Drug Development and Industrial Pharmacy, 23(1), 15–18 (1997)

RESEARCH PAPER

In Vivo Bioavailability of a Multiparticulate Matrix Sustained-Release Theophylline Preparation Under Fed and Fasted Conditions

Kok-Khiang Peh and Kah-Hay Yuen

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

ABSTRACT

The in vivo bioavailability of a novel multiparticulate matrix sustained-release theophylline preparation was compared under fed and fasted conditions. Twelve healthy volunteers participated in the study conducted according to a randomized, two-way crossover design. The parameters used for the comparison were: total area under the serum concentration–time curve ($AUC_{0-\infty}$), time to reach peak serum concentration (T_{max}), and peak serum concentration (C_{max}). No statistically significant difference was observed between the fed and fasted logarithmic transformed values of $AUC_{0-\infty}$ and C_{max}, as well as the fed and fasted values of T_{max}. In addition, the 90% confidence interval for the ratio of logarithmic transformed $AUC_{0-\infty}$ values of the fed condition over those of the fasted was calculated to lie between 0.90 and 1.04, which is within the bioequivalence limit of 0.80–1.25. These findings indicate that both the rate and extent of absorption of the novel preparation were not significantly affected by food, although a lag time in absorption was observed in the fed condition.

INTRODUCTION

The in vivo bioavailability of some sustained-release theophylline products was found to be affected by food, the effect being more pronounced with fat-rich diets (1). Both the rate and extent of absorption have been shown to be reduced (2). Some products, however, only exhibited a decrease in the rate but not the extent of absorption (3,4). A more serious effect of food was observed when both the rate and extent of absorption were increased due to dose dumping (5).

In our previous single- and multiple-dose studies (6,7), the in vivo performance of a novel multiparticulate matrix sustained-release theophylline preparation was found satisfactory when dosed after an overnight fast. In view of the variable effects of food, the

present study was thus conducted to evaluate the bioavailability of the preparation under fed and fasted conditions. The preparation comprised spherical pellets of 1.18–1.70 mm diameter, formulated from a mixture of microcrystalline cellulose, glyceryl monostearate, and anhydrous theophylline in a ratio of 4:6:10 (8).

MATERIALS AND METHODS

Study Design

The study protocol was approved by an ethics committee. Twelve healthy nonsmoking adult male volunteers between 29 and 43 years old, and weighing from 49 to 78 kg, participated in the study after providing written informed consent. The protocol used was a conventional, two-way, split groups, crossover study with six subjects in each of the two treatment groups. The volunteers were randomized to receive the preparation (equivalent to 250 mg theophylline) after a 12-hr overnight fast, or immediately after a standard breakfast comprising 2 slices of toasted white bread with butter, 2 fried eggs, 2 strips of bacon, 60 g of hash-browned potatoes, and 200 ml of whole milk (9). After a 1-week wash-out period, they were then dosed under the alternate food condition. Food and drinks were withheld for at least 4 hr after dosing. Alcohol and xanthine-containing food or beverages were forbidden 24 hr before and during both study periods. Blood samples of 5-ml volume were taken from the volunteers at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 18, 24, 30, and 36 hr after drug dosing. After clot retraction, the serum was separated and kept frozen until analysis. Analysis was performed using a reversed-phase high-performance liquid chromatographic method described previously (6).

Data Analysis

The bioavailability results under the fed and fasted conditions were compared using the peak serum concentration, C_{max}, time to reach peak serum concentration, T_{max}, and total area under the serum concentration–time curve, $AUC_{0-\infty}$. Whenever necessary, the T_{max} values were corrected for a lag time of absorption, T_{lag}, estimated by extrapolating the initial ascending portion of the individual serum concentration–time curves to the time axis. In addition, the elimination rate constant, k_e, elimination half-life, $t_{1/2}$, and the apparent volume of distribution, V_d, were also estimated from the individual fed and fasted serum curves. The fed and fasted values of $AUC_{0-\infty}$, C_{max}, k_e, $t_{1/2}$, and V_d were compared using an analysis of variance procedure appropriate for the study design (10). The $AUC_{0-\infty}$ and C_{max} values were logarithmic transformed prior to analysis. On the other hand, the T_{max} values were compared using a Wilcoxon signed-rank test for paired samples.

