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Research Article

# Bioavailability studies of Pioglitazone with Antacid – An *Invivo* Evaluation in Human Volunteers

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**ABSTRACT**:

The intestinal absorption of oral-anti diabetic drugs in the treatment of type-II diabetes mellitus is altered when they are concomitantly administered with antacids, and other antinuclear drugs, antibiotics and others. A randomized cross over study in two phases and a washout period of 4 weeks was carried out to evaluate the bioavailability of anti diabetic drug pioglitazone when used with Digene Gel (Magnesium Hydroxide, Simethicone, Aluminium Hydroxide), a drug for management of problems in gastrointestinal tract.The study has been approved by the institutional ethical committee of Raja muthiah medical college and Hospital, Annamalai University. In the present study 10 diabetic patients received Digene Gel (10 ml) for 5 days. After overnight fasting on 6$^{th}$ day a single dose of pioglitazone (30mg) was given. The blood samples following the intake were taken at different time intervals of 1, 2, 3, 4, 5, 7, 9 and 12 hours. The plasma samples (100µl) were injected into HPLC system after separation. The mobile phase comprised of Methanol: acetonitrile: mixed phosphate buffer (pH 2.6) at a ratio of (40:12:48). Analyses were run using C18 column (4.6 mm × 250 mm, 100 A) Luna. PHENOMINEX, USA was set at 30□ C at a flow rate of 1.2 ml.min$^{-1}$ with UV detector operating at a detection wave length of 269nm in HPLC and the pharmacokinetic parameters were calculated by using the software *Kinetica* (Version 4.4.1Innaphase, USA). The study reveals that the absorption of pioglitazone was delayed when it was concomitantly administered with Digene Gel.

**Keywords:** Bioavailability, Anti diabetic drugs, Pioglitazone, Digene Gel, Pharmacokinetics, Concomitant administration, Drug interaction.

## Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. Currently diabetic mellitus is a great threat to the world community with more than 100 million persons suffering from diabetes. The prevalence and incidence of diabetes is increasing in most populations, being more prominent in developing countries as follows, in USA more than 16 million, in republic of China more than 14 million, in Africa more than 20 million. India leads the world largest number diabetic subjects and is being termed the "diabetes capital of the world ". With 40.9 million people currently suffering from diabetes and expected to rise 69.9 million by 2025 [21]. Chronic elevation of blood glucose levels leads to many co-existing complications like diabetic retinopathy, diabetic neuropathy, peptic ulcer, diabetic foot ulcer. Drug therapy in Type II diabetes becomes more complex as many individuals are on multiple drug therapy and administer many drugs during the same period of time to treat secondary diabetic complications [3, 11, 13, and 16]. A closer monitoring and supervision of drug therapy is required so that drug related problems can be prevented or detected at an early stage. An increasing number of drug related problems are caused by drug inter actions. [3, 12-16]. Currently clinicians come across the problem of erratic absorption of oral anti diabetic drugs

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when administered with other drugs prescribed for co-existing diseases. Due to this, bioavailability of oral anti diabetic drugs is altered. Pioglitazone is a thiozolidinedione compound used in the treatment type II diabetes. It is an insulin sensitizer that acts as agonist of the preoxsome (PPAR - γ) [5, 8]. The main active metabolites are M – IV (a hydroxyl derivatives) and M – III (a ketone derivatives); the latter being formed from M –IV (Figure 1) [9]. Another metabolite M – II also has pharmacological activity, but it concentrations are low and it does not significantly contribute to the total amount of active species. The circulating concentrations of the metabolites M - IV and M - III are equal to or greater than those of the parent Pioglitazone and they have considerably longer half-life than Pioglitazone [2]. In vitro studies suggested that pioglitazone is metabolized by several cytochrome P450 (CYP) enzymes but mainly by CYP2C8 and CYP3A4 [5, 8]. The study will ensure that, if it shows no effect on pharmacokinetics of pioglitazone, it can be co-administered for the better management of problems occurs in gastrointestinal tract as co-existing diseases of type II diabetes.

**Materials and Methods**

**2.1. Materials**

The standard drug pioglitazone was received as gift sample from Paris Dakner Microspheres (P) Ltd, Chennai, India. The test drugs were Pioglitazone 30 mg tablets (PIOGLIT), Cipla, and Digene Gel 10 ml, Abbott India Limited. All other chemicals were used of analytical grade. Freshly double distilled deionised water, filtered through 0.2µm nylon filter (47 mm) in Millipore unit (USA), was used throughout the experiments. The drug analysis was carried out using HPLC system (Shimaddzu LC -10 AD) having gradient pump (LC 10 AD UP) Rheodyne injector port, and UV/Vis detector (SPD 10A VP). The data interpretation was done with Shimadzu system controller (SCL – 10 AVP).

