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Bioequivalence Study of Metformin HCl XR Caplet Formulations in Healthy Indonesian Volunteers

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Abstract

Aim: Determination of the bioequivalence of two metformin HCl (750 mg) caplet formulations (Glucophage XR® from Bristol-Myres Squibb Company, Indonesia as a reference formulation and Glumin XR® from Ferron Par Pharmaceutical, Indonesia as a test formulation). Material and method: The study was conducted according to an open label, randomized, Two-period crossover design with a 1 week washout period. Twelve volunteers participated and all completed the study successfully. Blood samples were obtained prior to dosing and at 1.0; 1.5; 2.0; 2.5; 3.0; 3.5; 4.0; 6.0; 8.0; 10.0; 14.0; 18.0; 24.0 and 30.0 hours after drug administration. Plasma will be separated by centrifuge and stored frozen at -20 degree Celcius. Plasma concentration of metformin HCl was monitored using high performance liquid chromatography (HPLC) with photo diode array (PDA) detection over a period of 30 hours after administration. The pharmacokinetics parameter AUC 0-30 h, AUC 0-∞ and Cmax were tested for bioequivalence after log transformation of data and ratios of Tmax were evaluated non parametrically. Result: The point estimates and 90% confidence interval for AUC 0-30 h, AUC 0-∞ and Cmax were 101.88 % (94.78-109.50%), 101.50% (93.77-109.87%) and 105.93 % (97.00-115.98%), respectively, satisfying the bioequivalence criteria of the European Committee for Proprietary Medicinal Products and The US Food and Administration Guidelines. Conclusion: These results indicate that two medications of metformin HCl are bioequivalent, thus, may be prescribed interchangeably.

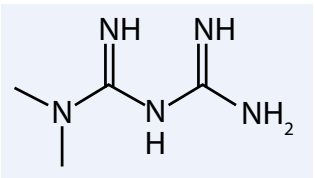
Keywords: Bioequivalence; Metformin HCl; plasma; HPLC; XR Caplet

Introduction

Metformin hydrochloride (N,N-Dimethyl-imido-di-carbonimidic diamide hydrochloride) is an oral antihyperglycaemic agent that improves glucose control in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose level [1]. Metformin HCl decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulphonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia [2,3].

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract with a bioavailability of 50 to 60 %. Peak plasma levels (C_{max}) of 1.6 ± 0.38μg/ml are reached (T_{max}) at 2.6 ± 0.8 h after oral administration of a single 500 mg dose. It is negligibly bound to plasma proteins and approximately 90 % of the absorbed drug is eliminated via the renal route within the first 24 hours, with plasma elimination half life of 3.6 – 6.2 h [2,3].

This study was intended to evaluate the bioequivalence of 750 mg metformin HCl XR tablet manufactured by Ferron Par Pharmaceutical, Indonesia, with the reference tablet manufactured by Bristol-Myres Squibb Company, Indonesia, in healthy Indonesian volunteers.



Chemical structure of Metformin HCl

Subject and Methods

Twelve healthy adult volunteers participated in this study. The ages of subjects were between 20 - 32 years old (23 ± 3.28 years), the body weights of subjects were between 50 - 72 kg (59.5 ± 7.79 kg) and the heights of the subjects were between 159-173 cm (168.33 ± 6.23 cm). Subjects were selected after screened by physical examination and clinical laboratory tests including renal function, liver function, routine blood (Hb, Ht, RBC, platelet, WBC, BUN, total bilirubin, glucose fasting, total protein, albumin, alkaline phosphatase, sGPT, sGOT), and urine analysis (specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC, cast). Subjects were excluded if they get pregnant (woman), nursing mother, smoker (if necessary, light smoker can be accepted), have a history of any illness of renal and liver, history of alcohol or other medicatons for long period of time [4]. This study was performed according to the Declarations of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practice. The protocol of this study was reviewed by the Committee of The Medical Research Ethics of The Faculty of Medicine University of Indonesia and was approved by National Agency of Drug and Food Control, Indonesia. All participants signed a written informed consent after they had been informed of the nature and details of the study in accordance with Indonesia Guidelines for Bioequivalence study [5].

