Plasma Concentrations and Bioavailability of Clofibric Acid from Its Calcium Salt in Humans

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Abstract □ The bioavailability of clofibric acid from formulations containing calcium clofibrate alone and mixed with calcium carbonate (1:1 w/w) was compared to that from a standard clofibrate formulation in a crossover study in 12 human subjects. The 95% confidence intervals of bioavailability differences were such that they were unlikely to be detected in clinical practice; all three formulations may be considered bioequivalent, although the bioavailability rate was probably greater from the formulation containing calcium clofibrate alone. Peaks of mean concentrations of 80 ± 13, 67 ± 16, and 64 ± 18 μg/ml ± *SD* occurred after administration of 853 mg of clofibric acid calcium salt alone, 809 mg of clofibric acid calcium salt mixed with calcium carbonate, and 885 mg of clofibrate, respectively; mean concentrations declined from peak levels with half-lives of 15–17 hr.

Keyphrases □ Clofibric acid—bioavailability from various formulations compared, humans □ Bioavailability—clofibric acid, various formulations compared, humans □ Antihyperlipidemic agents—clofibric acid, bioavailability from various formulations compared, humans

Clofibrate [ethyl 2-(4-chlorophenoxy)-2-methylpropanoate], which is hydrolyzed either during or after absorption to the active form, clofibric acid [2-(4-chlorophenoxy)-2-methylpropanoic acid] (1), is an antihyperlipidemic agent effective in the treatment of hyperlipoproteinemias primarily of Fredrickson Types III, IV, and V. Clofibrate also produces an antilipemic effect, mainly by reducing triglyceride levels, in patients with hyperlipoproteinemia of Type IIb (2–4).

Calcium also exerts an antilipemic action by forming insoluble complexes with bile salts and fatty acids within the intestinal lumen. Calcium lowered plasma cholesterol levels and, to some extent, triglyceride levels in patients with hyperlipoproteinemias of Types II and IV (5).

To obtain the benefit of the antilipemic actions of both clofibrate and calcium in patients with the most commonly occurring hyperlipoproteinemias, Types II and IV, a product containing calcium clofibrate and calcium carbonate, in approximately equal proportions, was formulated. In addition to broadening the antilipemic action, this combination provides a convenient solid dosage form as an alternative to the currently available liquid-filled capsule of clofibrate. However, the presence of calcium carbonate in the formulation may change the pH of the gut contents after oral administration (6–8) and affect clofibrate bioavailability. Therefore, plasma levels of the active metabolite, clofibric acid, were measured following administration of capsules containing similar doses of this test formulation, a formulation containing calcium clofibrate alone, and the reference agent, clofibrate.

EXPERIMENTAL

Drug Administration—Twelve healthy subjects, six males and six females, 19–52 years old and 52–87 kg, participated after being informed of the aim of the study and the nature of the drug. Before and after the study, each subject was given a complete physical examination, including routine laboratory screening tests. During the study, the subjects remained under medical supervision.

Each of the three drug formulations was administered with 100 ml of water in a crossover Latin-square design wherein the subjects were grouped by sex. There was a 1-week washout period between doses. Before dosing, the subjects fasted for 12 hr; afterwards, they did not eat or rest for 3 hr. Each subject received doses of 885 mg of clofibric acid as clofibrate (the reference[1] Formulation A), 853 mg as calcium clofibrate alone (Formulation B), and 809 mg as the calcium clofibrate–carbonate combination (1:1 w/w, Formulation C).

Blood samples (5 ml) were collected in tubes containing heparin just before dosing and at 1, 2, 3, 4, 6, 8, 12, 24, 32, and 48 hr after dosing. Plasma was separated and kept frozen until analysis.

Measurement of Plasma Clofibric Acid Levels—Clofibric acid was measured spectrophotometrically at 226 nm after extraction from acidified plasma by isooctane (9). The extraction efficiency (recovery) was 72% in the 10–100-μg/ml concentration range. Plasma clofibric acid levels were calculated by reference to a standard curve constructed by adding known amounts of clofibric acid to untreated human plasma. New standard curves were constructed for each batch of plasma analyzed.

