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Pharmacokinetics and Comparative Bioavailability of Two Metoprolol Tablet Preparations

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ABSTRACT

The bioavailability of a generic preparation of metoprolol (Beatrolol®) was evaluated in comparison with a proprietary product (Betaloc®). Twelve healthy volunteers participated in the study conducted according to a two-way crossover design. The bioavailability was compared using the parameters, total area under the plasma level–time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), and time to reach peak plasma concentration (T_{max}). No statistically significant difference was observed between the values of the two products in all three parameters. Moreover, the 90% confidence interval for the ratio of the logarithmic transformed $AUC_{0-\infty}$ values of Beatrolol over those of Betaloc was found to lie between 0.93 and 1.07, which is within the acceptable equivalence limit of 0.80–1.25. From the data obtained, it also appeared that a relatively high proportion of our volunteers were poor metabolizers of metoprolol. The mean elimination half-life ($t_{1/2}$), was found to be relatively larger than those reported in the literature. Furthermore, the mean volume of distribution (V_d), was also calculated to be larger than those of other studies where the drug was administered intravenously. This can be explained by the high first-pass metabolism of metoprolol when given orally, as employed in our study.

INTRODUCTION

Metoprolol is a selective β_1-adrenergic antagonist with no intrinsic sympathomimetic activity (1,2) and is widely used to treat essential hypertension (3) and angina pectoris (4). Though metoprolol is almost completely absorbed following oral administration, the systemic availability is only approximately 50%, because of first-pass metabolism (5,6). Plasma metoprolol concentrations may vary considerably between individuals, due to genetically determined differences in the metabolism of the drug (7).

As metoprolol is popularly prescribed, many formulations are available commercially. Therefore, information regarding their bioavailability would be useful to the prescriber, in order that the appropriate product could

be selected for use. In the present study, the bioavailability of a new tablet formulation of metoprolol (Beatrolol) produced locally was investigated, in comparison with an established proprietary product, Betaloc. An attempt was also made to study the pharmacokinetic behavior of metoprolol in the local volunteers.

MATERIALS AND METHODS

Products Studied

The metoprolol preparations were:

- Beatrolol tablets, 100 mg (Upha Pharmaceutical Manufacturing, Malaysia), batch no.: 1013, manufacturing date: 6/93, expiry date: 6/97, registration no.: PBKD/870063.
- Betaloc tablets, 100 mg (Astra, Sweden), batch no.: SG 719C, manufacturing date: 7/92, expiry date: 8/95, registration no.: PBKD/870064.
- Metoprolol tartrate reference standard and atenolol (internal standard) were obtained from the National Pharmaceutical Control Bureau of Malaysia.

In Vivo Study Design

The study was approved by an Ethics Committee on Bioavailability Studies. Twelve healthy adult male volunteers between 22 and 40 years old and weighing from 52 to 82 kg, participated in the study after providing written informed consent. All were judged to be healthy and were not taking any medication during the study. The volunteers were randomly divided into two groups of six each and administered the preparations according to the following schedule:

Group (6 volunteers/group)	Period I	Period II
1	Betaloc	Beatrolol
2	Beatrolol	Betaloc

On the first trial period, the volunteers in group I were each given 1 tablet (100 mg) of Betaloc; those of group 2, 1 tablet (100 mg) of Beatrolol. After a washout period of 1 week, each volunteer then received the other product. Both products were administered in the morning (9:00 a.m.) after an overnight fast, with 150 ml of water. Food and drinks were withheld for at least 2 hr after dosing. Lunch and dinner, comprising chicken with rice, were served at 3 hr and 9 hr after dosing, and water was given ad libitum. Blood samples of 5 ml volume were collected in vacutainers (containing sodium heparin as anticoagulant) at 0 (before dosing), 1/2, 1, 1-1/2, 2, 3, 4, 6, 8, 10, 14, 18, and 24 hr after dosing. An indwelling cannula was used for drawing the blood. The blood samples were centrifuged for 15 min at 2000 *g* and the plasma, was transferred to separate glass containers and kept frozen until analysis.

