Journal of Food and Drug Analysis, Vol. 11, No. 1, 2003, Pages 4-7 藥物食品分析 第十一卷 第一期

Comparative Pharmacokinetics of Two Atenolol Products

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(Received: July 4, 2002; Accepted: September 25, 2002)

ABSTRACT

The purpose of this study was to determine the pharmacokinetics and comparative bioavailability of atenolol tablets manufactured by two different drug companies. Pharmacokinetics (PK) and comparative bioavailability of atenolol tablets manufactured by two different drug companies were investigated in 12 healthy volunteers in an open, randomized cross-over trial. After a single oral dose of 100 mg atenolol tablets, the concentration of atenolol in plasma was determined by a modified high performance liquid chromatographic (HPLC) method with fluorimetric detection. Intra-day and inter-day coefficients of variation (CV) were within 12%. The detection limit was 0.02mg/L for plasma samples. The average bioavailability and pharmacokinetic parameters of the two atenolol tablets were as follows: peak plasma concentration (C_{max}): 0.98 ± 0.39 mg/L, 0.85 ± 0.32 mg/L; time to peak plasma concentration (T_{max}): 2.88 ± 1.03 hours, 2.96 ± 1.16 hours; plasma half-life ($T_{1/2}$): 6.19 ± 1.01 hours, 6.19 ± 1.38 hours; area under the plasma concentration-time curve ($AUC_{0\rightarrow\infty}$): 8.74 ± 3.85 mg-hr/L, 7.88 ± 2.69 mg-hr/L; $AUC_{0\rightarrow28}$: 8.34 ± 3.66 mg-hr/L, 7.50 ± 2.61 mg-hr/L; area under the first moment-time curve (AUMC): 81.03 ± 37.62 mg-hr^2/L, 74.86 ± 26.67 mg-hr^2/L; mean residence time (MRT): 9.27 ± 0.75 hours, 9.50 ± 1.35 hours for Ateol® tablets (Standard) and Tenormin® tablets (ICI), respectively. No statistically significant differences were observed for the PK parameters between the two products ($p > 0.05$). The narrow $CI_{90\%}$ values, high power values and the results of two one-sided t-tests also showed that the two products are very similar. The PK parameters obtained in this study are similar to those reported previously.

Key words: Comparative bioavailability; Pharmacokinetics; Atenolol

INTRODUCTION

Atenolol, a beta-2 receptor blocking agent, is widely used for treatment of hypertension and coronary artery disease at a dose of 50 – 100 mg daily *po*[1,2]. Previous pharmacokinetic studies found that only about 50 – 60% of an oral dose of atenolol was absorbed[3,4] and peak plasma concentrations (1 – 2 mg/L after 200 mg dose) were reached at 2 – 4 hours[1,5,6]. Food reduces the area under the plasma concentration-time curve (AUC) by 20% as compared to the fasting state[7]. Atenolol is not metabolized in the liver; approximately 40 – 50% of an oral dose is eliminated *via* the kidneys as unchanged drug and the other half is excreted in the feces. The elimination half-life is 6 to 7 hours in adults with normal renal function[5,8,9].

The purpose of this study was to compare the pharmacokinetic parameters and relative bioavailability of two different preparations of atenolol tablets in healthy volunteers based on results from a single dose clinical study.

MATERIALS AND METHODS

I. *Drugs*

Two preparations of atenolol tablets, Tenormin® tablets (Imperial Chemical Industries Limited, the United Kingdom, 100 mg/tab, lot no. NA358A) and Ateol® tablets (Standard Chemical and Pharmaceutical Co Ltd. Taiwan, 100 mg/tab., lot no.TA-070471) were used. One tablet of atenolol (100 mg) was administered orally with water (250 mL) after overnight fasting.

II. *Subjects*

Twelve healthy male volunteers, aged 21-25 years (23.42 ± 1.51 years), with body weights of 55-78 kg (65.17 ± 7.65kg) and body heights of 157-180 cm (173.21 ± 6.75 cm), were determined to be healthy on the basis of the medical history review, the results of physical examination and biochemical tests (serum creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, bilirubin, blood sugar, etc.). After signing written informed consents, they were randomly assigned to two groups. No medication was allowed for at least 14 days before the study and no drugs other than the required doses of atenolol were given during the study. Exclusion criteria included: hepatic, renal, gastrointestinal, cardiovascular disorders, abnormal serum creatinine, allergy to any beta-adrenergic blocker and hepatitis B carrier.

