Drug Development and Industrial Pharmacy, 24(10), 955–959 (1998)

RESEARCH PAPER

Pharmacokinetic and Bioequivalent Study of a Generic Metoprolol Tablet Preparation

Kah-Hay Yuen, Kok-Khiang Peh, Kit-Lam Chan, and Weng-Tuck Toh

School of Pharmaceutical Sciences University of Science Malaysia 11800 Penang, Malaysia

ABSTRACT

A study was conducted to compare the in vivo bioavailability of a generic metoprolol tablet preparation (Metoprolol®) with that of the innovator product, Betaloc®. Both preparations have a labeled dose of 100 mg metoprolol tartrate. Twelve healthy adult male volunteers participated in the study, which was conducted according to a standard two-way crossover design with a washout period of 1 week. The bioavailability was compared using the total area under the plasma level versus 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 logarithmically transformed $AUC_{0-\infty}$ values or the logarithmically transformed C_{max} values of the two preparations. However, a statistically significant difference was observed between the T_{max} values, but may not be therapeutically significant or important. Moreover, the 90% confidence interval (CI) for the ratio of the logarithmically transformed $AUC_{0-\infty}$ values of Metoprolol over those of Betaloc was calculated to be between 0.94 and 1.02, while that of C_{max} was between 0.98 and 1.01, both of which are within the acceptable limit of 0.80–1.25. From the data obtained, it was also observed that a high proportion of our volunteers of Asian origin appeared to be poor metabolizers of metoprolol, which was consistent with what had been observed in our previous study of another preparation of metoprolol.

INTRODUCTION

Metoprolol® is a selective β_1-adrenergic antagonist widely used in the treatment of essential hypertension (1) and angina pectoris (2). Its systemic availability is only approximately 50% because of high first-pass metabolism (3,4), and plasma concentrations vary considerably between individuals due to genetically determined differences in metabolism (5).

Because metoprolol is widely prescribed, many formulations are available commercially. We have previ-

ously demonstrated the bioequivalence of a local product of metoprolol with that of the innovator product Betaloc® (6). It was also observed that a high proportion of our local Asian volunteers appeared to be poor metabolizers of metoprolol. The present study was conducted to evaluate the bioavailability of another locally produced tablet formulation, of metoprolol tartrate (Metoprolol), with that of Betaloc. As in our previous study (6), an attempt was made to study the pharmacokinetics of metoprolol in our local volunteers.

MATERIALS AND METHODS

Products Studied

Metoprolol tablets, 100 mg (batch no: 12P42) were from Raza Pharmaceutical Manufacturing, Bangi, Malaysia and Betaloc tablets, 100 mg (batch no: SG 719C) were from Astra, Sodertalje, Sweden. Metoprolol tartrate and atenolol (internal standard) reference standards 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 of the University of Science Malaysia. Twelve healthy adult male volunteers between 22 and 42 years old and weighing from 52 to 84 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 protocol used was a conventional, two-way, split group crossover study with six subjects in each of the treatment groups. In the first trial period, the volunteers in group 1 were each given one tablet (100 mg) of Betaloc, whilst those in group 2 were given one tablet (100 mg) of Metoprolol. 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 drink 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 libitem. Blood samples of 5 ml volume were collected in Vacutainers tubes (containing sodium heparin as anticoagulant) at 0 (before dosing), 0.5, 1, 1.5, 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 2,000 × 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 with a high-pressure liquid chromatographic (HPLC) method described previously (6).

Data Analysis

The two preparations were compared using the parameters of total area under the plasma concentration-vs.-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} values were obtained directly from the plasma-concentration data (7), 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 with the trapezoidal formula while the latter was calculated by dividing the concentration at the last sampling time by 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-vs.-time plot, through logarithmic transformation of the concentration values and application of linear regression (8). 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 ($t_{1/2}$), was calculated from the quotient of $\ln 2/k_e$. 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 (ANOVA) procedure that distinguishes effects due to group, subjects per group, period of treatment, and treatment (9). The $AUC_{0-\infty}$ and C_{max} values were logarithmically transformed prior to the analysis. On the other hand, the T_{max} values of the two preparations were compared with the Wilcoxon's signed-rank test for paired samples.

RESULTS AND DISCUSSION

Figure 1 shows the mean plasma metoprolol concentration profiles obtained with Betaloc and Metoprolol. Both profiles appeared closely similar and are typical of that for conventional fast-release tablet formulations. Absorption was rapid, achieving peak plasma concentrations within approximately 1.5 hr after dosing. Relatively wide intersubject variation was also observed in the profiles of both products, attributable to differences in drug disposition and body weight among the volunteers.