Analysis for Plasma Levels of Metoprolol

Plasma levels of metoprolol were analyzed using a high-performance liquid chromatographic (HPLC) method reported by Buhring and Garbe (8), with slight modification. The HPLC system consisted of a Jasco PU-980 Pump, a Jasco 821-FP Spectrofluorometer, and a Rheodyne 7125 injection valve equipped with a 50-µl sample loop and a Hitachi D-2500 Chromato-Integrator. The spectrofluorometer was operated at an excitation wavelength of 225 nm and an emission wavelength of 300 nm. A LiChrosorb® Si-60 (5 µm, 125 × 4 mm internal diameter) column fitted with a refillable guard column was used for the chromatographic separation. The mobile phase comprised acetonitrile, distilled water, and 1 M ammonium phosphate buffer (pH 4) in a proportion of 5:90:5. Analysis was run at a flow rate of 1.0 mL/min.

Prior to analysis, the drug was extracted from the plasma using the following procedure: a 0.5-ml aliquot of plasma was accurately measured into a 10-ml glass tube with a Teflon-lined cap, followed by the addition of 50 µl of 1 µg/ml atenolol internal standard solution, 0.1 ml of 1 M sodium hydroxide solution, and 5 ml of dichloromethane as the extracting solvent. After mixing for 20 min, the mixture was centrifuged at 3000 rpm for 10 min. Approximately 4.5 ml of the extracting solvent was then pipetted off into a 5-mL reactivial, heated at 40°C, and evaporated to dryness under a gentle stream of nitrogen.

The residue was washed with *n*-hexane to remove lipophilic contaminants before injecting onto the HPLC column. This was carried out by first reconstituting the residue with 100 µl of 1 M acetic acid, followed by the addition of 3 ml of *n*-hexane. The mixture was vortexed for 5 min and the organic layer discarded. Any remaining *n*-hexane was removed in a stream of nitrogen. Finally, 50 µl of the reconstituted sample was injected into the column.

A standard curve was prepared by spiking drug-free plasma with a known amount of metoprolol tartrate at

a concentration range of 25–400 ng/ml. Recovery of the extraction procedure, accuracy, within-day, and between-day precision studies ($N = 6$) were performed using these plasma. The average recovery values for metoprolol and atenolol (internal standard) were 84.7% ($SD = 5.1\%$) and 86.5% ($SD = 5.7\%$), respectively. The within-day coefficient of variation was found to be 4.2% at 25 ng/ml, 6.6% at 50 ng/ml, 2.8% at 100 ng/ml, 2.3% at 200 ng/ml, and 2.0% at 400 ng/ml; whereas the percent error values for these concentrations were 2.7%, 4.5%, 5.6%, 1.5%, and 3.2%, respectively. On the other hand, for between-day assay, the coefficient of variation values for these concentrations were 6.8%, 7.0%, 6.2%, 6.6%, and 6.0%, respectively; and the percent error values were 3.1%, 4.2%, 2.9%, 3.6%, and 4.0%, respectively. The detector response was linear over a concentration range of 10–400 ng/ml and the detection limit of the method was approximately 2 ng/ml.

Data Analysis

The two preparations were compared using the parameters, total area under the plasma concentration–time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), and time to reach peak plasma concentration (T_{max}). The C_{max} and T_{max} were obtained directly from the plasma concentration data (9), while $AUC_{0-\infty}$ was obtained by adding the area from time zero to the last sampling time (AUC_{0-t}) and the area from the last sampling time to infinity ($AUC_{t-\infty}$). The former was calculated using the trapezoidal formula, and the latter by dividing the concentration of the last sampling time with the elimination rate constant, k_e. In all cases, the $AUC_{t-\infty}$ was less than 20% of $AUC_{0-\infty}$. The k_e value was estimated from the terminal slope of the plasma concentration versus time plot through logarithmic transformation of the concentration values and application of linear regression (10). In addition, the apparent volume of distribution (V_d) of the drug was also calculated as $Dose/(AUC_{0-\infty} \cdot k_e)$ and the elimination half-life ($t_{1/2}$), calculated from the quotient $\ln 2/k_e$. For each of the parameters, $AUC_{0-\infty}$, C_{max}, k_e, $t_{1/2}$, and V_d, the values obtained for the two products were analyzed statistically using an analysis of variance procedure (ANOVA) which distinguishes effects due to group, subjects/group, period, and treatment (11). The $AUC_{0-\infty}$ and C_{max} values were logarithmic transformed prior to the analysis. On the other hand, the T_{max} values of the two preparations were compared using the Wilcoxon signed-rank test for paired samples.