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All subjects avoided using other drugs for at least two weeks prior to the study and until after its completion. They were also refrained from ingesting alcohol, caffeine, chocolate, tea or coke containing beverages at least 24 hours before each dosing and until collection of the last blood sample. Each volunteer received an oral dose of 750 mg metformin HCl XR in standard 2-way crossover, randomized study [6,7]. The dose was taken with 250 ml of 20 % glucose solution in water. There was a 1 – week washout period between the doses. Subjects were asked to fast from 10 hours before until 4 hours after drug administration. The dietary regimen similar for all subjects in both trial period consist of three standard meals served at 4 hours (breakfast), then 8 hours (lunch), and 12 hours (dinner) after dosing. Carbohydrate was the main composition of the meals. Before bed time, to maintain glucose blood level we should gave 200 mL glucose solution to the subjects.

About 7 ml of blood samples were drawn into dry heparinized vacuum tube via forearm vein, at the following times : 0 (just before drug administration), 1.0, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 14.0, 18.0, 24.0, and 30.0 hours then after drug intake. Following centrifugation, plasma was separated and frozen at -20°C until being assayed.

HPLC assay of metformin HCl in plasma

The concentrations of metformin HCl in plasma were analyzed using HPLC method with photo diode array detector [8] in the Bioavailability and Bioequivalence Laboratory, Pharmacy Department,Faculty of Mathematic and Natural Sciences, University of Indonesia. (Depok, Indonesia) following the GLP rules. The mobile phase was acetonitrile - phosphate buffer with 10 mM sodium dodecyl sulphate (40 : 60) pH 7 pumped isocratically at 1.0 mL/min through a Kromasil® RP-18, 5µm, 250 x 4.6 mm i.d. column (Akzo Nobel). The wavelength was set at 234 nm. Briefly, 600µL of human plasma mixed in a 1.5 mL eppendorf vial with 30µL internal standard (diazepam, 1000µg/mL in destilled water) and 600µL of 10 % trichloroacetic acid. The sample shaked with vortex for 120 seconds and centrifuged at 10000 rpm for 5 minutes. After that

