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INFLUENCE OF FOOD ON THE BIOAVAILABILITY OF TRENTAL® (PENTOXIFYLLINE) IN MAN

R. J. Wills, E. S. Waller, S. K. Puri,[1] I. Ho,[1] and G. J. Yakatan[2]

Drug Dynamics Institute
College of Pharmacy
University of Texas
Austin, Texas 78712

[1]Hoechst-Roussel Pharmaceuticals, Inc.
Somerville, N. J. 08876

[2]Warner-Lambert Company
Pharmaceutical Research Division
Ann Arbor, Michigan 48105

ABSTRACT

Pentoxifylline is an investigational drug shown to improve impaired blood flow in diseased microvasculature. The present study objective was to determine the influence of a single test meal on the bioavailability of pentoxifylline. Single 400 mg oral capsule doses of pentoxifylline were administered to 16 healthy adult male volunteers in a complete crossover design in which the subjects received the drug after fasting overnight or 15 minutes

following a standard breakfast. The plasma concentrations of pentoxifylline and its major metabolite were determined as a function of time using a gas chromatographic procedure. The AUC values for both parent drug and metabolite for 0 to 10 hours showed no significant difference due to ingestion of food. A significant decrease in peak plasma concentration ($p < .05$) was shown for parent drug and metabolite when administered with food. The time-to-peak concentration was significantly delayed ($p < .001$) when the drug was administered with food. Food administered concomitantly with pentoxifylline delays absorption and lowers peak plasma concentration, although the extent of absorption is not different than when the drug is administered on an empty stomach.

INTRODUCTION

Pentoxifylline (1-[5-oxohexyl]-3,7-dimethylxantnine) has been extensively used abroad to treat patients suffering from cerebrovascular and peripheral vascular disease (1-4). In a recent biomedical profile (5), efficacy was reported to be based on hemorheological effects of improving local hyperviscosity, hyperaggregability of red blood cells and platelets, erythrocyte fluidity and hypercoagulability.

Pentoxifylline has been shown to be rapidly and completely absorbed after oral administration in rats, dogs and humans, 96, 101 and 98% respectively (6). The elimination half-life for pentoxifylline was reported to be 1.0 hr. in humans (6). Pentoxi-

fylline is highly metabolized with 94% of the total drug being eliminated in the urine (6,7). The major metabolite in blood (metabolite I) is 1-[5-hydroxyhexyl]-3,7-dimethylxanthine (7,8).

The objective of the present study was to determine the influence of food on the bioavailability of pentoxifylline following a single oral dose.

METHODS

Sixteen healthy males, 21 to 30 years of age (mean 25) weighing between 65 and 85 kg (mean 77), who were in good physical condition as determined by physical examination, medical history and clinical laboratory studies, volunteered to participate in the study. Informed consent was obtained from each subject. The protocol had approval of the University Human Investigations Review Committee.

Study Design

Subjects were instructed to take no other drugs or caffeine products for one week prior to and throughout the study. The subjects fasted overnight before each treatment and were permitted to eat no food, apart from the test meal, until four hours after dosing. On the morning of a treatment, each subject drank eight oz. of water on arising, at least one hour before dosing. Single oral doses of 400 mg of pentoxifylline (Trental®, supplied by Hoechst-Roussel Pharmaceuticals, Inc.) were given as two 200 mg capsules on

two separate study days in a complete crossover design. On the first day, eight subjects received the drug on an empty stomach, and eight subjects received drug 15 minutes after eating a standard breakfast. The breakfast consisted of 150 ml of low-fat milk, 100 ml of orange juice, one egg, two slices of toast, 20 gm of margarine, 20 gm of marmalade and 20 gm of cheese. On the second study day, the treatments were reversed. The study days were one week apart. Blood samples (10 ml) were collected from a forearm vein into heparinized vacuum tubes immediately before and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 10 hours after dosing. Plasma was separated and frozen at -20°C until assayed.