RESULTS AND DISCUSSION

The mean fed and fasted serum theophylline concentration–time curves of the novel preparation are shown in Fig. 1. Both curves are reflective of a slow and sustained rate of drug absorption. A lag time in absorption was, however, observed when the preparation was dosed with food but not when dosed fasted, resulting in a shift of the fed serum curve to the right. Yuen et al. (11) also reported similar findings with their theophylline pellets. However, the profiles of the two curves were essentially similar, indicating a comparable rate of drug absorption. Moreover, no dose dumping was observed in any of the individual serum profiles in the fed mode.

Table 1 shows the fed and fasted values of T_{lag}, T_{max}, C_{max}, and $AUC_{0-\infty}$, obtained with the preparation. No statistically significant difference was observed between the fed and fasted logarithmic transformed values of $AUC_{0-\infty}$ ($p = 0.472$) and C_{max} (P = 0.540), or between the fed and fasted values of T_{max} ($p = 0.125$). In addition, the 90% confidence interval for the ratio of the logarithmic transformed $AUC_{0-\infty}$ values of the fed condition over those of the fasted was calculated to lie between 0.90 and 1.04, which is within the bioequivalence

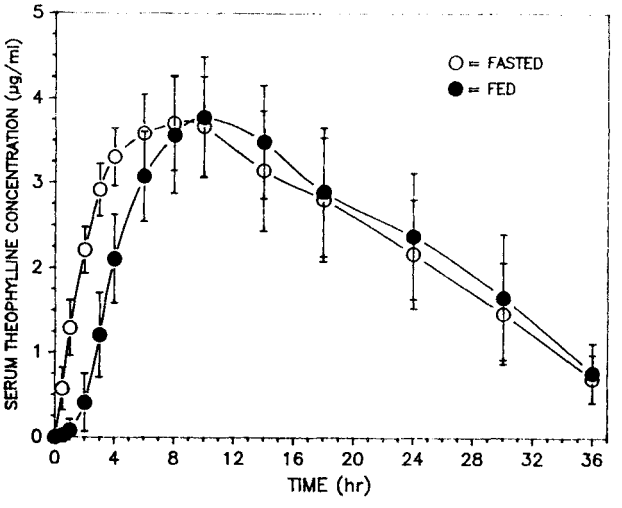

Figure 1. Mean serum theophylline concentration versus time curves of the novel preparation under fed and fasted conditions. Mean ± *SD*; $N = 12$.

Table 1

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

	Fed				Fasted		
Subject	T_{lag} (hr)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (hr·μg/ml)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (hr·μg/ml)
1	1.9	8.1	4.00	106.45	6.0	4.23	89.66
2	0.8	9.2	3.80	106.20	10.0	3.50	99.01
3	2.2	7.8	2.35	52.41	6.0	2.90	59.91
4	—	10.0	3.66	110.02	8.0	3.97	120.02
5	0.9	9.1	4.22	127.47	10.0	4.34	136.59
6	1.7	12.3	3.75	83.08	8.0	4.65	95.90
7	1.7	8.3	5.07	113.46	8.0	3.95	104.58
8	2.8	7.2	4.77	115.48	10.0	4.41	98.60
9	1.7	8.3	3.65	108.51	8.0	4.02	104.51
10	0.7	9.3	3.29	64.51	8.0	3.51	80.65
11	1.3	12.7	3.67	91.30	10.0	4.31	111.54
12	1.1	8.9	3.76	67.97	8.0	3.11	68.94
Mean	1.4	9.3	3.83	95.57	8.3	3.91	97.49
SD	0.8	1.7	0.69	23.56	1.4	0.54	21.13

limit of 0.80–1.25 (12). These findings indicate that both the rate and extent of absorption of the novel preparation were not significantly affected by food, although a lag time in absorption was observed. The delay in absorption may be attributed to a prolonged gastric residence time of the novel preparation in the fed condition. This has been observed by Yuen et al. (11) through monitoring the gastrointestinal transit behavior and absorption of their theophylline pellets using gamma scintigraphy.

Foods such as charcoal-broiled meat (13) and those rich in protein (14) have been reported to increase the elimination rate of theophylline. In view of such dietary influence, it was necessary to evaluate the disposition of theophylline under the two different food conditions used in the present study, as any change in the drug disposition will affect the analysis of the bioavailability data.

