Bioequivalence Study of Generic Atenolol Tablets in Healthy Thai Volunteers

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Abstract

Two preparations of 50 mg and 100 mg atenolol tablets were evaluated for their bioequivalence in twelve healthy Thai subjects (Prenolol®, Berlin Pharmaceutical Industry, as the test formulations *vs* Tenormin®, Zeneca Limited, as the reference formulations). A single oral dose of each preparation was administered in a randomized two-way crossover design, starting from either 50 mg of Prenolol® *vs* Tenormin®, thereafter, either 100 mg of Prenolol® *vs* Tenormin®. The washout period between each treatment was one week. Atenolol plasma concentrations were determined by the HPLC technique with fluorometric detection. Pharmacokinetic parametres were analyzed by the noncompartmental pharmacokinetic method using TOPFIT. The means and parametric 90 per cent confidence intervals of the ratio [Prenolol®/Tenormin®] of $AUC_{0-\infty}$ and C_{max} were 1.16 (1.05-1.27) and 1.23 (1.07-1.38) for 50 mg preparations and 1.10 (1.00-1.20) and 1.13 (0.95-1.31) for 100 mg preparations, respectively. These values were well within the acceptable bioequivalence ranges. The mean differences of T_{max} [Prenolol®-Tenormin®] were less than 20 per cent for both 50 mg and 100 mg preparations. Hence, Prenolol® and Tenormin® were bioequivalent with respect to the rate and extent of absorption.

Key word : Bioequivalence, Atenolol

Atenolol, a ß-blocker widely used for the treatment of hypertension and ischemic heart disease (1-3), is a synthetic, cardioselective $ß_1$-adrenergic receptor antagonist without intrinsic sympathomimetic activity (ISA). Because of its cardioselectivity, it has been shown to produce greater effects (reduction of blood pressure, cardiac output and heart rate) and less adverse effects (bronchoconstriction, peripheral vasoconstriction and glycemic control) than the noncardioselective ß-blockers(3-5). Moreover, its low lipid solubility and limited brain penetration result in a lower incidence of central

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nervous system adverse effects than that associated with propranolol[4,6]. Following oral administration, the drug is incompletely absorbed, however, most of the absorbed dose reaches the systemic circulation with minimal liver metabolism[7]. Atenolol's bioavailability is 40-60 per cent. Its volume of distribution is approximately 1 liter/kg and only small amount of the drug (6-16%) is bound to plasma protein. It is eliminated primarily by renal excretion with a terminal half-life of 5-7 hours and a clearanceof about 2 ml/kg/min[8-10]. Atenolol has been proved to be effective and well tolerated. The initial antihypertensive dose is usually 50 mg, given once daily. The dose may be increased up to 100 mg, however, a dose beyond 100 mg per day is not recommended since it is not associated with increasing antihypertensive effect[2,3]. Contraindication included sinus bradycardia, heart block greater than first degree, cardiogenic shock and compromised cardiac failure[8].

Prenolol®, an oral preparation of a generic atenolol manufactured from Berlin Pharmaceutical Industry, Bangkok, Thailand, is much less expensive than the innovator Tenormin® [Zeneca, Limited]. Generic equivalence based on *in vitro* dissolutiontest of Prenolol® and Tenormin® were demonstrated (Company product profiles). Nevertheless, generic substitution of the drugs should be based on *in vivo* proof of bioequivalence to assure the safety and efficacy[11-13]. Therefore, the purpose of this study was to determine the bioequivalence of Prenolol® in comparison to Tenormin®. The result would be useful for the medical practitioner who considers using a generic substitution of oral preparations of atenolol, particularly when the cost-effectiveness is concerned.

MATERIAL AND METHOD

Subjects

Twelve healthy nonsmoking volunteers consented to participate in this study. There were 7 men and 5 women who ranged in age from 21-47 years (mean ± SD = 31.08 ± 10.91). Weight and height ranged from 48-75 kg (mean ± SD = 60.08 ± 9.00) and 150-170 cm (mean ± SD = 161.13 ± 7.22), respectively. All were in good health on the basis of medical history, physical examination, electrocardiography, urinalysis, and laboratory investigations. The laboratory tests included complete blood count with differentials, blood urea nitrogen, creatinine, fasting blood sugar, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol and bilirubin, None had a history of bronchial asthma, diabetes mellitus, peripheral vascular disease or cardiovascular disease. Female subjects were not pregnant, confirmed by urine pregnancy test. Subjects with a known contraindications or hypersensitivity to beta-blocker were excluded as well as those with a known history of alcoholism or drug abuse. Subjects with gastrointestinal and/or kidney diseases were also excluded. Subjects refrained from food and beverages containing caffeine for at least 24 hours before drug administration. Other medications were not allowed for 2 weeks before and during the study. The protocol of the study was reviewed and approved by the Ethical Committee of the Chiang Mai University, Chiang Mai, Thailand.