Assay

The plasma samples were assayed by a modified gas chromatographic procedure utilizing a nitrogen specific detector (9). Fifteen µl of the internal standard solution (10 µg/ml of 1-[6-hydroxyhexyl]-3-methyl-7-propylaxanthine in 0.01 M hydrochloric acid) was added to 1 ml of plasma. Redistilled dichloromethane (5 ml) and 1 M sodium hydroxide (0.5 ml) were added and the plasma shaken on a mechanical rotary inversion mixer for 15 minutes at 20 r.p.m. The phases were separated by centrifugation at 2000 g for five minutes, and the upper layer carefully aspirated and discarded. The remaining dichloromethane phase was transferred to a tapered tube and evaporated to dryness in a water bath at 40° C under a gentle stream of nitrogen. A freshly prepared solution of 5% v/v

trifluoracetic anhydride in hexane (1 ml.) was added and the residue dissolved with the aid of a vortex mixer. The tube was stoppered and heated in a water bath for five minutes at 60° C. Excess reagent was removed in a gentle stream of nitrogen at 40° C and the residue taken up in HPLC grade toluene (50 µl), aliquots (5 µl) of which were analyzed by GLC.

The analyses were performed on a Varian 3700 gas chromatograph equipped with a nitrogen specific detector. A silanized gas column (2M x 1.75 mm i.d.) packed with 3% OV-25 on Chromosorb W-HP 100/120 mesh) was used for the separation. Other operating parameters were as follows: oven temperature was set at 250° C for six minutes then raised 80° C/min to a final temperature of 270° C; detector temperature was 300° C, carrier gas (He) flow rate was 30 ml/min, hydrogen flow rate was 3.3 ml/min and air flow rate was 100 ml/min. The current to the ceramic bead of the nitrogen detector was set by means of a potentiometer of the control box, the actual setting being dependent upon the age of the bead. Under these conditions, retention times for pentoxifylline, metabolite I and internal standard are 3.2 min., 4.4 min. and 7.24 min., respectively. The concentrations of pentoxifylline and metabolite I were determined by comparison to daily calibration curves obtained by assaying plasma standards in the range of 20 to 100 ng/ml for each compound. Linear calibration curves were obtained by plotting the ratio of the peak area of each compound to the peak area of the internal standard versus concentration of pentoxifylline or meta-

bolite in the plasma standard. Typical curves analyzed by linear least squares regression show correlation coefficients of 0.98 or greater.

Using the methodology above to assay seven sets of standards in the range of 20 to 100 ng/ml, the recovery for pentoxifylline ranged from 97.8 to 104% with a relative standard deviation of 18.8% at 20 ng/ml to 1.4% at 100 ng/ml; the recovery for metabolite I ranged from 96.6 to 104% with a relative standard deviation ranging from 3.5 to 10%. The limit of detection for either compound was approximately 1 ng/ml, although the limit of assay sensitivity was selected as 15 ng/ml.

Data Analysis

Area under the plasma concentration-time curve (AUC) was calculated for both zero to ten hours and zero to infinity using the trapezoidal rule. The AUC_0 included a terminal slope correction factor, C_p^n/k_e, where C_p^n is the last measured concentration-time point and k_e in the slope of the terminal log-linear phase of the semilog plot of concentration *versus* time.

The maximum plasma concentration achieved (C_{pmax}) and time to maximum plasma concentration (t_{pmax}) were observed from the measured plasma concentrations following drug administration.

All statistical evaluations were performed using Student's t-test for paired data. A *p* value of less than 0.05 was accepted as evidence of statistical significance.

RESULTS AND DISCUSSION

Mean plasma concentrations for pentoxifylline and metabolite I are given in Table 1 and the data depicted graphically in Figures 1 and 2. Inspection of the plasma concentration-time curves in Figures 1 and 2 reveals a slower rate of absorption of pentoxifylline, reduced peak plasma concentrations of both the drug and metabolite I, and delayed times-to-peak of both the drug and metabolite I when pentoxifylline is administered with food. These observations are supported by the bioavailability parameters determined for both pentoxifylline and metabolite I as displayed in Table 2. Depending on the therapeutic range of pentoxifylline plasma concentrations, the reduction in peak plasma concentration may be of no clinical consequence. The delay of 1.7 hours in the time-to-peak when the drug is given with food may also be of little clinical significance because of the chronic conditions for which pentoxifylline is given. The areas under the plasma concentration-time curves were not significantly different when pentoxifylline was given with food. The AUC_0^{10} and AUC_0^{∞} were nearly equal, indicating almost complete disappearance of the drug within the duration of the study sampling time. While food significantly slowed the rate of absorption of pentoxifylline, the lack of statistical significance between AUC values indicates food did not change the extent of absorption.