**2.2 Subjects**

Ten diabetic patients (men age range from (21-30) weight range (57-79kg) participated in the study after obtaining a written informed consent and were ascertained to be healthy by medical history Clinical examination and routine laboratory tests. No one even on medication. Study protocol was approved by ethics committee for studies in healthy subjects and primary care of the Rajah Muthiah Medical College and hospital, Chidambaram.

***2.3. Study design***

A randomized cross over study with two phases and a washout period of 4weeks was carried out. Volunteers took 10ml of Digene Gel orally once daily at 20.00 h (8 am) for 5 days. After an overnight fast on day 6 a single dose of Pioglitazone (PIOGLIT 30mg) was administered orally with 150ml of water [2]. Volunteers received a standard meal 3h after dosing. Volunteers received light standard meals $7^{th}$ h and $11^{th}$ h after dosing.

**2.4. PHARMACOKINETICS OF PIOGLITAZONE**

Blood samples (5ml) were drawn after administered of Pioglitozone by orally at 1, 2, 3, 4, 5, 7, 9, 12 later through median capital vein, and collected in EDTA treated vacationers tubes. Blood samples were immediately centrifuged at 5000rpm for 10 min to obtain plasma and stored at -20°C until analysis. Pioglitazone concentration was determined by addition of 100µl acetonitrile with 100µl of plasma to deprotinise the proteins. The mixture was vortex mixed for 5 min after which it was centrifuged at 10000rpm for 10 min.100µl of supernatant liquid was injected into the HPLC system for analysis [5.9] .The UV detector was set at 269 nm for the present analysis. C18 column (4.6 mm × 250 mm, 100 A) Luna. PHENOMINEX, USA was set at 30□ C. The mobile phase comprised of Methanol: acetonitrile: mixed phosphate buffer (pH 2.6) at a ratio of (40:12:48) at a flow rate of 1.2 $ml.min^{-1}$[3].

***2.5. Pharmacokinetic analysis***

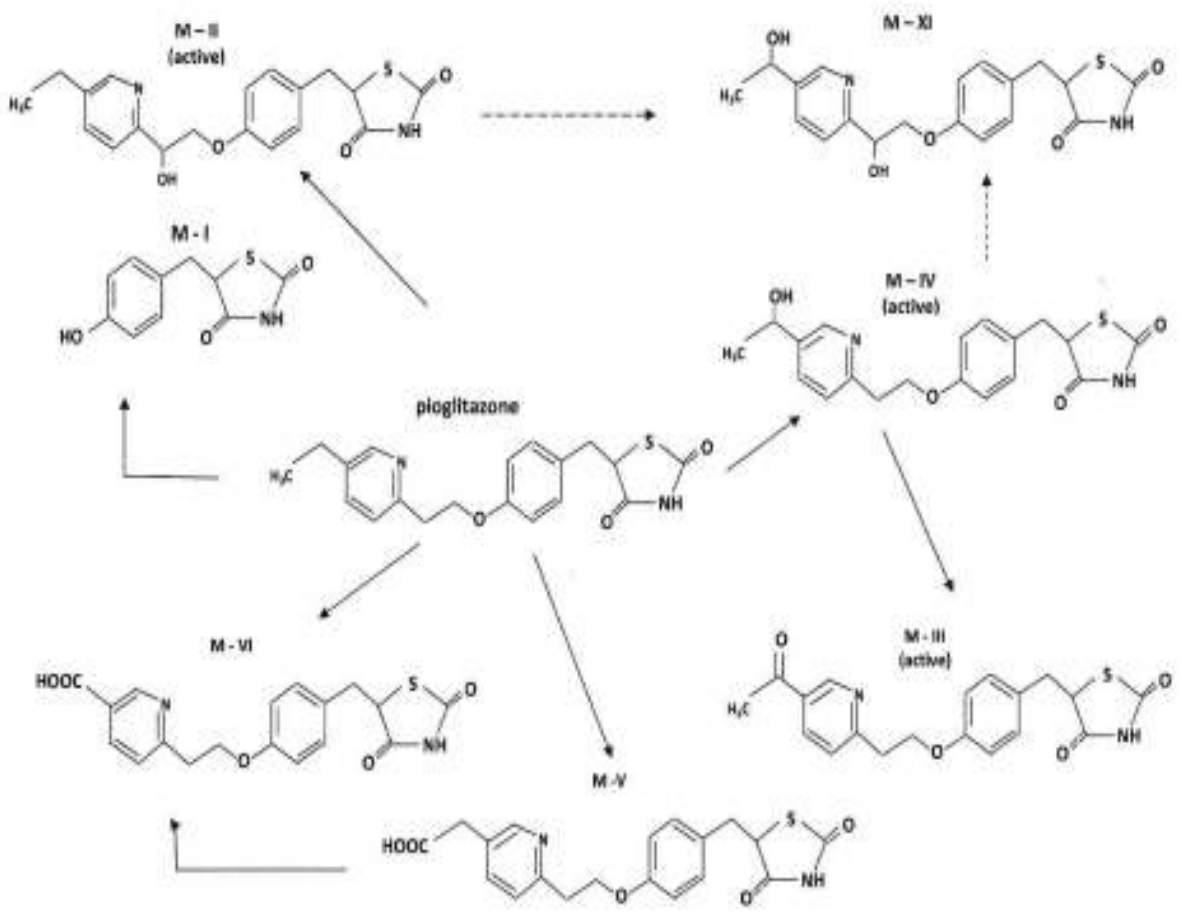
Peak plasma concentration ($C_{max}$), Time to $C_{max}$ ($t_{max}$), AUC from 0 to 12h ($AUC_{0-12}$), t½. All the pharmacokinetic and statistical data were calculated by using the software *Kinetic*, (Version 4.4.1, Innaphase, USA).