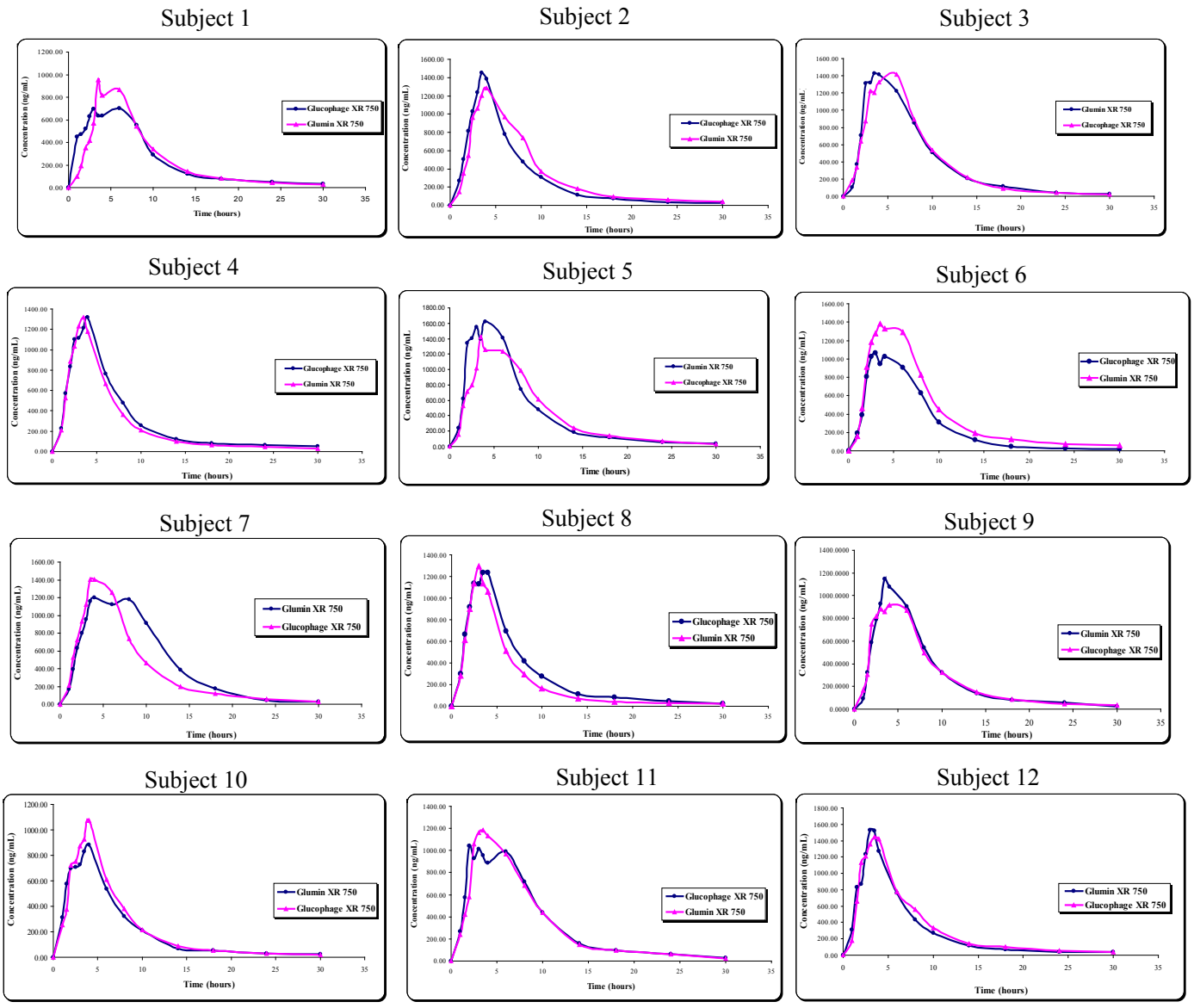

Figure 1: Plasma concentration-time of Metformin in each subject after administration of each product.

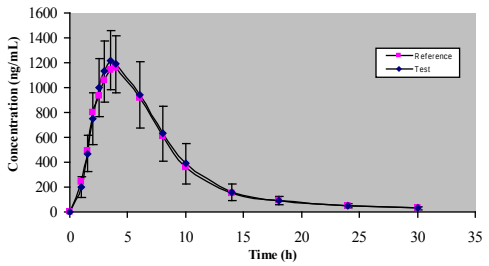

Figure 2: Plasma concentration-time versus of metformin HCl after oral administration of two different formulations containing 750 mg of metfromin HCl. Data are shown as`mean ± SD for 12 subjects.

Parameter	Test Formulation	Reference Formulation
$AUC_{0\text{-}30\ h}$ (ng x h/mL) Geometric mean Range	9425.41 6230.64 – 13717.76	9248.57 6859.31 – 12387.35
$AUC_{0\text{-}\infty}$ (ng x h/mL) Geometric mean Range	9810.29 6568.96 – 13887.61	9664.95 7114.34 – 12623.70
C_{max} (ng/mL) Geometric mean Range	1251.27 884.95 – 1623.95	1181.23 702.42 – 1448.87
T_{max} (h) mean ± SD	3.58 0.36	3.96 1.12
$t_{1/2}$ (h) Geometric mean Range	7.67 3.86 – 11.47	7.96 5.40 – 19.97

Table 1: Mean pharmacokinetic characteristics for metformin HCl after administration of the two formulations to 12 subjects.

Parameter	$AUC_{0\text{-}30\ h}$	$AUC_{0\text{-}\infty}$	C_{max}
T/R point estimate 90% CI	101.88	101.50	105.93
Lower Limit	94.78	93.77	97.00
Upper Limit	109.54	109.87	115.98

Table 2: Statistical evaluation of comparison of 12 subjects $AUC_{0\text{-}30\ h}$, $AUC_{0\text{-}\infty}$, and C_{max} of two formulations.