The individual numerical values of the parameters $AUC_{0-\infty}$, C_{max}, and T_{max} obtained with the two preparations

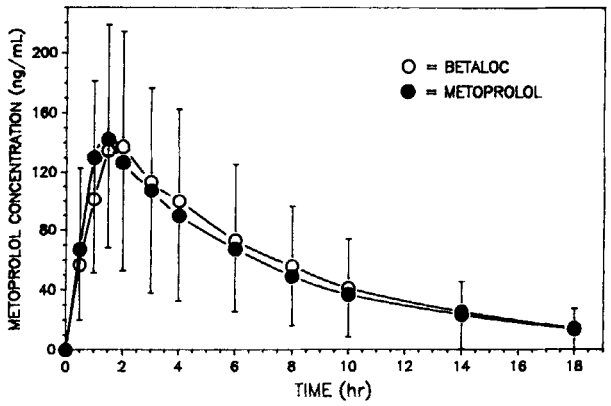

Figure 1. Mean plasma metoprolol concentration vs. time profiles after administration of Betaloc and Metoprolol. Mean ± SD, $N = 12$.

are given in Table 1. The parameters T_{max} and $AUC_{0-\infty}$, are related to the respective rate and extent of drug absorption, while C_{max} is related to both of these two processes (10), with all three measures being useful for comparing the bioavailability of the two preparations. When they were analyzed with the ANOVA procedure described previously, no statistically significant difference was observed between the logarithmically transformed $AUC_{0-\infty}$ values ($p = 0.9378$) or the logarithmically transformed C_{max} values ($p = 0.7337$) of the two preparations. However, a statistically significant difference was observed between the T_{max} values ($p = 0.0342$) of the two products when analyzed with Wilcoxon's signed-rank test, although the slight difference (1.7 hr for Betaloc and 1.4 hr for Metoprolol) may not be therapeutically significant or important. Moreover, the 90% confidence interval (CI) for the ratio of the logarithmically transformed $AUC_{0-\infty}$ values for Metoprolol over those of Betaloc was calculated to be between 0.86 and 1.10, while that of C_{max} was between 0.89 and 1.12, both of which are within the acceptable bioequivalence interval of 0.80–1.25 (11,12). Therefore, on the basis of the above analysis, the two products can be considered bioequivalent.

The intrasubject variation of the parameters $AUC_{0-\infty}$ and C_{max} was estimated by calculating the respective coefficient of variation (CV), using the mean square error obtained from the ANOVA procedure (13). For both parameters, the CV appeared relatively small, with values of 16.8% and 15.7%, respectively. From the CV values, the power of the test procedure ($1 - \beta$) in detecting a 20% difference in the parameter values of the two products at a type 1 error rate (α) of 0.05 was estimated to be greater than 80% in both cases when the number of subjects used was 12 (7). This is consistent with the power estimated from the results of our previous study with another product of metoprolol (6).

The numerical values of the pharmacokinetic parameters k_e, $t_{1/2}$ are given in Table 2. No statistically significant difference was observed between the values of the two

Table 1

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

	Betaloc			Metoprolol		
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	101.0	2.0	694.2	104.6	1.5	694.7
2	86.6	2.0	500.9	113.8	1.0	607.4
3	265.5	2.0	2110.9	224.3	1.5	1868.7
4	136.1	1.5	1026.3	135.5	1.0	748.1
5	91.1	1.0	484.6	140.0	1.5	758.22
6	267.6	1.5	2558.0	300.5	1.0	2632.6
7	96.4	2.0	524.4	73.9	1.0	551.5
8	96.2	3.0	765.0	82.3	2.0	587.3
9	68.7	1.5	317.7	94.0	1.5	400.1
10	161.4	1.0	1104.5	115.8	1.5	896.2
11	326.5	1.5	2129.7	296.2	2.0	2060.6
12	125.9	1.5	882.7	102.5	1.5	657.6
Mean	151.9	1.7	1091.6	148.6	1.4	1038.6
SD	85.9	0.7	751.7	80.0	0.4	723.3

Table 2

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

	Betaloc			Metoprolol		
Subject	k_e (hr^{-1})	V_d (L/kg)	$t_{1/2}$ (hr)	k_e (hr^{-1})	V_d (L/kg)	$t_{1/2}$ (hr)
1	0.1335	12.8	5.2	0.1372	12.5	5.1
2	0.2413	13.6	2.9	0.2305	11.7	3.0
3	0.1204	6.5	5.8	0.1264	6.9	5.5
4	0.1330	10.9	5.2	0.1562	12.8	4.4
5	0.1850	15.9	3.7	0.1559	12.1	4.4
6	0.1178	6.0	5.9	0.0898	7.7	7.7
7	0.1776	17.3	3.9	0.2062	14.2	3.4
8	0.0957	16.3	7.2	0.1153	17.5	6.0
9	0.2184	17.2	3.2	0.2124	14.0	3.3
10	0.1251	12.1	5.5	0.1593	11.6	4.4
11	0.1597	5.9	4.3	0.1630	6.0	4.3
12	0.1583	11.9	4.4	0.1577	16.1	4.4
Mean	0.1555	12.2	4.8	0.1591	11.9	4.7
SD	0.0440	4.2	1.3	0.0409	3.5	1.3

products for any of the three parameters. In addition, the values were comparable to those obtained in our previous study with another generic preparation of metoprolol (6).