III. *Study Design*

This randomized, open label and two-way cross-over trial was conducted with a 7-day washout period in the

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healthy volunteers after a single oral dose of atenolol (100 mg). The subjects were refrained from ingesting any food or fluids for 10 hours prior to dosing. The study started at 8 AM with the oral intake of atenolol (100 mg) and water (250 mL). No food was allowed until 4 hours later. Blood samples, 10 mL each, were withdrawn from a catheter in the cubital vein at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 28 hour after dosing and added into a heparinized tube. Plasma was immediately separated by centrifuge and stored frozen at -20˚C until analyzed. For safety, blood pressure (BP) and heart rate (HR) were closely monitored 10 minutes before each dosing and prior to each sampling during the dose administration phase and the conclusion of the study. The volunteers were encouraged to report any untoward reactions.

IV. *Reagents and Chemicals*

Atenolol reference standard was provided by Imperial Chemical Industries Limited, the United Kingdom (ICI, UK). All other chemicals and solvents were HPLC grade.

Standard plasma atenolol solutions for the construction of standard curves were prepared by dissolving atenolol quantitatively in blank plasma.

V. *Instruments*

A high performance liquid chromatography (HPLC) system was used to analyze the samples. Samples were injected by a Jasco 851AS Sampler. Fluorescence spectra were obtained with a Hitachi Fluorescence Spectrophotometer F1000 and integrated with a SIC Chromatocorder 11. Flow rate was controlled by a Waters MC 5 solvent delivery system.

VI. *Chromatographic Conditions*[10,11]

Separation was performed on a LichroCART 125-4 Lichrospherer 100 RP-18 reversed phase column (5 µm, 125 4 mm, Merck®). The composition of the mobile phase was acetonitrile: 0.05M phosphate buffer (10:90 v/v). Samples were analyzed at a flow rate of 1.5 mL/min detector with fluorescent excitation at 230 nm and emission wavelength at 300 nm.

VII. *Sample Preparation*

An aliquot of each plasma sample (1.0 mL) was placed in a 15-mL centrifuge tube and 5 N sodium hydroxide (0.1 mL) and ethyl acetate (3 mL) were added. The tube was vortexed for 30 seconds. The organic layer was transferred to a clean tube and evaporated to dryness under nitrogen gas. 0.2 mL of acetonitrile: 0.05 M phosphate buffer (10:90 v/v) was added to the residue in the culture tube. An aliquot of the resulting solution (50 µL) was transferred into an injection vial and analyzed by the HPLC system.

VIII. *Validation of the Analysis*

For selectivity, each blank sample was tested for interference, and selectivity was ensured at the lower limit of the quantification (LLOQ). The detection limit or LOD was defined as a trazodone HCl peak that was consistently three-fold greater than the baseline noise and the LLOQ was defined as the lowest concentration that fits the accuracy and precision requirements described below.

The intra-day and inter-day variations were determined by spiking with atenolol (0.02 µg/mL, 0.50 µg/mL, and 2.00 µg/mL) in triplicate runs 2 times within 1 day and in at least 1 run per day for 6 days. Coefficient of variation (CV) served as the indicator of the precision.

Accuracy (bias) and precision were assessed using low, medium, and high QC levels. Accuracy, defined as [(measured concentration - nominal concentration) /nominal concentration] × 100%, was measured using a minimum of 5 determinations per concentration. The mean value should be within 15% of the actual value except at low QC levels, where it should not deviate by more than 30%.

Spiked samples of known drug concentrations were analyzed together with the plasma samples to assure quality. The detection limit was defined as an atenolol peak that was consistently three-fold greater than the baseline noise.

Recovery was determined by comparing the analytical results for extracted samples at the 3 concentrations listed above with the nominal concentrations.

IX. *Data Analysis*

Pharmacokinetic parameters were calculated by noncompartmental analysis. Peak plasma concentration (C_{max}) and time to peak concentration (T_{max}) were determined after each treatment without interpolation. The log-linear portion of the last several points of each set of plasma concentrations was used to determine the terminal phase hybrid constant (β).