Study drug

The four formulations tested were

- Test drugs : Prenolol® [Berlin Pharmaceutical Industry, Bangkok, Thailand] 50 mg (Lot No. 960232) and 100 mg tablets (Lot No. 960244)
- Reference drugs: Tenormin® [Zeneca Limited, Macclesfield Cheshire, United Kingdom] 50 mg (Lot No. LO 949) and 100 mg tablets (Lot No. PO 9808)

Study design

Each formulation was administered as a single oral dose, starting from either 50 mg of Prenolol® or Tenormin® thereafter, either 100 mg of Prenolol® or Tenormin® according to a randomized two-period crossover design. The sequence of the assigned treatments was obtained from a computer generated list of randomization. Since the elimination half-life of oral atenolol is approximately 5 to 7 hours (2, 3, 8) the wash out period between each treatment was at least 1 week to ensure the total clearance of the previous administered drug. The doses were administered at the same time on each study day and the wash out interval was identical for all subjects.

On the study day, subjects were admitted to the Clinical Pharmacology Unit of the Faculty of Medicine, Chiang Mai University at 7 a.m. after an overnight fast. Base line supine blood pressure (systolic, diastolic and mean arterial pressure) and heart rate were measured by automate sphygmomanometer. A peripheral intravenous catheter for blood sample collection was inserted into a forearm vein

and the zero-hour blood sample was drawn. Subjects were randomly assigned to take one tablet of atenolol with 200 ml of water (either one tablet of 50 mg Prenolol® or Tenormin®, followed by either one tablet of 100 mg Prenolol® or Tenormin®). Ten ml of blood samples were collected into heparinized tubes just before the 50 mg dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15 and 24 hours after dosing. Similarly, for the 100 mg preparations, the blood samples were drawn at the same interval but the 15-hour sample was omitted and the 30-hour sample was added. The blood samples were immediately centrifuged and the plasma was stored at -20°C until analysis. Supine blood pressure and heart rate were recorded at each blood sampling time. Exercise was not allowed during the study period. All subjects remained fasted for 4 hours post dose. Water and juice were allowed 2 hours after dosing. Lunch was served after the 4-hour blood drawn was completed. Meals and fluid intake were identical for all study periods.

Drug Assay

Plasma concentrations of atenolol were determined by high-performance liquid chromatographic (HPLC) method using model LC-10A pump HPLC (Shimadzu, Japan) with RF-10 AXL spectrofluorometric detector and CTO-10A/10AC column oven. The methods being developed were modified from the HPLC technique using solid phase extraction procedure[10]. In brief, 400 μL of plasma samples were vortexed and pipetted onto a 1.0 ml disposable solid phase extraction columns packed with 100 mg cyanopropylsilane-bonded silica gel (Cyano Accubond extraction cartridges, J&W Scientific, Folsom, CA). The extraction columns were preconditioned with methanol (2 x 1 ml), and 20 per cent methanol (2 x 1 ml). After the plasma samples had passed through, the cartridges were washed sequentially with distilled water (2 x 1 ml), 20 mM $NH_4H_2PO_4$ (2 x 1 ml), acetonitrile (2 x 1 ml), and methanol (2 x 1 ml) (carried out on a J&W Vacuum Manifold). Thereafter, atenolol was eluted with 1 per cent triethylamine in methanol (1000 μL) into 2 ml Eppendorf centrifuge tubes and the solvent was evaporated on a Savant Speed Vac Concentrator (Savant Instrument Inc., U.S.A.). The residue was reconstituted with 400 μL mobile phase, thereafter, an appropriate aliquot of 20 μL was injected into the HPLC system. Chromatographic analysis was carried out at 40°C, using a 150 x 4.6 nm Inersil C_8 column (GL Sciences Inc., Tokyo, Japan), a mobile phase of $NH_4H_2PO_4$ (7.5 mM, adjusted to pH 4.85) and acetonitrile in the ratio of 9.3 : 0.7 (flow rate 1 ml/min), and detected by fluorescence detector with excitation and emission wavelength of 230 nm and 310 nm, respectively.