Table 2 shows the numerical values of k_e, $t_{1/2}$, and V_d obtained under the fed and fasted conditions. The fed

Table 2

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

	Fasted			Fed		
Subject	k_e (hr^{-1})	$t_{1/2}$ (hr)	V_d (liter/kg)	k_e (hr^{-1})	$t_{1/2}$ (hr)	V_d (liter/kg)
1	0.0871	8.0	0.5928	0.0605	11.5	0.7189
2	0.0593	11.7	0.6911	0.0624	11.1	0.6184
3	0.0758	9.1	0.7541	0.0942	7.4	0.6927
4	0.0636	10.9	0.4199	0.0613	11.3	0.4752
5	0.0613	11.3	0.4090	0.0609	11.4	0.4412
6	0.0740	9.4	0.5504	0.0803	8.6	0.5855
7	0.0647	10.7	0.7540	0.0748	9.3	0.6012
8	0.0643	10.8	0.6464	0.0695	10.0	0.5106
9	0.0808	8.6	0.4699	0.0600	11.6	0.6095
10	0.0891	7.8	0.4701	0.0949	7.3	0.5518
11	0.1212	5.7	0.2760	0.1241	5.6	0.3291
12	0.1078	6.4	0.4485	0.1012	6.9	0.4841
Mean	0.0791	9.2	0.5402	0.0787	9.3	0.5515
SD	0.0195	2.0	0.1502	0.0208	2.1	0.1100

and fasted values of all three parameters were essentially similar and not significantly different statistically (p = 0.917 for k_e, 0.789 for $t_{1/2}$, and 0.703 for V_d). Therefore, a valid comparison could be made between the bioavailabilities under the two different food conditions.

CONCLUSION

The rate and extent of drug absorption of the novel preparation were essentially unaffected by food, although a lag time in absorption was observed. The delay in absorption could be attributed to a prolonged gastric residence time of the novel preparation when taken with food. In addition, the disposition of theophylline was not significantly affected by the different food conditions.

ACKNOWLEDGMENT

The authors would like to thank Ho Yan Hor Company, Malaysia, for its support in providing some of the materials used in the study.

REFERENCES

1. H. Tada, M. Ishikawa, E. Sato, T. Suzuki, K. Unno, K. Miura, Y. Ohmiya, and K. Nakai, J. Clin. Pharm. Ther., 14, 145 (1989).
2. A. Karim, T. Burns, L. Wearmer, J. Streicher, and M. Palmer, Clin. Pharmacol. Therapeutics, 38, 77 (1985).
3. S. L. Spector, A. S. Rohr, G. S. Rachelefsky, R. M. Kartz, S. C. Siegel, J. Wo, and V. Gracey, J. Allergy Clin. Immunol., 75, 105 (1985).
4. L. Hendeles and M. Weinberger, J. Allergy Clin. Immunol., 78, 743 (1986).
5. G. Milavetz, L Vaughan, M. Weinberger, J. Harris, and T. Mullenix, J. Allergy Clin. Immunol., 77, 146 (1986).
6. K. K. Peh and K. H. Yuen, Drug Dev. Ind. Pharm., 22(4), 351 (1996).
7. K. K. Peh and K. H. Yuen, Drug Dev. Ind. Pharm., 22(11), 1133 (1996).
8. K. K. Peh and K. H. Yuen, Drug Dev. Ind. Pharm., 21(13), 1545 (1995).
9. J. P. Skelly, Division Guidelines for the Evaluation of Controlled Release Products, Division of Biopharmaceutics, Food and Drug Administration, 1984.
10. J. G. Wagner, in *Fundamentals of Clinical Pharmacokinetics*, 1st ed., Drug Intelligence, Hamilton, IL, 1975, p. 285.
11. K. H. Yuen, A. A. Deshmukh, J. M. Newton, M. Short, and R. Melchor, Int. J. Pharm., 97, 61 (1993).
12. W. J. Westlake, in *Biopharmaceutical Statistics for Drug Development* (K. E. Peace, ed.), Marcel Dekker, New York, 1988, p. 329.
13. A. Kappas, A. P. Alvares, K. E. Anderson, E. J. Pantuck, C. B. Pantuck et al., Clin. Pharmacol. Ther., 23, 445 (1978).
14. K. E. Anderson and A. Kappas, in *Sustained Release Theophylline in the Treatment of Chronic Reversible Airways Obstruction* (Jonkman et al., eds.), Excerpta Medica, Amsterdam, 1984, p. 83.