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COMMUNICATION

Comparative Bioavailability Study of Two Controlled-Release Pentoxifylline Tablet Preparations

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ABSTRACT

The bioavailability of a generic preparation of pentoxifylline sustained-release (SR) tablet was evaluated in comparison with a proprietary product (Trental 400®). For the study, 12 healthy male volunteers participated; the study was conducted according to a randomized, 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. The 90% confidence interval for the ratio of the logarithmic transformed* $AUC_{0-\infty}$ *values of the generic pentoxifylline over those of Trental 400 was found to lie between 0.83 and 1.00, while that of the parameter* C_{max} *was between 0.91 and 1.29. In addition, elimination half-life* $t_{1/2}$ *and apparent volume of distribution* V_d *were calculated. There was no statistically significant difference between the* $t_{1/2}$ V_d *values obtained from the data of the two preparations.*
Key Words: *Bioavailability; Controlled release; Pentoxifylline.*

INTRODUCTION

Pentoxifylline is a xanthine derivative used as a hemorrheologic agent for the treatment of peripheral arterial disease (1) and intermittent claudication (2). It reduces blood viscosity and increases erythrocyte flexibility (2). Pentoxifylline has a short elimination half-life and is completely absorbed following oral administration. Therefore, a sustained-release (SR) dosage form of pentoxifylline was formulated to avoid the necessity of frequent dosing.

Pentoxifylline has a low and variable systemic avail-

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ability. This is due to the fact that pentoxifylline undergoes extensive metabolic transformation intrahepatically and extrahepatically (3). Following oral administration of pentoxifylline sustained-release tablet, the absolute bioavailability was found to be 19% (4).

In the present study, the bioavailability of a new sustained-release tablet formulation of pentoxifylline produced locally was investigated in comparison with an established proprietary product, Trental 400®.

EXPERIMENTAL

Materials

The pentoxifylline preparations were pentoxifylline SR tablets, 400 mg (CCM Pharma, Malaysia), batch PTX 09, manufacturing date May 1997; Trental tablets, 400 mg (Quimica Hoechst, Mexico), batch 96F0518A, manufacturing date July 1996, expiry date July 1998; pentoxifylline standard was obtained from Chemagis Limited (Israel); and chloramphenicol (internal standard) was obtained from the U.S. Pharmacopeia.

Methods

In Vivo Study Design

For the in vivo study, there were 12 healthy male volunteers between 32 and 46 years old and weighing from 55 to 78 kg. They participated in a standard two-period, two-sequence crossover study after providing written informed consent. All were judged healthy and were not receiving any medication during the study period. The volunteers were divided randomly into two groups of 6 each.

For the first trial period, each volunteer in group 1 was given 1 tablet of Trental 400, while those of group 2 were given 1 tablet of pentoxifylline SR. After a washout period of 1 week, each volunteer then received the alternate product. All products were administered in the morning (10:00 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 (chicken with rice) were served at 3 hr and 9 hr after dosing. Blood samples of 5 ml volume were collected in vacutainers (containing sodium heparin as an anticoagulant) at 0 hr (before dosing), 20 min, and 40 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 14, 18, and 24 hr after dosing via an in-dwelling cannula placed in the forearm. The blood samples were centrifuged for 15 min at 2000*g*, and the plasma was transferred to separate glass containers to be kept frozen until analysis.

The protocol for the study was approved by the Joint School of Pharmaceutical Sciences, University of Science Malaysia, General Hospital Penang Committee on Bioavailability Studies. Volunteers were given information on the drug and the nature of the study in advance of the trial.

Plasma Pentoxifylline Concentration Analysis

The plasma samples were analyzed using a reversed-phase high performance liquid chromatographic (HPLC) method described by Wong et al. (5).