**Results and discussion**

Currently the management of type II diabetes becoming more complex since the recommended global approach of combination drug therapy has increased the risk of pharmacokinetics interactions in patients with diabetes [21]. The activity of one drug could alter the pharmacokinetics of another drug and it may be due to risk of the enzyme inverse reaction upon the plasma levels of concomitantly administered drugs [22]. Pioglitazone is rapidly absorbed in GIT, its oral bioavailability exceeds 80%, and it is extensively metabolized by hydroxylation and oxidation to form active and inactive metabolites in the liver [23]. *In vivo* studies suggest that the drug is metabolized by several cytochrome P450 (CYP) enzymes, but mainly by CYP2C8 and CYP3A4 [22]. The main active metabolites of Pioglitazone are M-IV (a hydroxyl derivative) and M-III (a ketone derivative). The M-III being formed from M-IV (Figure 1). The circulating concentrations of the metabolites M-IV and M-III are equal to or greater than those of the parent Pioglitazone and they have considerably longer half-lives than Pioglitazone [2] .The Digene Gel (Each 10 ml contains Magnesium hydroxide IP 185 mg, Simethicone IP 50 mg, Dried Aluminium hydroxide Gel IP 830 mg) .

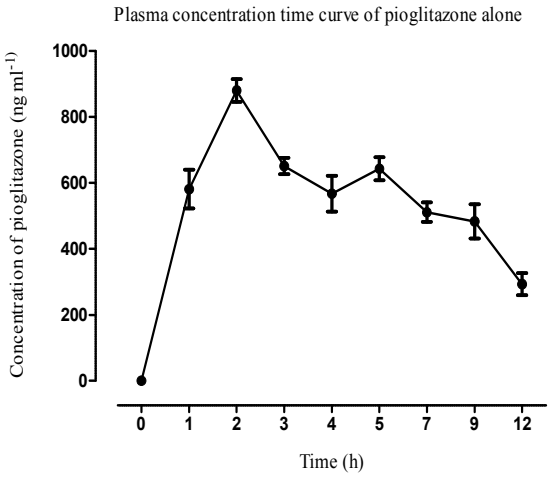
The effect of Digene Gel on the pharmacokinetics of Pioglitazone was assessed using a randomized, two cross over study with wash out period of 4 weeks. Volunteers took 1o ml of Digene Gel orally once daily at 20.00 hrs (8pm) for 5 days. After an overnight fasting on 6 day at 9.00 am single dose of 30mg Pioglitazone (PIOGLIT) was administered orally with 150ml of water. The blood samples were drawn before and after administration of Pioglitazone. The separated plasma was analyzed in HPLC system. The data obtained from the analysis shows that of Digene Gel delays the absorption of Pioglitazone due to that increases the $C_{max}$, AUC and t½ of Pioglitazone after 2hrs (Figure 2 & 3). The study has been carried out with five volunteers. Antacid delays the absorption of Pioglitazone and alters $t_{max.}$ There is no interaction in metabolism of Pioglitazone. Physiologic factors like pH of GIT, Gastric emptying time, intestinal transit time, and body posture, emotional status etc., to be discussed and conformed. Hence the absorption of Pioglitazone delayed by the concomitant administration of Digene Gel and may produce hyperglycemia in the systemic circulation. It may lead to the increasement of other complications like adverse reaction and toxicity of Pioglitazone.