An interesting observation, common to both of our studies, was the high variability of the $t_{1/2}$ values obtained, which ranged from 2.9 to 7.7 hr with a mean 4.8 hr in the present study, and from 2.7 to 6.9 hr with a mean 5.0 hr in the previous study (6). Both mean values were larger than those obtained by Sandberg et al. (14) and Regardh et al. (15), who reported mean $t_{1/2}$ values of 3.5 and 3.2 hr, respectively. The larger values that we obtained were due to the high proportion of our volunteers, namely 6 of 12 in the present and 8 of 12 in the previous study (6), who had $t_{1/2}$ values of more than 5 hr, and who may be classified as poor metabolizers of metoprolol (14)—a quality that can be phenotyped in the same way as for debrisoquine and sparteine (16). In comparison, only 2 of the 10 volunteers used in the study by Sandberg et al. (14) had a $t_{1/2}$ value of more than 5 hr, while all 5 volunteers in the study of Regardh et al. (15) had values of less than 4 hr.

Four volunteers participated in both of our studies, where three consistently had $t_{1/2}$ values of more than 5 hr and one had a value below 5 hr. Thus, of the total of 20 volunteers used in our two studies, 11 were found to be poor metabolizers of metoprolol. In view of the high percentage (more than 50%) of poor metabolizers observed in our study group of Asian origin, more studies may need to be done to better characterize the metabolic patterns of metoprolol in Asian populations since there may be a need to revise the dose used for poor metabolizers of the drug.

CONCLUSION

In summary, the generic preparation of metoprolol (Metoprolol) investigated in our study was found to be comparable to Betaloc in the extent of its absorption, but exhibited a marginally faster absorption rate, which may not be therapeutically important or significant. It was also observed that a high proportion of our volunteers of Asian origin appeared to be poor metabolizers of metoprolol, in accord with our findings in an earlier study.

REFERENCES

1. J. I. S. Robertson, Drugs, 25(Suppl. 2), 11 (1983).
2. L. G. Ekelund, A. G. Olsson, L. Oro, et al, Br. Heart J., 38, 155 (1976).
3. G. Johnsson, C. G. Regardh, and L. Solvell, Acta Pharmacol. Toxicol., 36(Suppl. 1.V), 31 (1975).
4. L. Jordo, P. O. Attman, M. Aurell, L. Johansson, G. Johnsson, and C. G. Regardh, Clin. Pharmacokinet., 5, 169 (1980).

5. M. S. Lennard, J. H. Silas, S. Freestone, and J. Trevethick, Br. J. Clin. Pharmacol., 14, 301 (1982).
6. K. H. Yuen, K. L. Chan, W. T. Toh, K. K. Peh, H. H. Ang, and B. L. Ong, Drug Dev. Ind. Pharm., 22(4), 329 (1996).
7. D. L. Weiner, in *Statistics in the Pharmaceutical Industry* (C. R. Buncher, J. Y. Tsay, eds.), Marcel Dekker Inc., New York, 1981, p. 205.
8. M. Gibaldi and D. Perrier, *Pharmacokinetics*, 2nd Ed, Marcel Dekker Inc., New York, 1982, p. 145.
9. J. G. Wagner, in *Fundamentals of Clinical Pharmacokinetics*, 1st Ed., Drug Intelligence Publications, Inc., Hamilton, IL, 1975, p. 285.
10. A. Grahnen, Pharm. Int., 5, 100 (1984).
11. W. J. Westlake, in *Biopharmaceutical Statistics for Drug Development*, (K. E. Peace, ed.), Marcel Dekker Inc., New York, 1988, p. 329.
12. W. J. Westlake, Biometrics, 32, 741 (1976).
13. E. Diletti, D. Hauschke, and V. W. Steinijans, Int. J. Clin. Pharmacol. Ther. Toxicol., 29, 1 (1991).
14. A. Sandberg, B. Abrahamsson, and J. Sjogren, Int. J. Pharm., 68, 167 (1991).
15. C. G. Regardh, K. O. Borg, R. Johansson, G. Johnsson, and L. Palmer, J. Pharmacokinet. Biopharm., 2, 347 (1974).
16. D. W. J. Clark, Drugs, 29, 342 (1985).