Calibration standards in distilled water containing 15-1500 ng/ml of atenolol were used to establish calibration curves for assay validation and for clinical assay (least squares quadratic regression analysis). From a regression equation obtained from a standard calibration curve, the area under the peaks were used to calculate atenolol concentrations in plasma. Assay recovery was determined by comparing the peak area of atenolol samples in distilled water with the peak area of atenolol in plasma. Mean atenolol recovery from plasma was 85 per cent and the lower limit of quantitation was 10 ng/ml. The per cent correlation coefficient (%CV) of inter and intraassay validation was less than 4 per cent.

Statistical methods and data analysis

Maximal plasma concentration (C_{max}) and time to attain the peak (T_{max}) were obtained directly by visual inspection of each subject's plasma concentrations-*versus* time profile. The pharmacokinetic parameters including area under the plasma concentration-time curve (AUC), area under the moment curve (AUMC), mean resident time (MRT), and plasma elimination half-life ($t_{1/2}$) were analysed by model-independent pharmacokinetic method with the use of TOPFIT, a pharmacokinetic and pharmacodynamic data analysis program for PC.

Bioequivalence testing comprised equivalence assessment with respect to the rate (C_{max}, T_{max}) and extent (AUC) of absorption[11-13]. The C_{max} and AUC were analyzed statistically by parametric [logarithmically (ln) transformed the data and performed a three-way ANOVA]. Thereafter, using the variance estimate (VAR) obtained from the analysis of variance, calculated the 90 per cent confidence intervals from the following formulation[7,11,13].

$$(\mu_A - \mu_B) = (\bar{X}_A - \bar{X}_B) \pm t^{\nu}_{0.1} \sqrt{\frac{2VAR}{n}}$$

Where $\bar{X}_A$, $\bar{X}_B$ were the observed means of the (ln) transformed parameters (either C_{max} or

AUC) for the test product (A) and the references (B), VAR was the error variance obtained from the three-ways ANOVA (the residual mean square of a three-way crossover study), n was the number of subjects and $t^{v}_{0.1}$ was the tabulated two-tail *t* value for 90 per cent CI and v was the number of degrees of freedom of the mean square from the analysis of variance. The bioequivalence limits expressed as the ratio of the test and reference product (Prenolol®/Tenormin®) were obtained by taking the antilogarithm of the confidence intervals.

RESULTS

Twelve healthy subjects completed this study without any serious adverse effects. The mean plasma concentration-time curves of 50 mg and 100 mg of Prenolol® *vs* Tenormin® were dipicted in Fig. 1 and 2, respectively. The calculated pharmacokinetic parameters following a single oral dose of 50 mg Prenolol® and Tenormin® were summarized and shown in Table 1. The mean C_{max} (ng/ml), T_{max} (h), $AUC_{0-\infty}$ (ng.h/ml) and $t_{1/2}$ (h) of 50 mg Prenolol® and Tenormin® were 554.33 ± 212.07 and 436.5 ± 154.6 , 3.25 ± 0.87 and 2.88 ± 1.23, 4,278 ± 1,057 and 3,639 ± 932, 5.62 ± 0.80 and 6.21 ± 1.05, respectively. The calculated pharmacokinetic parameters following a single oral dose of 100 mg Prenolol® and Tenormin® were summarized and shown in Table 2. The mean C_{max} (ng/ml), T_{max} (h), $AUC_{0-\infty}$ (ng.h/ml) and $t_{1/2}$ (h) of 100 mg Prenolol® and Tenormin® were 907.33 ± 247.51 and 880.50 ± 399.60, 3.92 ± 1.14 and 3.58 ± 1.47, 8,133 ± 1,583 and 7,710 ± 2,562, 6.34 ± 0.66 and 6.47 ± 0.90, respectively.

Table 3 illustrates 90 per cent CI and point estimate of 50 mg (Prenolol®/Tenormin®) of $AUC_{0-\infty}$ and C_{max} as well as the T_{max} differences of (Prenolol®-Tenormin®). The mean and 90 per cent CI of the ratio (Prenolol®/Tenormin®) of $AUC_{0-\infty}$ and C_{max} were 1.16 (1.05-1.27) and 1.23 (1.07-1.38), respectively. The mean T_{max} differences of Prenolol®-Tenormin® was 0.38 h (13%).