The absorbance of extracts of the predose plasma was subtracted from the absorbance of postdose samples before calculation of clofibric acid concentrations. The precision of the method was such that, with 95% confidence, clofibric acid could be measured within ±6% of the mean of 10 replicate analyses.

Data Processing—Apparent half-lives of drug elimination were calculated by least-squares regression analysis of log concentration against time from measurements during the terminal linear phase of the log concentration–time curves. Areas under the plasma concentration–time curves (scaled to equal doses of 885 mg of clofibric acid) to 48 hr were calculated by the trapezoidal rule. Although areas beyond 48 hr contributed approximately 10% of the total area to infinite time, plasma concentrations at the last sampling time were close to the limit of sensitivity of the analytical method. Areas to 48 hr were linearly related to the total areas ($r = 0.95$), and bioavailability was estimated from the areas to 48 hr. Estimates from the total areas were similar.

Areas, peak plasma concentrations (scaled to equal doses of 885 mg) and times of occurrence, and apparent half-lives of elimination were analyzed by an analysis of variance for crossover designs. The total variance was separated into that due to sex, subjects, day of administration, formulation, and residual.

Table I—Mean Plasma Clofibric Acid Concentrations (Micrograms per Milliliter) after Administration of the Three Formulations

Hours	Clofibrate[a]	Calcium Clofibrate	Calcium Clofibrate–Carbonate Combination
1	19.7 (81.4)[b]	48.4 (49.1)	27.6 (82.5)
2	44.3 (50.8)	69.0 (30.0)	46.9 (41.2)
3	53.8 (43.6)	80.4 (16.8)	58.5 (32.5)
4	62.8 (39.2)	78.2 (13.7)	67.1 (23.8)
6	64.1 (28.9)	72.2 (19.0)	63.6 (25.4)
8	62.7 (18.9)	63.9 (17.7)	59.9 (23.6)
12	54.1 (9.4)	50.5 (18.6)	52.6 (20.4)
24	35.1 (21.1)	29.6 (16.4)	39.9 (20.8)
32	25.3 (18.9)	19.7 (38.9)	26.4 (27.5)
48	9.0 (61.4)	8.3 (57.3)	9.2 (73.4)

[a] Reference formulation. [b] Coefficients of variation (percent) in parentheses.

RESULTS

Plasma Clofibric Acid Levels—Mean concentrations of clofibric acid in plasma after administration of slightly different doses in the three

[1] Atromid-S capsules manufactured by ICI Pharmaceuticals, Macclesfield, England, and marketed in the United States by Ayerst Laboratories, Division of American Home Products Corp., New York, N.Y.

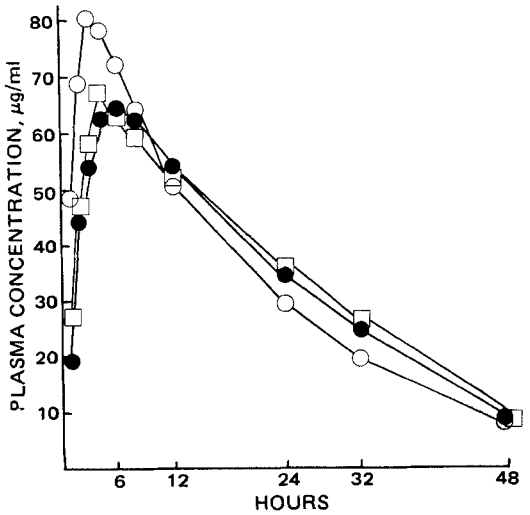

Figure 1—*Plasma clofibric acid concentrations after administration of clofibrate (●), calcium clofibrate (○), and the calcium clofibrate–carbonate combination (■).*

formulations are shown in Table I and Fig. 1. Mean concentrations were similar after administration of Formulation C and the reference Formulation A. Mean concentrations were higher after administration of Formulation B. Peak plasma levels in individual subjects were similar after administration of Formulations A (mean of 71 μg/ml ± 17 *SD*) and C (mean of 73 μg/ml ± 15 *SD*) and higher after Formulation B (mean of 85 μg/ml ● 13 *SD*). Plasma clofibric acid levels were slightly higher than those reported previously (10).