Data Analysis

The pharmacokinetic parameters peak plasma drug concentration C_{max}, time to reach peak plasma concentration T_{max}, and total area under the plasma drug concentration-time curve $AUC_{0-\infty}$ were estimated from the plasma concentration-time profiles of the two preparations for each volunteer. The values of C_{max} and T_{max} were obtained directly from the measured plasma concentration data (6). The $AUC_{0-\infty}$ was calculated by adding the area from time zero to the last sampling time t (AUC_{0-t}) and the area from time t to infinity ($AUC_{t-\infty}$). The former was calculated using the trapezoidal rule, and the latter by dividing the last measurable plasma drug concentration by the elimination rate constant k_e. In all cases, the $AUC_{t-\infty}$ was found to be less than 20% of the $AUC_{0-\infty}$. The k_e was estimated from the terminal slope of the individual plasma concentration-time curves after logarithmic transformation of the serum concentration values and application of linear regression (7). On the other hand, the elimination half-life $t_{1/2}$ was calculated from the quotient $\ln 2/k_e$, while the apparent volume of distribution V_d was calculated as dose/(AUC · k_e). For each of the parameters $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and V_d, the values obtained for the two products were analyzed statistically using analysis of variance (ANOVA), which distinguishes effects due to group, subjects/group, period, and treatment (8). 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 profiles of mean plasma concentration versus time of pentoxifylline obtained with pentoxifylline SR and

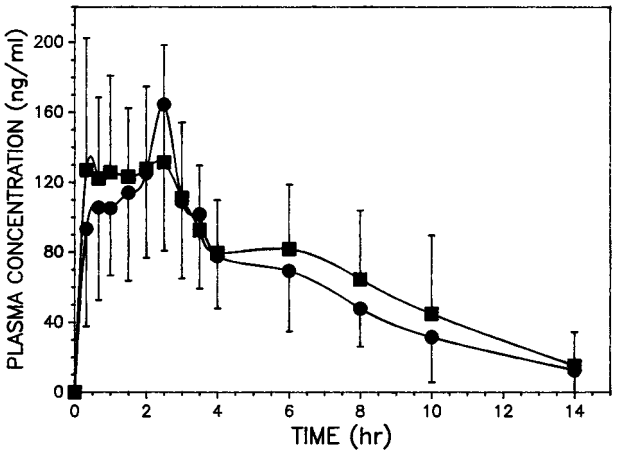

Figure 1. Profiles of mean plasma pentoxifylline concentration versus time of ● Pentoxifylline SR and ■ Trental 400 (mean ± SD, $N = 12$).

Trental 400 are shown in Fig. 1. It can be inferred from Fig. 1 that both products showed a slow and sustained rate of drug absorption, and the two profiles obtained were on the whole quite similar in nature. In both cases, there was an initial rapid increase in plasma drug concentrations indicative of initial rapid drug absorption. However, this was then followed by a relatively sustained plasma concentration, reaching a peak approximately 3 hr after dosing. Thereafter, the plasma drug concentration declined gradually.

The individual numerical values of $AUC_{0-\infty}$, C_{max}, and T_{max} obtained with pentoxifylline SR and Trental 400 are given in Table 1. The parameters T_{max} and $AUC_{0-\infty}$ are related to the rate and extent of absorption, respectively, while C_{max} is related to both processes (9). 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, T_{max} and C_{max}, are also important features of the plasma level profile that are related to the therapeutic use of many drugs (10) and hence are also considered in the present analysis.

Referring to Table 1, it can be seen that Trental 400 achieved a slightly higher mean $AUC_{0-\infty}$ value than pentoxifylline SR, but had a slightly lower mean C_{max} value than the latter. However, no statistically significant difference was observed between the logarithmically transformed $AUC_{0-\infty}$ ($p = .1128$), as well as the logarithmically transformed C_{max} ($p = .4071$) values of the two preparations. The sequences (or group) effects were not statistically significant for both preparations, indicating that there was no significant treatment-by-period interac-