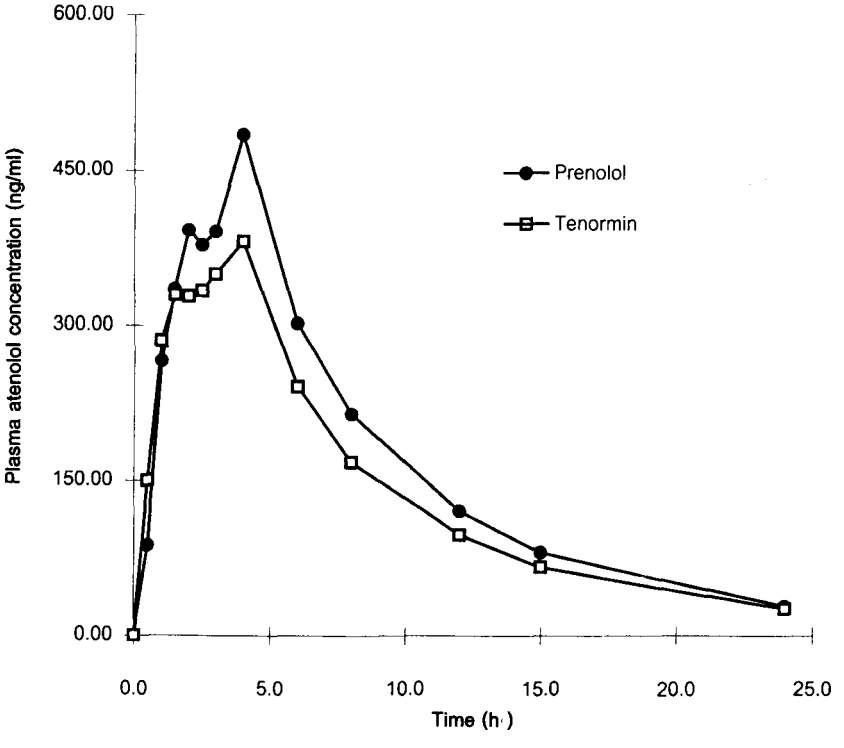

Fig. 1. Mean plasma concentration-time curves following a single oral dose of 50 mg Prenolol® and Tenormin®.

Table 4 illustrates 90 per cent CI and point estimate of 100 mg (Prenolol®/Tenormin®) of $AUC_{0-\infty}$ and C_{max} as well as the T_{max} differences of (Prenolol®-Tenormin®). The mean and 90 per cent CI of the ratio (Prenolol®/Tenormin®) of $AUC_{0-\infty}$ and C_{max} were 1.10 (1.00-1.20) and 1.13 (0.95-1.31), respectively. The mean T_{max} differences of Prenolol®-Tenormin® was 0.33 h (11%).

DISCUSSION

The mean plasma concentration-time curves of 50 mg and 100 mg atenolol were relatively consistent with little variation in plasma atenolol levels at each time point. It was noted that only the AUC-extrapolation to infinity ($AUC_{0-\infty}$) serves as a characteristic of the extent of absorption in single-dose studies[11-13]. The reason being was from the fundamental pharmacokinetic relationship;

