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Comparative Bioavailability of Two Brands of Atenolol 100 mg Tablets (Tensotin and Tenormin) in Healthy Human Volunteers

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ABSTRACT: A bioequivalence study of two oral formulations of 100 mg atenolol was carried out in 24 healthy volunteers following a single dose, two-sequence, cross-over randomized design at the International Pharmaceutical Research Centre (IPRC), as a joint venture with Al-Mowasah Hospital, Amman, Jordan. The two formulations were Tensotin (Julphar, UAE) as test and Tenormin (Zeneca, UK) as reference product. Both test and reference tablets were administered with 240 ml of water to each subject after an overnight fast on 2 treatment days separated by a 1 week washout period. After dosing, serial blood samples were collected for a period of 36 h. Whole blood was analysed for atenolol by a sensitive, reproducible and accurate HPLC method with fluorescence detection capable of detecting atenolol in the range of 20–1600 ng/ml with a limit of quantitation of 20 ng/ml. Various pharmacokinetic parameters including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$ and λ_Z were determined from blood concentrations of both formulations and found to be in good agreement with reported values. AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were tested for bioequivalence after log-transformation of data using ANOVA and 90% confidence interval and were found within the acceptable range of 80%–125%. Based on these statistical inferences, it was concluded that Tensotin is bioequivalent to Tenormin. Copyright © 2004 John Wiley & Sons, Ltd.

Key words: atenolol; bioequivalence; pharmacokinetics; HPLC; Julphar

Introduction

Bioequivalence of two formulations of the same drug comprises equivalence with respect to the rate and extent of their absorption. The area under the concentration time curve (*AUC*) generally serves as the indicator of the extent of absorption while the peak concentration (C_{max}) and the time of its occurrence (T_{max}), reflect the rate of absorption, especially in fast releasing drug formulations [1,2]. In the present study the bioequivalence of two atenolol tablets was evaluated by comparing the above pharmacokinetic parameters as derived from the blood concentration of atenolol.

Atenolol is a cardioselective beta-adrenergic blocking agent used in the treatment of hypertension and ischemic heart diseases [3]. The drug has no intrinsic sympathomimetic activity (ISA) or membrane stabilizing properties [4,5,6]. Chemically it is 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy] benzeneacetamide ($C_{14}H_{22}N_2O_3$) with a molecular weight of 266.34 [7].

β-adrenergic antagonists counter the effect of sympathomimetic neurotransmitters by competing for receptor sites. Similar to metoprolol, atenolol, in low doses, selectively blocks sympathetic stimulation mediated by β1-adrenergic

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receptors in the heart and vascular smooth muscle. The pharmacodynamic consequences of this activity include: a reduction of resting heart rate and, subsequently, cardiac output; a reduction of both systolic and diastolic blood pressure at rest and with exercise; and a possible reduction of reflex orthostatic hypertension [8].

Absorption of atenolol from the gastrointestinal tract is rapid but incomplete. After oral administration about 46%–60% of the dose is rapidly absorbed reaching a peak concentration within 2 to 4 h, and the remainder is excreted unchanged in the faeces [8–14]. Food does not affect the bioavailability [15]. Total protein binding is less than 5% [16,17] and atenolol is distributed throughout the body and into breast milk. It also crosses the placenta, with fetal serum atenolol concentrations approaching those of the mother. Unlike propranalol, atenolol distribution into the CNS averages only 10% due to low lipophilicity and low protein binding [8].

The serum half-life of atenolol is 6–7 h in adults and about 4.6 h in children [8–14]. The half-life increases progressively as renal function is impaired. Minimal, if any, metabolism occurs in the liver, and 40%–50% of an oral dose is excreted renally as unchanged drug.

Objectives of the study

The aim of this study was to assess the bioequivalence of two commercial 100 mg tablets of atenolol, locally available in the UAE market, by statistical analysis of the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as recommended by FDA. Tensotin from Julphar, UAE was used as the test while Tenormin from Zeneca was used as the reference product in the study.