$AUC_{0\to\infty}$ values were the sum of AUC between 0 to 28 hours ($AUC_{0\to28}$) and AUC extrapolated (AUC_{ex}). $AUC_{0\to28}$ was calculated by summation of each individual area between two consecutive time intervals from time 0 to the final observed plasma concentration at 28 hours (Cp_{28}) using the linear trapezoidal rule. AUC_{ex} was calculated by dividing Cp_{28} by β. Plasma half-life ($T_{1/2}$) was calculated as $T_{1/2} = 0.693/\beta$.

The first moment curve was constructed by the time course data obtained by multiplying the plasma concentration Cp with the corresponding time point, i.e., $Cp_t \times t$. The trapezoidal rule was then used to obtain the area under the first moment curve (AUMC). The tail area of moment curve (beyond the last data point) was estimated by the equation: tail $AUMC = Cp_t/\beta + Cp/\beta^2$. Mean residence time (MRT) was calculated by dividing total AUMC by $AUC_{0\to\infty}$. Total $AMUC = AUM_{0\to28}$ + tail AUMC.

The results of the pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\to\infty}$, $AUC_{0\to28}$) are given as mean ± standard

deviation (SD). All data were analyzed by two-way analysis of variance with residual effect (WinNonlin version 3.0, Pharsight Corporation) and two one-sided t-tests, with power analysis and 90% confidence interval ($CI_{90\%}$). T_{max} was also analyzed by the Chi-square test. A result of $p < 0.05$ was regarded as significant.

RESULTS

I. *Validation of the Analytical Method*

Selectivity was ensured at the LLOQ by comparing the chromatogram of the blank plasma and the plasma sample spiked with the drug. The limit of quantification for the plasma extract was 0.02 mg/L with a CV of less than 10%. Intra-day and inter-day CV values and biases were within 10%.

II. *Pharmacokinetic and Statistical Analysis*

The mean plasma concentration-time curves of atenolol after oral administration of Ateol® tablets from Standard Pharmaceutical Industrial Inc. and Tenormin® tablets from ICI, UK in twelve volunteers were shown in Figure 1. The bioavailability and pharmacokinetic parameters are listed in Table 1. No statistical difference was found in C_{max}, $AUC_{0\to\infty}$, $AUC_{0\to28}$, AUMC, MRT, and $T_{1/2}$ between Ateol® tablets and Tenormin® tablets. The $CI_{90\%}$ of C max, as well as those of $AUC_{0\to\infty}$, and $AUC_{0\to28}$, fell within the range of 80% to 120% of the mean of Tenormin® tablets after log transformation.The two one-sided t-tests showed that the chance that these parameters for Ateol® fell out of the 80% to 120% range of the Tenormin® mean values was 0% after log transformation. The ratio of $AUC_{0\to\infty}$, $AUC_{0\to28}$, C_{max}, $T_{1/2}$, AUMC, and MRT for Ateol® tablets and Tenormin® tablets was 100.84% ($CI_{90\%}$ 99.19-102.44%), 100.81 % ($CI_{90\%}$ 99.20-102.48%), 101.80% ($CI_{90\%}$ 99.20-104.40%), 99.99% ($CI_{90\%}$ 89.26-110.73%), 108.24% ($CI_{90\%}$ 89.16-127.32%), and 97.51% ($CI_{90\%}$ 90.61%-104.41%), respectively (Table 1). The statistical power was 1.000, 1.000, 1.000, 0.862, 0.376, and 0.994 for $AUC_{0\to\infty}$, $AUC_{0\to28}$, C_{max}, $T_{1/2}$, AUMC, and MRT, respectively. These two products are bioequivalent

DISCUSSIONS

The HPLC assay method employed in this study is similar to that described by Winkler et al[11]. It is simple, sensitive and reproducible for the assay and pharmacokinetic study of atenolol with a small sample volume.

The bioavailability and pharmacokinetic parameters, such as C_{max}, T_{max}, $T_{1/2}$, obtained in this study (Table 1) were in agreement with those from earlier studies[1,5,6]. For example, after taking 100 mg Ateol® (Standard) orally, a peak concentration of 0.98 ± 0.39 mg/L was reached at 2.88 ± 1.03 hours, while previous pharmacokinetic studies showed that atenolol reached peak plasma concentrations (1-2 mg/L after 200mg dose) at 2-4 hours[1,5,6]. The termi-