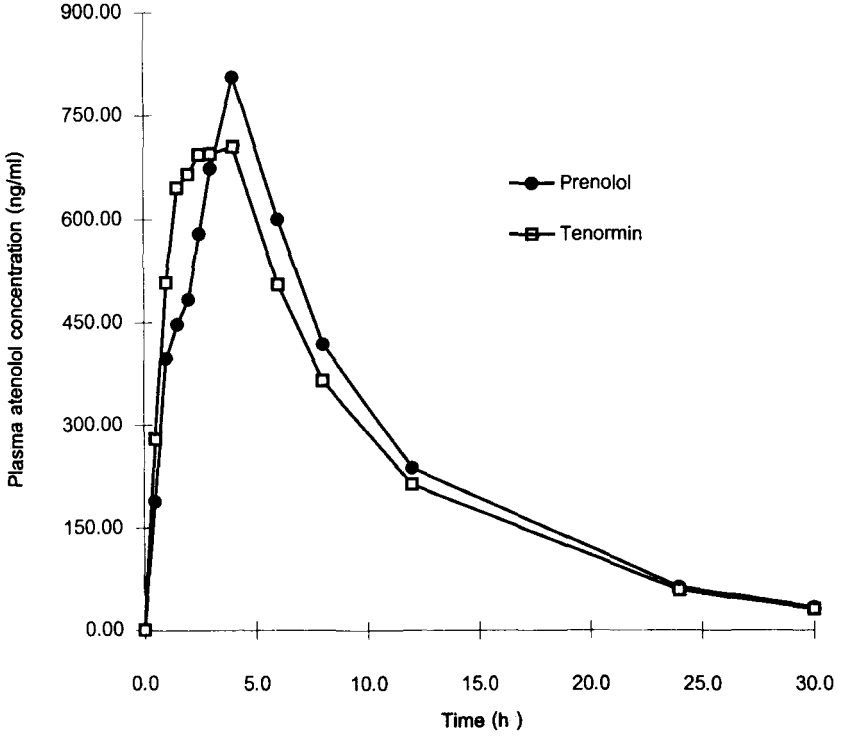

Fig. 2. Mean plasma concentration-time curves following a single oral dose of 100 mg Prenolol® and Tenormin®.

Table 1. Mean (± SD) pharmacokinetic parameters of atenolol 50 mg following a single oral administration of Prenolol® and Tenormin® tablets.

Pharmacokinetic parameters	Prenolol®	Tenormin®
C_{max} (ng/ml)	554.33 ± 212.07	436.50 ± 154.60
T_{max} (h)	3.25 ± 0.87	2.88 ± 1.23
$MRT_{0-\infty}$ (h)	8.74 ± 1.08	8.98 ± 1.35
$AUC_{0-\infty}$ (ng.h/ml)	4,278 ± 1,057	3,639 ± 932
$t_{1/2}$ (h)	5.62 ± 0.80	6.21 ± 1.05

Table 2. Mean (± SD) pharmacokinetic parameters of atenolol 100 mg following a single oral administration of Prenolol® and Tenormin® tablets.

Pharmacokinetic parameters	Prenolol®	Tenormin®
C_{max} (ng/ml)	907.33 ± 247.51	880.50 ± 399.60
T_{max} (h)	3.92 ± 1.14	3.58 ± 1.47
$MRT_{0-\infty}$ (h)	9.59 ± 0.97	9.31 ± 1.24
$AUC_{0-\infty}$ (ng.h/ml)	8,133 ± 1,583	7,710 ± 2,562
$t_{1/2}$ (h)	6.34 ± 0.66	6.47 ± 0.90

Table 3. Parametric 90% comfidence intervals for the mean pharmacokinetic parameters of atenolol 50 mg.

Parameters	Prenolol® / Tenormin® Mean	90% CI
$AUC_{0-\infty}$ (ng.h/ml)	1.16	1.05-1.27
C_{max} (ng/ml)	1.23	1.07-1.38
Parameter	Prenolol® - Tenormin® Mean	
T_{max} (h)	0.38 (13%)*	

* was within the ± 20 per cent of Tenormin® T_{max}

Table 4. Parametric 90% comfidence intervals for the mean pharmacokinetic parameters of atenolol 100 mg.

Parameters	Prenolol® / Tenormin® Mean	90% CI
$AUC_{0-\infty}$ (ng.h/ml)	1.10	1.00-1.20
C_{max} (ng/ml)	1.13	0.95-1.31
Parameter	Prenolol® - Tenormin® Mean	
T_{max} (h)	0.33 (11%)*	