Materials and Methods

Study products

Test product:	Tensotin—Atenolol 100 mg tablet
Batch no.:	0014, Expiry: 12/2005 Gulf Pharmaceutical Industries—Julphar, United Arab Emirates
Reference product:	Tenormin—Atenolol 100 mg tablet
Batch no.:	UHA 981, Zeneca, UK. Expiry: 11/2004

Study subjects

Twenty-four healthy adult male volunteers participated in this comparative study at Al-Mowasah Hospital, Amman, Jordan, as a joint venture with the International Pharmaceutical Research Center (IPRC) Amman, Jordan. Their mean age was 23.04 ± 4.68 years with a range of 18–39 years; mean body weight was 70.46 ± 7.45 kg with a range of 54–85 kg and mean body height was 172.75 ± 6.60 cm with a range of 162–188 cm. The volunteers were free from significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal or haematological diseases, as determined by their medical history, physical examination and routine laboratory tests (haematology, blood biochemistry and urine analysis) and were negative for hepatitis B antigen. They were instructed to abstain from taking any drug including over-the-counter (OTC) for 2 weeks prior to and during the study period. The volunteers were informed about the aims and risks of the study by the clinical investigator and signed a written informed consent statement before entering the study. The study protocol was approved by Institutional Review Board (IRB) of Al-Mowasah Hospital, Amman, Jordan.

Drug administration and sample collection

The volunteers were hospitalized at 6:00 p.m. and had a standard dinner in hospital. After an overnight fasting (10 h) they were given a single dose of either formulation (reference or test in a randomized fashion) of atenolol 100 mg tablet with 240 ml of water. Food and drinks (other than water, which was allowed after 2 h) were not allowed until 5 h after ingestion of the tablets and then standard breakfast, lunch and dinner were given to all volunteers according to a time schedule. Beverages and food containing caffeine were not permitted over the entire course of study. Volunteers sat or walked around until the 5-h blood collection, and were prohibited from strenuous activity. They were under direct medical supervision at the study site. Approxi-

mately 10 ml blood samples for atenolol assay were drawn into evacuated heparinized glass tubes through indwelling cannula before (0 h) and at 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 h after dosing. Blood samples were stored frozen at –20°C pending drug analysis. Vital signs, BP, pulse rate and temperature, were recorded at 2, 3, 4, 6, 10 and 24 h. After a period of 7 days the study was repeated in the same manner to complete the crossover design.

Sample preparation for HPLC injection

100 µl of the internal standard working solution (bemethane 3.0 µg/ml) was added to 0.5 ml whole blood sample. The samples were vortexed for 30 s, 300 µl of 1M sodium carbonate was added and then samples were vortexed for 30 s. 7 ml of extraction solvent (ethyl acetate) was added and vortexed for 1 min then centrifuged for 5 min at 3000 rpm. The supernatant (organic layer) was transferred to another 10 ml glass tube and evaporated to dryness in a water bath at 45°C under nitrogen, then reconstituted with 200 µl of mobile phase, vortexed for 30 s and transferred to an eppendorf tube (0.75 ml), and centrifuged for 2 min at 13,000 rpm. A 100 µl aliquot sample was injected into a Lichrospher RP-select B (5 µm) (250 × 4 mm) HPLC cartridge column, where atenolol and internal standard were separated from endogenous substances.

Chromatographic conditions

Blood samples were analysed for atenolol according to a sensitive, selective and accurate HPLC method [13] that was validated before the study. All solvents used were of HPLC grade, while other chemicals and reagents were of analytical grade; atenolol and bemethane were obtained from Julphar, UAE.

The HPLC system was from Shimadzu Kyoto, Japan, and it consisted of a solvent delivery pump (LCD-10AD), a system controller (SCL-10A), an auto-injector (SIL-10A), and a fluorescence detector (RF-10A); integration was done using Class VP-5 software version 5.03. Chromatographic separation was performed using Lichrospher RP-select B (5 µm) (250 × 4 mm) HPLC cartridge column (Merck, Germany). The mobile phase consisted of 90% 0.05 M potassium dihydrogen orthophosphate and 10% acetonitrile, and eluted at a flow rate of 1.5 ml/min at ambient temperature. The effluent was monitored using a fluorescence detector at 230 nm for excitation and 300 nm for emission. The peak area was measured, and the peak area ratio of drug to internal standard and the concentration were calculated by Class VP-5 software (version 5.03) Shimadzu. Each analysis required less than 6 min. The method was validated by following international guidelines [18].

Pharmacokinetic and statistical analysis

Pharmacokinetic and statistical analysis was performed by means of a model independent method using a Kinetica™ 2000 computer program [19]. The elimination rate constant (λ_Z) was obtained as the slope of the linear regression of the log-transformed concentration values versus time data in the terminal phase. The elimination half-life ($T_{1/2}$) was calculated as $0.693/\lambda_Z$. The area under the curve to the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-t}+C_t/\lambda_Z$, where C_t is the last measurable concentration. Two-way analysis of variance (ANOVA) for crossover design was used to assess the effect of formulations, periods, sequences and subjects on these parameters. 90% confidence intervals [20] based on the ANOVA of the mean test/reference (T/R) ratios of *AUCs* and C_{max} were computed.

