{0\rightarrow t}$ และ $AUC_{0\rightarrow\infty}$ ตามลำดับ ค่าคงที่ของการขจัดยาออกจากร่างกายมีค่าเท่ากับ 0.08 $\pm$ 0.04 ต่อชั่วโมง ค่าครึ่งชีวิต ($t_{1/2}$) 11.19 $\pm$ 7.38 ชั่วโมง อัตราการขจัดยามีค่า 2.26 $\pm$ 1.22 ลิตรต่อชั่วโมง และค่าปริมาตรที่ยากระจายยาในร่างกาย มีค่า 30.19 $\pm$ 13.06 ลิตร*

***สรุป**: พารามิเตอร์ทางเภสัชจลนศาสตร์ของพิโอกลิตาโซน ขนาด 30 มิลลิกรัมในอาสาสมัครคนไทย มีอัตราการดูดซึมเร็ว มีค่าปริมาตรการกระจายตัวของยาต่ำ และค่าครึ่งชีวิตค่อนข้างสั้น*