BIOEQUIVALENCE STUDY OF GENERIC FINASTERIDE
IN HEALTHY MALE VOLUNTEERS

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Abstract The bioequivalence of 5-mg of the generic finasteride tablet, as a test, and the original finasteride tablet, as a reference products, were evaluated. The two products were administered to 12 healthy Thai male volunteers as a single oral dose according to a randomized two-way crossover design. The washout period was 1 week. After drug administration, serial blood samples were collected over a period of 30 hours. Plasma finasteride concentrations were measured by HPLC coupled with UV detection. The pharmacokinetic parameters were analyzed by noncompartmental analysis. The maximum finasteride concentrations (Cmax, ng/mL) and the median time to reach the Cmax (Tmax, hr) for the test and reference were 34.05 (range 26.5-47.49) and 34.39 (23.79-45.96), and 2.25 (0.5-4.0) and 2.50 (1.0-2.5), respectively. Analysis of variance for bioequivalence revealed the mean (90% CI) of the AUC 0-∞ and Cmax ratios [for Test /Reference] of 0.98 (0.81-1.17) and 0.99 (0.89-1.10), respectively. These values were within the bioequivalence range of 0.80-1.25, thus, our study demonstrated the bioequivalence of the two products. Chiang Mai Med Bull 2003;42(4):131-137.

Keywords: finasteride, bioequivalence

Finasteride (Proscar®) is a synthetic 4-azasteroid prescribed for the treatment of benign prostatic hypertrophy (BPH). The mechanism of action involves inhibition of 5 alpha-reductase, which metabolizes testosterone to the more potent androgen, dihydrotestosterone (DHT). Deprivation of DHT in the prostate results in a marked regression of the prostate volume and decrease symptoms associated with urinary tract obstruction. Since circulating levels of testosterone are not affected, the desired androgen mediated effects on muscle strength, bone density and sexual function are thus preserved. Treatment with finasteride for four years among men with symptoms of urinary obstruction...
and prostatic enlargement can maintain the control of BPH, while decreasing disease progression and significantly reducing the probability of surgery and acute urinary retention.\(^{(7)}\) Finasteride may also be used to prevent hair loss in younger man.\(^{(8)}\)

Finasteride is well absorbed and widely distributed after oral administration. It undergoes extensive hepatic metabolism to inactive metabolites, which are eliminated through the bile and urine.\(^{(4)}\) Its mean bioavailability is 63\%, (range from 33 to 108\%).\(^{(9)}\) Maximum plasma concentration averages 37 ng/mL (range 27 to 49 ng/mL) and is reached at 1 to 2 hours postdose.\(^{(9)}\)

The aim of this study was to determine the pharmacokinetics of finasteride in 12 healthy volunteers after single oral doses of 5 mg Proscar® and the generic finasteride in order to obtain the bioequivalence approval.

Subject, materials and methods

**Drugs used:** Proscar® at 5 mg (Merck Sharp & Dohme, Australia) Lot No. A 6454 was used as a reference product and Harifin® at 5 mg (the T.O. Chemical 1979 Ltd., Bangkok, Thailand) Lot No. HAR5-01 was used as a test product.

**Subjects**

Twelve healthy Thai male volunteers aged between 32-47 years old, with a body mass index between 18-24 participated in this study. The subjects were free from medical illness judging from a physical examination and routine blood test. Cigarette smokers, alcohol consumers as well as subjects currently taking any drug known to induce or inhibit hepatic metabolizing enzyme were excluded from the study. All subjects signed a written informed consent before participating in the study.

**Method of drug administration**

This was a randomized, double-blind, 2-period crossover study. Each subject was randomly assigned to receive a single 5 mg dose of finasteride orally in the morning after an overnight fast. Subjects continued fasting for at least 2 hours after drug administration. Water and lunch were served at 2 hours and 4 hours after dosing. Blood samples were collected immediately before dose administration and thereafter at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 15, 24 and 30 hr. The washout period was 1 week and the subjects were crossed - over to receive the other preparation in the same manner.