Results and Discussion

Atenolol was well tolerated by all volunteers; unexpected incidents that could have influenced the outcome of the study did not occur. There was no drop-out and all volunteers who started the study continued to the end and were discharged in good health.

The described analytical method was proven sensitive and accurate for the determination of atenolol in blood. Both formulations were readily absorbed from the gastrointestinal tract and

atenolol was measurable at the first sampling time (0.33 h) in the majority of the volunteers. The mean concentration-time profile of the two formulations is shown in the Figure 1. All calculated pharmacokinetic parameter values were in good agreement with reported values [6,10,13,14,21–23].

Table 1 shows the pharmacokinetic parameters for the two brands of atenolol 100 mg tablets. 90% confidence intervals for the log-transformed data were also calculated according to the FDA guidelines [20] and the results are shown in Table 1.

On the basis of the blood levels of the 24 volunteers completing this study (see Figure 1), the mean relative bioavailability of Tensotin 100 mg tablets was 114.50% for AUC_{0-t}, 112.58% for $AUC_{0-\infty}$ and 115.50% for C_{max}.

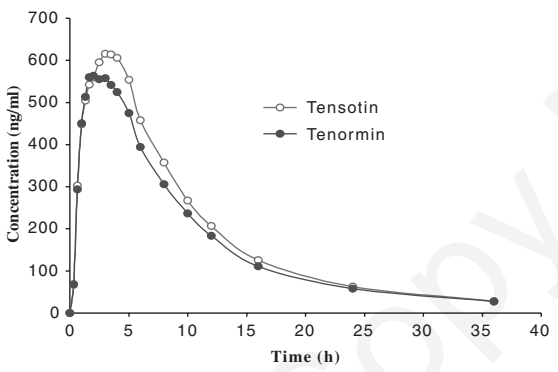

Figure 1. Mean blood concentrations of atenolol after oral administration of two brands to 24 healthy human volunteers

The most important objective of bioequivalence testing is to assure the safety and efficacy of generic formulations. When two formulations of the same drug are equivalent in the rate and extent to which the active drug becomes available to the site of drug action, they are bioequivalent and thus considered therapeutically equivalent [24]. To demonstrate bioequivalence certain limits should be set depending on the nature of drug, patient population, and clinical end points. It is generally accepted that for basic pharmacokinetic characteristics, such as *AUC* and C_{max}, the standard equivalence range is 0.8–1.25 [20].

The mean and standard deviation of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the two formulations did not differ significantly, suggesting that the blood profiles generated by Tensotin are comparable to those produced by Tenormin. Analysis of variance (ANOVA) for these parameters, after log-transformation of the data, showed no statistically significant difference between the two formulations either in periods, formulations or sequence, with p value greater than 0.05. The 90% confidence intervals also demonstrated that the ratios of AUC_{0-t}, $AUC_{0-\infty}$ or C_{max} of the two formulations lie within the FDA acceptable range of 80%–125%.

For T_{max} the parametric point estimate of difference (test–reference) was 0.55 h, within the acceptance limits ($\pm$ 20% of reference mean).

Blood levels may be used as surrogate parameters for clinical activity; therefore the data of this study, by providing appropriate statistical

Table 1. Pharmacokinetic/statistical analysis of atenolol 100 mg tablets (mean $\pm$ standard deviation, n=24)

Pharmacokinetic parameter	Tensotin (test)	Tenormin (reference)	Statistical analysis	
			ANOVA	90% CI
AUC_{0-t} (ng/ml.h)	6732.83 $\pm$ 1748.42	5963.14 $\pm$ 1355.91	0.0181 (0.8868)	103.96–120.47%
$AUC_{0-\infty}$ (ng/ml.h)	7130.16 $\pm$ 1752.92	6384.43 $\pm$ 1342.46	0.0267 (0.7734)	103.84–117.99%
C_{max} (ng/ml)	748.92 $\pm$ 204.44	672.29 $\pm$ 177.68	0.0725 (0.3731)	101.02–122.19%
T_{max} (h)	3.35 $\pm$ 1.57	2.80 $\pm$ 1.61		
$T_{1/2}$ (h)	8.08 $\pm$ 1.29	7.86 $\pm$ 1.24		
λ_Z (/h)	0.09 $\pm$ 0.02	0.09 $\pm$ 0.01		

Parenthesis values indicate analysis for periods.

results, suggest equal clinical efficacy of the two brands of atenolol.

Conclusion

Based on the statistical results it can be concluded that Tensotin®, manufactured by Gulf Pharmaceutical Industries, UAE is bioequivalent to Tenormin®, manufactured by Zeneca, UK and that both products can be considered equally effective in medical practice.

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