RESULTS AND DISCUSSION

The mean plasma concentration versus time profiles of metoprolol obtained with Betaloc and Beatrolol are shown in Figure 1. It can be seen that relatively wide intersubject variation in plasma levels was observed for both products, which can be attributed to differences in drug disposition and body weight among the volunteers. However, the two plots are almost superimposable. Both products achieved rapid absorption, producing peak plasma concentrations at approximately 1.5 hr after dosing, and no lag time in absorption was observed. Table 1 shows the individual values of $AUC_{0-\infty}$, C_{max}, and T_{max} obtained with Betaloc and Beatrolol. The parameters T_{max}, and $AUC_{0-\infty}$, are related to the rate and extent of absorption respectively, while C_{maxs} is related to both processes (12). The extent of absorption is a key characteristic of a drug formulation, and therefore the $AUC_{0-\infty}$ is an important parameter for analysis in a comparative bioavailability study. However, the other two parameters, namely T_{max} and C_{max}, are also important features of the plasma level profile that are related to the therapeutic use of many drugs (13) and hence are also considered in the present analysis.

When the parameters obtained with the two products were analyzed using the ANOVA procedure, no statistically significant difference was observed between the values of Betaloc and Beatrolol for all three parameters ($p = 0.5006$ for C_{max} , 0.0640 for T_{max}, and 0.8150 for $AUC_{0-\infty}$). In addition, the 90% confidence interval for the ratio of the logarithmic transformed $AUC_{0-\infty}$ values of Beatrolol over those of Betaloc was calculated to lie between 0.93 and 1.07. This is within the acceptable

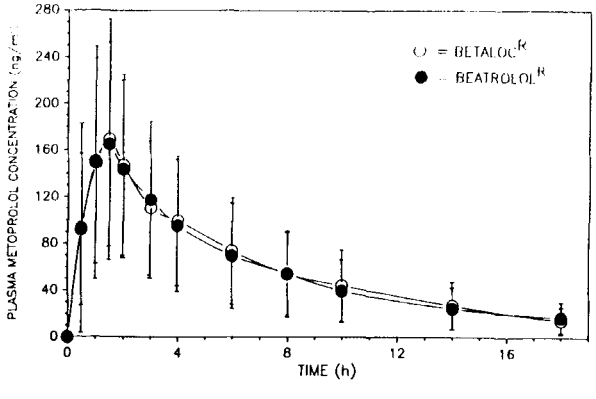

Figure 1. Mean plasma metoprolol concentration versus time profiles after administration of Betaloc and Beatrolol. Mean ± *SD*, $N = 12$.

Table 1

Individual C_{max}, T_{max} and $AUC_{0-\infty}$ Values of Betaloc and Beatrolol

	Betaloc			Beatrolol		
Subject	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0-\infty}$ (hr · ng/ml)	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0-\infty}$ (hr · ng/ml)
1	230.5	2.0	2219.8	213.0	3.0	2286.8
2	88.9	1.5	721.4	76.6	2.0	885.2
3	140.6	2.0	1198.7	221.4	1.5	1559.4
4	72.0	2.0	476.6	91.6	1.0	483.8
5	366.4	1.5	1923.8	296.0	1.5	2139.2
6	164.8	1.0	708.4	104.5	1.5	546.3
7	101.0	2.0	724.3	104.6	1.5	751.7
8	344.3	1.0	2453.2	311.4	1.0	2555.2
9	166.0	1.5	820.3	164.7	1.0	855.4
10	258.8	1.5	1993.8	271.9	1.5	1752.7
11	125.0	1.0	676.2	102.6	1.0	547.9
12	135.0	1.5	583.7	114.3	1.0	575.8
Mean	182.8	1.5	1208.4	172.7	1.5	1245.0
SD	97.0	0.3	725.0	86.3	0.7	221.6
CV%[a]	53.5	23.1	60.0	49.9	46.2	20.1

[a]CV: coefficient of variation.

bioequivalence interval of 0.80–1.25 (14,15). On the basis of the results obtained from the above analysis, it can be concluded that the two products are comparable in both the rate and extent of absorption.