Eight of the 16 subjects experienced side effects. Headache, dizziness and nausea were the most common side effects and occurred more frequently in subjects taking the drug while fasting. Most

TABLE 1

Mean Plasma Concentrations (ng/ml) of Pentoxifylline and Metabolite I After Administration of Pentoxifylline 400 mg PO to Sixteen Healthy Males (Mean ± S.D.)

	PENTOXIFYLLINE		METABOLITE I	
Sampling Time (Hours)	Pentoxifylline without food	Pentoxifylline with food	Pentoxifylline without food	Pentoxifylline with food
0.17	1.1 ± 4.4	0.0	0.0	0.0
0.33	528.1 ± 1153.3	5.2 ± 12.2	129.1 ± 152.4	1.1 ± 4.5
0.50	947.0 ± 950.6	22.6 ± 44.1	760.7 ± 696.3	4.6 ± 13.5
0.75	769.1 ± 681.1	67.1 ± 63.4	1437.9 ± 1363.5	54.8 ± 89.1
1.00	490.5 ± 268.6	134.1 ± 87.3	1521.9 ± 1162.2	146.3 ± 166.7
1.50	371.0 ± 163.6	197.6 ± 129.3	1205.0 ± 701.1	327.5 ± 334.4
2.00	246.9 ± 126.8	286.5 ± 157.7	1013.8 ± 459.0	444.1 ± 224.5
3.00	120.8 ± 76.5	336.0 ± 231.5	620.6 ± 343.6	751.7 ± 472.7
4.00	61.4 ± 41.2	255.2 ± 191.8	316.2 ± 244.3	761.6 ± 613.4
6.00	19.3 ± 18.6	80.3 ± 78.5	60.2 ± 59.5	220.4 ± 161.2
8.00	6.1 ± 9.7	27.8 ± 33.0	10.3 ± 16.2	68.9 ± 58.4
10.00	0.9 ± 3.8	3.0 ± 8.8	1.1 ± 4.4	13.9 ± 28.9

TABLE 2

Mean Bioavailability Parameters for Pentoxifylline and Metabolite I After Pentoxifylline 400 mg PO in Sixteen Healthy Males (Mean ± S.D.)

Pentoxifylline

Parameter	Without Food	With Food	Statistical Significance
Peak Plasma Concentration (ng/ml)	1289.4 ± 1234	433.4 ± 212	$p < 0.05$
Time-to-Peak (hours)	0.84 ± .52	2.55 ± .95	$p < 0.001$
AUC_0^{10} (ng/ml·hr)	1365 ± 784	1340 ± 595	NS
AUC_0^{∞} (ng/ml·hr)	1366 ± 793	1351 ± 638	NS

Metabolite I

Parameter	Without Food	With Food	Statistical Significance
Peak Plasma Concentration (ng/ml)	1841.3 ± 1183	980.0 ± 610	$p < 0.05$
Time-to-Peak (hours)	1.28 ± .53	2.88 ± .79	$p < 0.001$
AUC_0^{10} (ng/ml·hr)	3760 ± 2079	3177 ± 1716	NS
AUC_0^{∞} (ng/ml·hr)	3762 ± 2082	3215 ± 1727	NS

side effects occurring when the drug was given without food presented within 45 minutes of drug ingestion. The time of presentation of side effects correlated well with the individual peak concentrations of pentoxifylline in six subjects.

In summary, the absorption of pentoxifylline is delayed when given with food, although the extent of absorption is not altered.