1000µL supernatant was separated in a clean vial before adding 60µL of 4 N NaOH [9]. The mixture was vortexed for 5 seconds and 100µL aliquot of sample was injected on to the equilibrated HPLC System. The analytical method was conveniently validated [10]. The assay was linear over the concentration range of 20 – 2500 ng/mL.

Pharmacokinetic and statistical analysis

Plasma concentration time data for each subject and each drug will be analyzed by non compartmental method. The Area under the plasma level curve from 0 to infinity ($AUC_{0\text{-}\infty}$) will be calculated as follows:

$$AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}$$

AUC_{0-t} will be calculated by trapezoidal rule, where t is the time of last measurable point. $AUC_{t-\infty}$ will be calculated by dividing C (concentration) by the slope which will be estimated from the elimination phase by regression analysis. Time to peak (t_{max}) and peak plasma concentration (C_{max}) will be taken from the experimental data. The elimination half life ($t_{1/2}$) will be also calculated for additional evaluation.

The obtained values of $AUC_{0-\infty}$ $AUC_{t-\infty}$ and C_{max} for both products, were analyzed statistically by means of the variance analysis (ANOVA), to determine if significant differences in the values of the studied variables appear, had to each one of the variation sources: products, subjects, periods and sequences of administration.

The 90% confidence interval of ratio (Test/Reference) will be calculated for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} parameters. The individual value of each parameter will be transformed prior to analysis using a logarithmic transformation. The test drug preparation will be considered bioequivalent to the reference/standard preparation if the 90% confidence interval of the ratio of each bioavailability parameter fall inside the interval of 70% – 143% for C_{max} parameter and 80 – 125% for AUC parameters. T_{max} and $t_{1/2}$ will be analyzed (as additional evaluation) by nonparametric method (Wilcoxon sign rank test) without logarithmic transformation. All statistical analyses were performed using EquivTest PK 2.0 statistical programme.

Result and Discussion

All 12 volunteers successfully completed the trial according to the protocol. Both metformin HCl formulations were well-tolerated at the administered dose and no serious adverse clinical events were observed. In this study, plots of individual plasma profiles for both formulations are depicted in (Figure 1) and the mean metformin concentration versus time profiles for both formulations are shown in (Figure 2).

The objective of this crossover study was to test the bioequivalence of a Metformin HCl 750-mg XR caplet formulation, produced by PT Ferron Par Pharmaceuticals, compared to reference caplet formulation (Glucophage caplet). As the drug product is extended release product, the drug was administered in single dose. The pharmacokinetic parameters used to asses the bioequivalence of the test formulation versus the reference were $AUC_{0\text{-}30h}$, $AUC_{0\text{-}\infty}$ for the extent of the absorption and C_{max} and t_{max} for the rate absorption. Descriptive statistic of the pharmacokinetic parameter for metformin HCl test and reference preparations are summarized in Table 1 which shows the geometric mean values and the range for the $AUC_{0\text{-}30\ h}$, $AUC_{0\text{-}\infty}$, C_{max} and $t_{½}$ values obtained for each formulations. The pharmacokinetics characteristic t_{max} is presented as mean (± SD).

The result of the bioequivalence analysis are given in Table 2. The parametric 90% confidence intervals for ratio T/R ranged from 94.78 -109.54 (point estimate 101.88) for $AUC_{0\text{-}30h}$, 93.77 - 109.87 (point estimate 101.50) for $AUC_{0\text{-}\infty}$, 97.00-115.98 (point estimate 105.93) for C_{max}, respectively, and were entirely included withion the bioequivalence acceptance limits 80- 125 % [CPMP 2001].

In conclusion, of the two metformin formulations are equivalent with respect to the rate and extent of absorption and it can be assumed to be therapeutically equivalent and exchangeable in clinical practice.

Acknowledgement

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