The mean half-life of clofibric acid in plasma after administration of Formulation B (15.4 hr ± 3.0 *SD*) was slightly shorter but not significantly different (Tables II and III) from those after administration of Formulations A and C (17.2 ± 2.0 and 16.9 ± 3.0 hr ± *SD*, respectively). Similar half-lives of 19 and 15–17 hr were reported previously (11, 12).

Bioavailability Parameters—The mean ratio of areas showed that the bioavailability of clofibric acid from Formulations B and C was 101 and 110%, respectively, of that from Formulation A. An analysis of variance of areas showed that formulation-related differences were not significant (Table III). However, subject-related effects were significant ($p < 0.01$), and two male subjects provided consistently higher areas regardless of the formulation administered.

The 95% confidence limits (13, 14) of differences between the mean areas after administration of Formulations B and C were from −10.7 to +13.4 and from +1.2 to +22.9%, respectively, of the mean for Formulation A. Significant formulation-related differences were found for peak plasma concentrations (scaled for equal doses) and their times of occurrence (Tables II and III).

DISCUSSION

Differences in the extent of bioavailability of clofibric acid between formulations containing clofibrate, calcium clofibrate, or the calcium clofibrate–carbonate combination were not statistically significant ($p > 0.05$). Clinical usage is unlikely to detect differences of the orders found, and all three formulations may be regarded as bioequivalent. However, higher plasma clofibric acid levels at earlier times were provided by single doses of calcium clofibrate alone, and the bioavailability rate was probably greatest after administration of this formulation. Differences in bioavailability rates are of less importance with drugs, such as clofibric acid, that are administered chronically to achieve a steady-state plasma level.

The 95% confidence limits of differences in areas under the concentration–time curves indicated that formulation as the calcium salt of clofibric acid had little effect on the extent of drug bioavailability. Clofibrate is almost completely absorbed, 98% of a daily dose of 2 g being excreted in the urine as the free and conjugated acid (12). The *in vivo* performance of the formulations of calcium clofibrate compared favorably with that reported for the basic aluminum salt of the acid, which gave significantly lower plasma levels at all times of sampling after 500-mg doses when tested against four other preparations of clofibrate (11).

Table II—Mean Bioavailability Parameters of Clofibric Acid from the Three Formulations

Parameter	Clofibrate[a]	Calcium Clofibrate	Calcium Clofibrate–Carbonate Combination
Area[b], μg hr/ml	1683 (12)[c]	1706 (18)	1866 (17)
Peak concentrations[b] in individuals, μg/ml	71 (24)	88 (15)	80 (21)
Time of peak concentration, hr	6.3 (48)	3.6 (40)	4.6 (57)
Half-life, hr	17.2 (12)	15.4 (20)	16.9 (18)

[a] Reference formulation. [b] Scaled to equal doses of 885 mg. [c] Coefficients of variation (percent) in parentheses.

Table III—Levels of Significance of Sources of Variation in the Analyses of Bioavailability Parameters

Source of Variation	Parameter: Area	Peak Concentration	Peak Time	Half-Life
Sex	NS[a]	$p < 0.01$	NS	NS
Subjects	$p < 0.05$	NS	NS	NS
Day of administration	NS	NS	NS	NS
Formulation	NS	$p < 0.01$[b]	$p < 0.05$[b]	NS

[a] NS = not significant ($p > 0.05$). [b] The reference Formulation A (clofibrate) was significantly different from B (calcium clofibrate) but not from C (clofibrate–carbonate combination). Formulations B and C were not significantly different.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 2, 1976, from the *Department of Metabolism and Pharmacokinetics, Huntingdon Research Centre, Huntingdon, PE18 6ES, England.*

Accepted for publication January 12, 1977.

The authors express their gratitude to Dr. P. Gooding of the Bristol-Myers Co. International Division, New York, N.Y., for advice and interest. They also thank Dr. C. White for medical supervision of the subjects and Mr. D. Assinder for technical assistance.

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