**Determination of the plasma finasteride concentrations**\(^{(10-11)}\)

Finasteride in plasma was quantified by high performance liquid chromatography (HPLC) with UV detection (220 nm) after C8 solid phase extraction (Sep-Pak® 1 mL, 100 mg, Waters Corporation, MA, USA) and separation on C18 (Inersil®, 150 x 4.6 mm, 5 µm, GL Sciences Inc., Tokyo Japan) at 25 °C. The mobile phase was a mixture of 15 mM Phosphate buffer (pH 3.5)/Acetonitrile/Tetrahydrofuran (50/39/1, v/v/v). The retention times for finasteride and internal standard were approximately 10.27 and 13.26 minutes, respectively. Solutions of finasteride that ranged from 2-50 ng/mL were prepared in plasma to
establish the calibration curve for the 
validation assay. Linear regression ana-
lysis of the peak-height ratios of finas-
teride/internal standard (IS) versus finas-
teride concentrations consistency gave 
determinant ($R^2$) coefficients of 0.999 or 
better. Finasteride concentration were 
quantified from the calibration standard 
lines with the use of linear regression. 
The method was validated using 4 sets of 
5 control samples (12 samples) from 
each of 3 different concentrations (7.5, 
15, 30 ng/mL) of quality control (QC) 
samples, and a single calibration curve 
rann concurrently for within-day accuracy 
and precision. For inter-day assay precision, 
5 sets of three concentrations of QC 
samples were studied on 4 independent 
days with 4 concurrent standard calibration 
curves. The average %CV for within-
day and inter-day assays was 6.8% and 
10.02%, respectively. The lower limit of 
quantitative analysis (LLQ) was 2 ng/mL 
(%CV = 14.7) and the mean recovery of 
finasteride determined from 5 aliquots of 
each QC sample was 85.3%.

**Pharmacokinetic analysis**

Maximal plasma concentration ($C_{\text{max}}, \text{ng/mL}$) and time to reach the peak concen-
tration ($T_{\text{max}}, \text{hr}$) were obtained directly 
by visual inspection of each subject's 
plasma concentration-time profile. The area under the plasma concentration-time 
curve (AUC) from time 0-infinity ($AUC_{0-\infty}, \text{ng*hr/mL}$) to half-life ($t_{1/2}, \text{hr}$) was 
determined by non-compartmental 
analysis. The slope of the terminal log-
linear portion of the concentration-time 
profile was determined by least-squares 
regression analysis and used as the elimi-
nation rate constant ($K_e$). The elimina-
tion half-life was calculated as $0.693/K_e$. 
The $AUC_{0-t}$ from time zero to the last 
quantifiable point (Ct) was calculated 
using the trapezoidal rule, and extrapo-
lated AUC from Ct to infinity ($AUC_{t-\infty}$) 
was determined as $Ct/K_e$. Total $AUC_{0-\infty}$ 
was the sum of $AUC_{0-t}$ + $AUC_{t-\infty}$. The 
calculation was performed by using the 
TopFit, pharmacokinetic data analysis 
program for PC.

**Statistical analysis**

An analysis of variance (ANOVA) 
was performed to determine the statisti-
cal differences of pharmacokinetic para-
eters ($AUC_{0-\infty}, C_{\text{max}}, \text{and } T_{\text{max}}$), which 
represented the extent and rate of drug 
absorption. Statistical analysis of $AUC$ 
and $C_{\text{max}}$ was performed on logarithmi-
cally (ln) transformed data. The 90% 
confidence intervals for the ratio of $AUC$ 
as well as $C_{\text{max}}$ values of the test prepara-
tion over those of the reference product 
were estimated using the following 
equation:

\[
90\% \text{ CI ( } \mu_T - \mu_R \text{ ) = ( } \bar{X}_T - \bar{X}_R \text{ ) } \pm t_{0.1} \sqrt{\frac{2S^2}{n}}
\]

- $\bar{X}_T$ and $\bar{X}_R$ are the observed mean 
of the (ln) transformed parameters (either 
$C_{\text{max}}$ or $AUC$) for the test (T) and 
reference products (R).
- $S^2$ is obtained from the analysis 
of variance.
- $n$ is the number of subjects.
- $t_{0.1}$ is the tabulated two-tail $t$ value 
for 90 % CI. $v$ is the number of degrees 
of freedom of the error mean square.
The antilogarithm of the confidence interval ($\mu_T - \mu_R$) expressed the bioequivalence as a ratio of the test and reference product [$\mu_T/\mu_R$].

The bioequivalence intervals of 0.8-1.25 for the ratio $\frac{\mu_T}{\mu_R}$ of the average $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ were accepted by the Thai FDA. Regarding analysis of $T_{\text{max}}$, the limits for the bioequivalence range were expressed as untransformed data (absolute differences) and the accepted stipulated bioequivalence range of $T_{\text{max}}$ difference $[\text{Test}-\text{Reference}]$ was ±20% of the $T_{\text{max}}$ of the reference formulation.

**Result and discussion**

All subjects completed the study without any adverse effects. Fig. 1 shows that the mean plasma concentration-time curves of the reference and test were comparable, although the peak finasteride concentration of the reference was slightly higher than that of the test.