Table 1

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

	Trental 400			Pentoxifylline SR		
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	115.79	3.0	638.85	156.48	2.5	649.12
2	140.80	2.5	1021.98	301.37	2.5	1414.08
3	181.18	3.5	1440.97	260.00	2.5	1251.99
4	180.99	2.0	2175.42	199.97	2.5	1762.40
5	119.28	2.0	575.11	142.81	2.0	679.13
6	291.18	0.3	997.32	179.44	0.3	714.99
7	121.68	2.0	877.08	107.35	2.5	713.17
8	289.65	2.5	1202.14	197.38	2.5	906.29
9	75.87	3.5	833.46	79.98	3.5	818.99
10	117.16	2.5	577.66	95.36	2.5	516.85
11	224.13	2.5	1808.23	266.06	2.5	1611.45
12	145.21	2.0	790.03	194.07	2.0	639.01
Mean	166.91	2.4	1078.19	181.69	2.3	973.12
SD	69.43	0.8	502.14	69.92	0.7	423.87
CV%	41.60	33.33	46.57	38.48	30.43	43.56

Table 2

Individual Numerical Values of $t_{1/2}$ *and* V_d

	Trental 400		Pentoxyfylline SR	
Subject	$t_{1/2}$ (hr)	V_d (L/kg)	$t_{1/2}$ (hr)	V_d (L/kg)
1	3.54	3.19	3.36	2.99
2	1.00	0.56	6.14	2.51
3	2.28	0.91	2.48	1.14
4	3.72	0.99	5.01	1.64
5	1.83	1.83	1.95	1.66
6	2.96	1.71	2.94	2.37
7	2.88	1.89	3.94	3.19
8	2.18	1.05	2.33	1.49
9	5.13	3.55	5.50	3.88
10	3.54	3.54	2.60	2.90
11	3.72	1.19	3.69	1.32
12	1.63	1.19	2.30	2.07
Mean	2.87	1.80	3.52	2.26
SD	1.14	1.06	1.38	0.85
CV%	39.72	58.83	39.20	37.68

tion. The T_{max} values of the two preparations were also not significantly different ($p > .05$) when analyzed using the Wilcoxon signed rank test.

In addition, the 90% confidence interval for the ratio of the logarithmically transformed $AUC_{0-\infty}$ values of pentoxifylline SR over those of Trental 400 were calculated to lie between 0.83 and 1.00, which is within the acceptable bioequivalence interval of 0.80–1.25 (11). In the case of C_{max}, the 90% confidence interval was between 0.91 and 1.30, with the higher end being slightly above the 1.25 limit, but this is acceptable. Furthermore, the parameter C_{max} has an inherently greater variability compared to $AUC_{0-\infty}$, and a recommended bioequivalence range of 0.70 and 1.30 has been cited in the literature (12). Thus, on the basis of the results obtained from the above analysis, it can be considered that the two products are bioequivalent in their rate and extent of absorption.

Relatively wide intersubject variation was observed in the values of the parameter $AUC_{0-\infty}$, which could be attributed to differences in body weight and drug disposition among the volunteers. However, the intrasubject variation, estimated using the mean square error obtained from the ANOVA analysis (13), appeared to be small, with a coefficient of variation (CV) value of approximately 13.3%. Based on this value, the number of 12 volunteers used in the study was found sufficient to provide a power ($1 - \beta$) of greater than 80% for concluding a bioequivalence between the $AUC_{0-\infty}$ values of the products at a type 1 error rate α of 0.05 if the true difference is equal to or less than 20% (13).

The numerical values of the parameters $t_{1/2}$ and V_d obtained from the two products are given in Table 2. The values obtained with the two products were similar. No statistically significant difference was observed between the $t_{1/2}$ ($p = .1743$) or the V_d ($p = .0541$). The $t_{1/2}$ values were found to vary widely between 1.00 and 6.20 hr, but a majority of the volunteers had a value between 2.0 and 4.0 hr that was consistent with those reported by Beerman et al. (4), who obtained a mean $t_{1/2}$ value of 3. 43 hr.

CONCLUSION

In summary, the pentoxifylline SR was found to be comparable to Trental 400 in both the rate and extent of absorption. The $t_{1/2}$ values obtained were found comparable to those reported in the literature.

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