The numerical values of the parameters k_e, $t_{1/2}$, and V_d obtained from the two products are given in Table 2. As would be expected, the values obtained from the two products were closely similar and not significantly

Table 2

Individual k_e, V_d and $t_{1/2}$ Values of Betaloc and Beatrolol

	Betaloc			Beatrolol		
Subject	k_e (hr^{-1})	V_d (liters/kg)	$t_{1/2}$ (hr)	k_e (hr^{-1})	V_d (liters/kg)	$t_{1/2}$ (hr)
1	0.1307	6.3	5.3	0.1307	6.0	5.3
2	0.1012	18.0	6.9	0.1277	10.4	5.4
3	0.1035	13.4	6.7	0.1003	10.0	6.9
4	0.2498	12.7	2.8	0.2595	11.4	2.7
5	0.1288	7.1	5.4	0.1257	6.4	5.5
6	0.1462	14.2	4.7	0.1175	21.6	5.9
7	0.1331	13.1	5.2	0.1355	11.7	5.1
8	0.1278	6.8	5.4	0.1244	6.3	5.6
9	0.1910	11.3	3.6	0.1670	11.7	4.2
10	0.1245	7.4	5.6	0.1244	7.9	5.6
11	0.1811	12.9	3.8	0.1623	16.8	4.3
12	0.2157	13.9	3.2	0.1836	15.8	3.8
Mean	0.1528	11.4	4.9	0.1466	11.3	5.0
SD	0.0464	3.8	1.4	0.0426	4.8	1.0
CV%[a]	30.37	33.4	12.2	29.06	42.9	20.1

[a]CV: coefficient of variation.

different statistically ($p > 0.05$). The $t_{1/2}$ values were found to vary widely between 2.7 and 6.9 hr, but a majority of the volunteers (about two-thirds) have a value of greater than 5 hr. This may explain the larger mean value observed in our study, compared to those of Regardh et al. (16) and Sandberg et al. (17), who obtained a mean of 3.2 and 3.5 hr, respectively. In the study of Sandberg et al. (17), only 2 of the 10 volunteers were found to have a $t_{1/2}$ value of greater than 5 hr, whereas all 5 volunteers in the study of Regardh et al. (16) have a value of less than 4 hr.

Although a value of as high as 9.5 hr has been obtained by Regardh and Johnsson (18), they also observed that, in the majority of healthy volunteers, the $t_{1/2}$ was between 2.5 and 5 hr. Those with a larger $t_{1/2}$ value can be classified as poor metabolizers of metoprolol (17) and may be phenotyped according to that for debrisoquine and sparteine (19). Thus, it appears that our study group has a high proportion of poor metabolizers of metoprolol, compared to the other workers, and this may be attributed to the ethnic differences of the volunteers among the studies. In view of its wide usage and the therapeutic implications involved, this may necessitate further studies to better characterize the metabolic patterns of our local population.

On the other hand, the mean V_d value of approximately 11.4 liters/kg obtained in our study, is very much larger (more than twice) than those obtained by Regardh et al. (16) and Sandberg et al. (17), where the drug was administered intravenously. This discrepancy can be explained by the difference in the route of drug administration employed by the other workers. Although metoprolol is completely absorbed from the gastrointestinal tract (16), only approximately 50% of the oral dose reaches the systemic circulation because of presystemic elimination (5,6). Since this was not taken into consideration during our computation of the V_d using the relationship, $Dose/AUC_{0-\infty} \cdot k_e$, the value obtained can be expected to be much larger than that obtained from studies in which metoprolol was administered intravenously.

CONCLUSION

In summary, Beatrolol was found to be comparable to Betaloc in both the rate and extent of absorption. It was also observed that a high proportion of our volunteers, who are of Asian origin, appeared to be poor metabolizers of metoprolol. Furthermore, the apparent volume of distribution was calculated to be relatively larger than those of other studies in which the drug was administered intravenously.

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