* was within the ± 20 per cent of Tenormin® T_{max}

f x dose = clearance x $AUC_{0-\infty}$, $1, \geq f > 0$ (f = bioavailability). Therefore, the fraction of the ultimately absorbed dose was proportional to $AUC_{0-\infty}$ and clearance was the proportionality factor. It is important that the extrapolation fraction should not exceed 20 per cent of the total AUC [11,13]. In this study, the average AUC-extrapolated portion was less than 10 per cent of the total AUC, since the duration of blood samplings was greater than 3 times the terminal half-life and the anlytical technique is fairly sensitive. Thus, the $AUC_{0-\infty}$ following a single dose in this study could represent the extent of absorption. The means (parametric 90% CI) of the ratio (Prenolol®/Tenormin®) of $AUC_{0-\infty}$ and C_{max} were 1.16 (1.05-1.27), 1.23 (1.07-1.38) for 50 mg preparations and 1.10 (1.00-1.20), 1.13 (0.95-1.31) for 100 mg preparations, respectively. These values were well within the acceptable bioequivalence ranges of 0.8-1.25 and 0.7-1.43 for the ratio [Test/Reference] of $AUC_{0-\infty}$ and C_{max}, respectively[11,13]. A small range of confidence interval observed in this study verified that an adequate number of subjects were enrolled. It can be seen from Table 1 and 2 that atenolol was rapidly absorbed after oral administration. The mean T_{max} of 50 mg and 100 mg Prenolol® and Tenormin® did not reach statistical differences between the two preparations and were comparable to the mean T_{max} values of 2-4 hours, reported from other studies[3,8,14,15]. The means of T_{max} differences (Prenolol®-Tenormin®) were 0.38 (13%) and 0.33 (11%) h for 50 mg and 100 mg preparations, respectively. The mean values overlapped the stipulated bioequivalence range of T_{max} differences (± 20% of the T_{max} of the reference formulation) of ± 0.58 h and ± 0.72 h for 50 mg and 100 mg preparations, respectively. Similarly, the MRT (h) of the two products were nearly identical at the same dosage formulations (Table 1, 2). The mean $t_{1/2}$ were 5-7 hours which was consistent with those values reported in the literature[3,8,10,14,15]. Since their 90 per cent CI of the ratio (Prenolol®/Tenormin®) of $AUC_{0-\infty}$, C_{max}, and T_{max} difference were within the bioequivalence range, Prenolol® possessed as high a probability of demonstrating practical equivalence as Tenormin®.

SUMMARY

We conducted a bioequivalence testing of two preparations of 50 mg and 100 mg formulations of atenolol [Prenolol® *vs* Tenormin®] in 12 Thai healthy volunteers. The result showed no significant difference between the two brands concerning the rate and extent of absorption. The parametric 90 per cent CI and point estimates of the mean difference of these parameters were within the acceptible range based on standard bioequivalence guidelines. Atenolol elimination half-life obtained from this study was also comparable to those values reported in the literature. Therefore, the generic Prenolol®, and Tenormin®, can be used interchangeably when cost-effectiveness is concerned.

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การศึกษาชีวสมมูลของยาอะทีโนลอลชนิดกินที่ผลิตจากบริษัทต้นตำรับกับบริษัทอื่นในอาสาสมัครคนไทยที่มีสุขภาพดี

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การศึกษาชีวสมมูลของยาอะทีโนลอลชนิดเม็ดกินขนาด 50 มิลลิกรัม และ 100 มิลลิกรัม ที่ผลิตโดยบริษัทยาในประเทศไทย ยาพรีโนลอล (บริษัทเบอร์ลิน ฟาร์มาซูติคอล จำกัด) กับยาต้นตำรับ ทีนอร์มิน (บริษัทซีนิกา จำกัด) ในอาสาสมัครสุขภาพดีจำนวน 12 คน ตรวจวัดความเข้มข้นของยาอะทีโนลอลโดยวิธีโครมาโตกราฟฟีชนิดของเหลวสมรรถนะสูง จากการศึกษาพบว่าค่าเฉลี่ยและช่วงความเชื่อมั่นร้อยละ 90 ของอัตราส่วนระหว่างยาพรีโนลอล/ยาทีนอร์มินของพื้นที่ใต้กราฟที่เวลา 0–อสงไขย และความเข้มข้นสูงสุดของยาในพลาสมามีค่าเท่ากับ 1.16 (1.05–1.27) และ 1.23 (1.07–1.38) สำหรับยาอะทีโนลอลขนาด 50 มิลลิกรัม สำหรับขนาด 100 มิลลิกรัม มีค่าเท่ากับ 1.10 (1.00–1.20) และ 1.23 (0.95–1.31) ตามลำดับ ซึ่งอยู่ในช่วงของชีวสมมูลที่ยอมรับได้ ค่าเฉลี่ยความแตกต่างของเวลาที่ระดับยาสูงสุดในพลาสมาระหว่างยาพรีโนลอลและยาทีนอร์มินขนาด 50 และ 100 มิลลิกรัม มีค่าน้อยกว่าร้อยละ 20 ของระดับยาสูงสุดในพลาสมาของยาทีนอร์มินซึ่งอยู่ในช่วงชีวสมมูลที่ยอมรับได้เช่นกัน แสดงว่ายาพรีโนลอลมีชีวสมมูลกับยาทีนอร์มินในด้านปริมาณและอัตราการดูดซึมของยา

คำสำคัญ : ชีวสมมูล, อะทีโนลอล

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