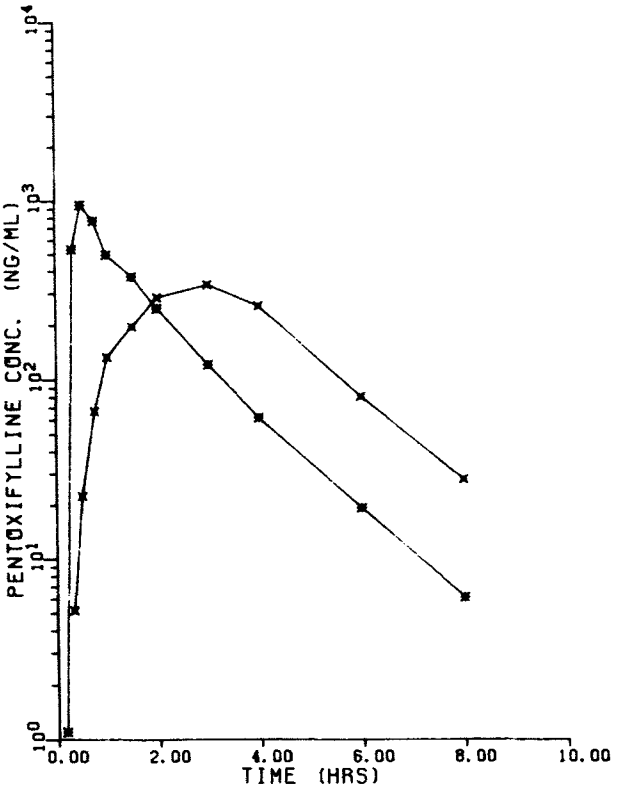

FIGURE 1

Mean Plasma Concentrations of Pentoxifylline Following a 400 mg. Oral Dose of Pentoxifylline with Food (x) and without Food (*) to 16 Healthy Male Volunteers.

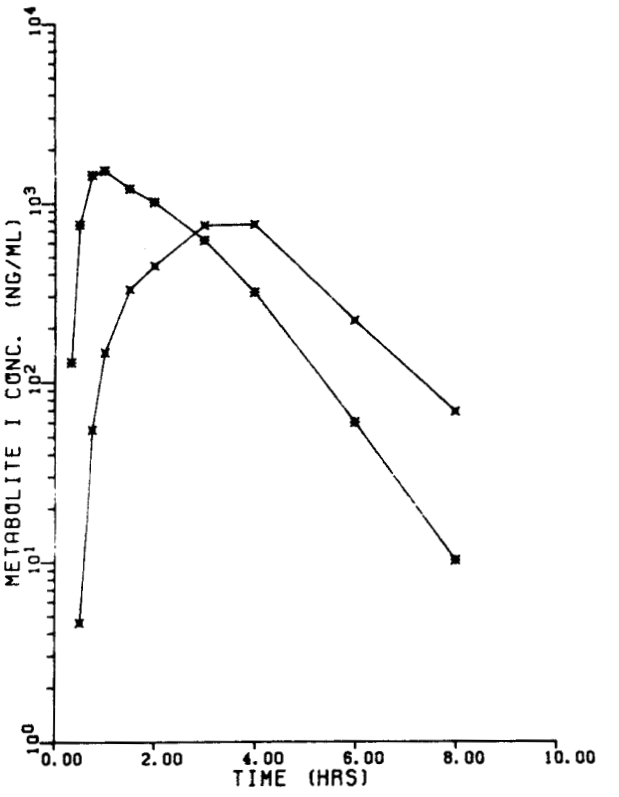

FIGURE 2

Mean Plasma Concentrations of Metabolite I Following a 400 mg. Oral Dose of Pentoxifylline with Food (x) and without Food (*) to 16 Healthy Male Volunteers.

Mean peak plasma concentrations are lowered when the drug is ingested with food. Side effects occur more commonly when pentoxifylline is administered under fasting conditions. If therapeutic efficacy can be maintained with pentoxifylline given with food, an administration schedule with food should be recommended to avoid minor side effects.

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