Table 1 compared the mean values of pharmacokinetic parameters ($C_{\text{max}}$, $T_{\text{max}}$, $\text{AUC}_{0-\infty}$ and $t_{1/2}$) of Proscar® and the test product. Following a single oral dose, the median time to reach the maximum concentration ($T_{\text{max}}$) for the test (2.25 hr, range 0.5-4.0 hr) was faster than that for the reference (2.5 hr, range 1.0-2.5 hr). The 90% CI for the $T_{\text{max}}$ difference ($\mu_T - \mu_R$) ranged from -0.58 to 0.5 hour, which was outside the stipulated bioequivalence range of ±0.42 hour, hence, equivalence with respect to the $T_{\text{max}}$ could not be concluded. In spite of this, the average (±SD) $C_{\text{max}}$ and $\text{AUC}_{0-\infty}$ for the test were not significantly different from those for the reference (34.05±6.43 vs 34.39±6.46 ng/mL, and 299.09±79.11 vs 299.94±

![Figure 1](image-url)  
**Figure 1.** Mean plasma concentration-time profiles after single oral administration of 5 mg finasteride [Reference (- -), Test (- - -)].
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The C<sub>max</sub> of finasteride obtained from this study was comparable to those values reported in the literature [average C<sub>max</sub> 37 (range 27-49 ng/mL)]. Furthermore, the mean elimination half-lives (t<sub>1/2</sub>, hr) of the test [8.01±3.42 (range 2.71–16.6)] and reference [7.12±1.64 (range 4.02–9.79)] were similar to the values reported in the literature(3-16 hr), with no statistical difference between the two preparations. The relative bioavailability (F<sub>rel</sub>) calculated from C<sub>max</sub> and AUC<sub>0-∞</sub> of the Test/Reference was 101.58 % and 103.31 %, respectively. Bioequivalence analysis (Table 2) showed that the mean (90% CI) of the C<sub>max</sub> and AUC<sub>0-∞</sub> ratios for the Test/Reference were 0.99 (0.89-1.10) and 0.98 (0.81-1.17), respectively. As these were well within the bioequivalence range of 0.8-1.25, our study demonstrated the bioequivalence of the test and reference.

**Conclusion**

We conducted a bioequivalence study in 12 healthy Thai male volunteers with 5 mg of oral formulations of the generic finasteride. The results showed that both formulations were well tolerated. The pharmacokinetic parameters (C<sub>max</sub> and T<sub>1/2</sub>) of finasteride obtained from the study were comparable to those values reported in the literature. We also demonstrated the bioequivalence of the two formulations.
products concerning the rate ($C_{\text{max}}$) and extent ($\text{AUC}_{0-\infty}$) of absorption based on the 90% CI, which was well within the acceptable range of standard Thai FDA guidelines.

**References**

การทดสอบชีวสมมูลของยาฟินาเทอไรด์เปรียบเทียบกับยาต้นแบบ
ในอาสาสมัครสุขภาพดี

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บทคัดย่อ การศึกษานี้มีวัตถุประสงค์เพื่อทดสอบชีวสมมูลของยาเม็ดฟินาทีรอยด์ขนาด 5 มิลลิกรัม โดยให้ยาทดสอบฟินาเทอไรด์ที่ผลิตในประเทศไทย และยาต้นแบบซึ่งศึกษาแบบสุ่มไขว้ ครั้งเดียว ระยะเวลาการศึกษา 12 ราย หลังจากให้ยาตัวอย่างเลือดภายใน 30 ชั่วโมง ได้ผลการวิเคราะห์ความเข้มข้นของยาฟินาเทอไรด์ โดยวิธีโครมาโตกราฟฟิวซิตี้ของเหลวสมรรถนะสูง และประเมินการดื่มยาฟินาเทอไรด์โดยวิเคราะห์แบบ non compartment ผลการศึกษาพบว่าระดับยาสูงสุดในเลือดมีค่าเฉลี่ย 34.05 (26.5-47.49) และ 34.39 (23.79-45.96) นาโนกรัม/มิลลิลิตร ในกลุ่มยาต้นแบบ 2.25 (0.5-4.0) และ 2.50 (1.0-2.5) ชั่วโมง ตามลำดับ การวิเคราะห์ชีวสมมูลโดยใช้อะโนวาบวกค่าความเชื่อมั่นร้อยละ 90 ของการดื่มยาฟินาเทอไรด์พบว่าช่วงความเข้มข้นของยาที่ 0.80-1.25 ดันนิยมการใช้ยาฟินาเทอไรด์ในอาสาสมัครสุขภาพดี

คำสำคัญ: ฟินาเทอไรด์ ชีวสมมูล