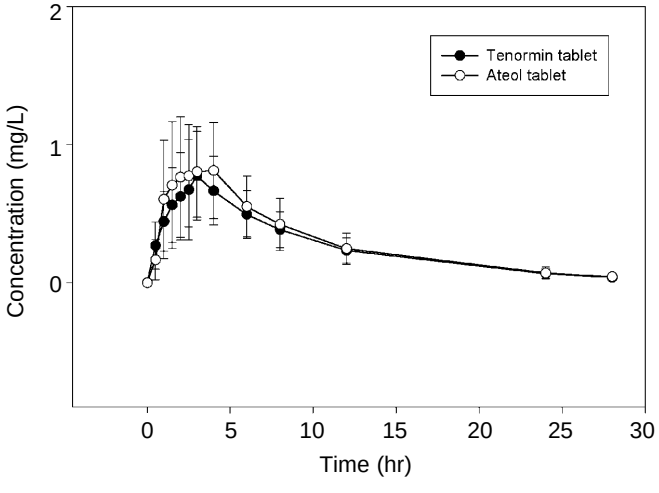

Figure 1. Mean plasma atenolol concentrations following oral administration of 100 mg Ateol® tablets and Teormin® tablets in 12 volunteers

Table 1. Bioavailability and pharmacokinetic parameters following administration of Ateol® tablets and Tenormin® tablets in 12 healthy volunteers

Parameters	Ateol® tablet (mean ± SD)	Tenormin® tablet (mean ± SD)	Ateol / Tenormin ratio (%)	$CI_{90\%}$ of Ateol / Tenormin ratio (%)	$CI_{95\%}$ of Ateol / Tenormin ratio (%)	*p*	Two one-sided t-test: probability for <80% or >120%	1-β
C_{max} (mg/L)	0.98 ± 0.39	0.85 ± 0.32						
LN C_{max} [a]	6.81 ± 0.42	6.69 ± 0.34	101.80	99.20-104.40	98.61-104.99	> 0.05	0.00%	1.000
$AUC_{0-\infty}$ (mg-hr/L)	8.74 ± 3.85	7.88 ± 2.69						
LN $AUC_{0-\infty}$ [a]	8.99 ± 0.41	8.92 ± 0.32	100.84	99.19-102.44	98.81-102.82	> 0.05	0.00%	1.000
AUC_{0-28} (mg-hr/L)	8.34 ± 3.66	7.50 ± 2.61						
LN AUC_{0-28} [a]	8.95 ± 0.41	8.87 ± 0.32	100.81	99.20-102.48	98.83-102.85	> 0.05	0.00%	1.000
AUMC (mg-hr^2/L)	81.03 ± 37.62	74.86 ± 26.67	108.24	89.16-127.32	84.78-131.69	> 0.05	15.64%	0.376
MRT (hr)	9.27 ± 0.75	9.50 ± 1.35	97.51	90.61-104.41	89.03-106.00	> 0.05	0.06%	0.994
$T_{1/2}$ (hr)	6.19 ± 1.01	6.19 ± 1.38	99.99	89.26-110.73	86.80-113.19	> 0.05	0.70%	0.862
T_{max} (hr)	2.88 ± 1.03	2.96 ± 1.16	97.18	82.56-111.81	79.21-115.16	> 0.05	3.84%	0.597

a: data obtained after log transformation; The unit of C_{max} was changed to mcg/L before transformation of AUCs & C_{max}.

nal phase half-lives of the two products in the present study were 6.19 ± 1.01 hours and 6.19 ± 1.38 hours, respectively, while previous pharmacokinetic studies found terminal phase half-lives of 6 to 7 hours in adults with normal renal function[5,6,8,9]. Similarity between the current data and the reported data was observed. The T_{max} and MRT values revealed that there were no significant differences in the rate of absorption for the two products. The C_{max} and $AUC_{0\rightarrow\infty}$ values further demonstrated that there was no significant difference in the extent of absorption of the two products.

Although some studies showed that decreases in blood pressure are not correlated with serum atenolol concentrations[12,13], bioavailabilty or bioequivalent studies are often mandated to ensure the quality of generic drugs. In our study, there were no statistically significant differences in the pharmacokinetic parameters of the proprietary atenolol from ICI and the generic preparation of atenolol from Standard chemical and Pharmaceutical Co. Ltd. There were no clinically important differences in their bioavailability in humans. This study provides valuable information for clinicians who do not have confidence in generic atenolol. For patients with unexpected clinical responses, the effect of food should be considered. As food reduces the AUC by 20% as compared to the fasting state[7], patients should be advised to take the drug on an empty stomach.

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