**Figure 1**



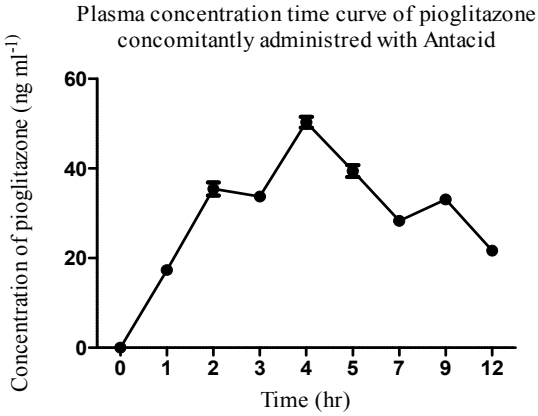

The metabolism of pioglitazone in humans [9]. The metabolite M-XI is a previously unrecognized metabolite. The image Courtesy: Tiina Jaakkola, *et al.,* Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

**Figure 2**




Plasma Concentration time curve of Pioglitazone after its oral administration (30mg) in human volunteers. The experiments were carried out by using by the plasma samples of diabetic patients. Each point represents the mean ± standard deviation (n=10)

**Figure 3**




Plasma Concentration – time curve of Pioglitazone after its oral administration (30mg) with Digene Gel (10ml) in pre-treated human volunteers. The experiments were carried out by using by the plasma samples of diabetic patients. Each point represents the mean ± standard deviation (n=10)

**Table. 1 Pharmacokinetic parameters of Pioglitazone inAntacid pretreated human volunteers**

| Pharmacokinetics parameter | Pioglitazone alone | Pioglitazone with Antacid |
|---|---|---|
| $AUC_{0-t}$ (ng *h/mL) | 382.0.13±18.483 | 609.754 ±7.803 |
| $C_{max}$ (ng/mL) | 49.19 ± 45.11 | 50.97 ± 38.23 |
| $T_{max}$ (h) | 2.00 ± 0.58 | 4.00 ± 0.16 |
| $K_{el}$ (ng/mL) | 0.078 ± 0.03 | 0.049 ± 0.03 |
| $t_{1/2}$ (h) | 4.59 ± 0.39 | 7.66 ± 0.51 |

Volunteers took 30mg Pioglitazone (PIOGLIT) orally once daily for 5 days. After an overnight fast on the day 6 a single dose of 10ml of Digene Gel was administered orally there after pharmacokinetics of Pioglitazone was carried out. $T_{max}$ - Time to Reach; $C_{max}$ - Peak Plasma Concentration; AUC - Area Under the Plasma Concentration Curve; $t_{1/2}$ - Half Life.

## CONCLUSION

The present study was carried out with an attempt to investigate any possible interaction occurs between Digene Gel and Pioglitazone in the treatment of Type II diabetes with the problems of gastrointestinal tract. The drug concentration was compared to standard chromatograms. Digene Gel was found to delay the absorption of pioglitazone upto 4 hrs. From 2 hr onwards as compared to standard phase (pioglitazone alone), decreases elimination rate (t½) of pioglitazone in plasma (Table 1) and also revealed that Cmax of pioglitazone was not affected much. It clarifies that there is no change in the intestinal microsomal activity but changes the hepatic microsomal activity by CYP3A4 mediated inhibition. This finding indicates that Digene Gel delays the absorption of pioglitazone during absorption phase. There is no inter individual variation in AUC of Pioglitazone from 0–12 hrs as compared to standard phase (pioglitazone alone). The increase in $t_{max}$ and $t_{1/2}$ of Pioglitazone was found to be higher when it is co-administered administered with Digene Gel and it may increase the blood glucose lowering efficacy of Pioglitazone. This may lead to accumulation of drug in the body, which may lead to toxicity. Therefore, it is advisable to monitor blood glucose level when starting the therapy with Digene Gel to adjust the required dosage of Pioglitazone.

In conclusion, the present study suggests that Digene Gel delays the concentration of pioglitazone causes substantial increase in plasma concentration of pioglitazone and it may lead the risk of toxicity in diabetic patients.

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