THE COMPARATIVE BIOEQUIVALENCE STUDY OF A GENERIC (Dynormin from Dynapharm (M) Sdn Bhd) AND THE PROPRIETARY (Tenormin from AstraZeneca) 50 MG ATENOLOL TABLET IN HEALTHY HUMAN VOLUNTEERS

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Methodology

This study was carried out in accordance with the principles of ICH and Malaysia Good Clinical Practice (GCP), the EC and Malaysian Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

This is a single-dose, blinded, randomised, two-way crossover study (2 treatments, 2 periods & 2 sequences) with a one-week washout period involving 16 healthy volunteers under fasting conditions. The subjects, research physicians and analysts are blinded – the drug allocation is known by the principal investigator and study co-ordinator. 16 healthy volunteers (10 males, 6 females) age of (mean, range) 27, 22-45 years, weight of (mean, range) 59.7, 50.2-74.8 kg and BMI of (mean, range) 20.6, 19.0-26.1 were enrolled into this study.

Atenolol concentration was measured in blood plasma using Agilent 1100 Series High Performance Liquid Chromatography (HPLC) method developed by Info Kinetics Sdn Bhd. This method was validated to demonstrate adequate sensitivity, specificity, linearity, recovery, accuracy and precision (inter and intra-assay variability).

Statistical Procedures

Standard descriptive statistics were used for the demographic data and derived pharmacokinetics parameters such as Kel and $t_{½}$. Analysis of variance and 90% confidence interval for the mean of "test/reference" ratio of pharmacokinetics parameters such as Cmax and $AUC_{0-\infty}$, were carried out with and without $\log_{10}$ transformation. As Tmax is a discrete variable dependent on the selected blood sampling times, a nonparametric statistical method (Wilcoxon Signed Ranks test) was used. The $t_{½}$ was tested using t-test. All tests were considered significant if $p < 0.05$ at $\alpha = 0.05$ following two-tailed distribution.

Results

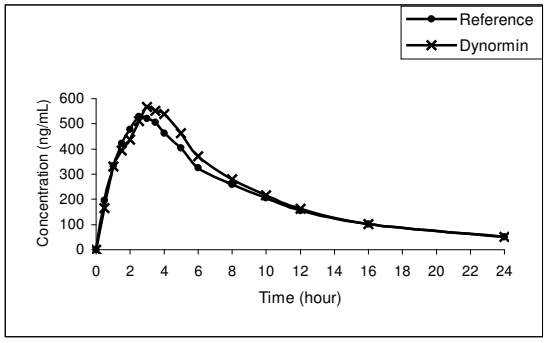

Figure 1

Figure 1 shows the plot of mean plasma atenolol concentration for both test and reference products.

	Dynormin(T)	Reference(R)
Cmax (ng/mL)	257.19	224.09
Cmax Ratio (T/R)	114.4	
90%CI Log_{10} Cmax	**70.8 – 129.2**	
$AUC_{0-\infty}$ (ng.h/mL)	2204.42	2074.81
$AUC_{0-\infty}$ Ratio (T/R)	107.0	
90%CI Log_{10} $AUC_{0-\infty}$	**97.2 – 117.8**	

Table 1. Cmax & AUC Results

The mean values for Cmax and $AUC_{0-\infty}$ are presented in Table 1. Their respective test / reference (T/R) ratio and the 90% Confidence Intervals are also presented.

The time to maximum concentration, Tmax and half life (t ½) of Dynormin and reference product were not statistically significant.

For Cmax, the US FDA accepted range is 80-125% for transformed Cmax. The EC EMEA guidelines allow a wider range of 75-133% for transformed Cmax, whilst the WHO guidelines require 70-143% for transformed Cmax. All the three guidelines require 80-125% for transformed AUC respectively.

The statistical power for the ANOVA was >84% for log_{10}Cmax. The Anderson-Hauck probability outside 75-133% was $p < 0.06$, indicating that the probability of a value not within 80-125% was 6 in 100. This probability is higher than the conventionally accepted probability of 5 in 100, and therefore indicating less than 95% of the products fall within 80-125%. However, the difference was small i.e. only 0.01.

The statistical power for the ANOVA was above 96% for log_{10} $AUC_{0-\infty}$. The Anderson-Hauck probability outside 80-125% was $p < 0.007$, indicating that the probability of a value not within 80-125% was 7 in 1000. This probability is lower than the conventionally accepted probability of 5 in 100, and therefore indicating more than 95% of the products fall within 80-125%.

No serious or unexpected adverse events were reported or observed during the entire study. Both treatments were well tolerated and the overall clinical safety was good. 20 non-serious adverse events (AEs) were reported during the study. From this total, 1 AE was likely to be due to the study drug, another 5 AEs have a "possible" causal relationship with the drug and the other 14 AEs were not caused by the drug.