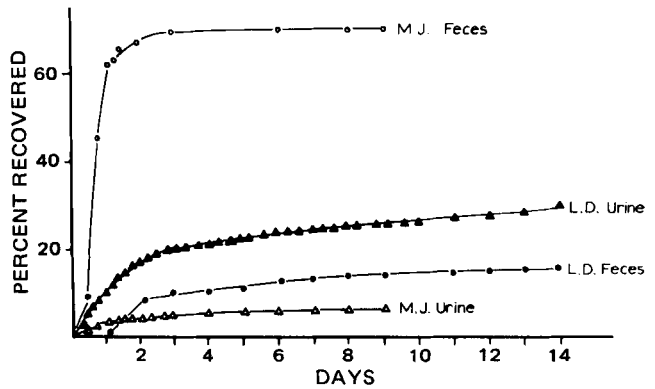

Figure 4—*Cumulative elimination of radioactivity in urine and feces from Subjects LD and MJ.*

lactose formulation, and the areas under the blood level radioactivity curves differed by a factor of four. Furthermore, twice as much radioactivity was excreted in urine as compared to feces in the subject receiving the oil formulation. In the subject receiving the lactose formulation, 12 times as much radioactivity appeared in feces as compared to urine, a likely result of poor absorption.

The data obtained for Subject LD after the initial 2 weeks following drug administration (Fig. 4) suggested that a fraction of the administered radioactivity may have been contained in a deep body compartment from which small amounts were leached out over a prolonged period.

Results of contragestational potency studies in rats employing a 20-mg/ml suspension[2] and the comparative bioavailability studies in rats described in the present report indicated that systemic absorption of biologically effective amounts of I was primarily proportional to the amount of drug in solution at the time of administration. For rats, when the amount of I in the volume of administered sesame oil exceeded the equilibrium solubility of the drug, the expected relationship of systemic absorption and contragestational potency to dose was not maintained.

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Relative Bioavailability of Meprobamate Tablets in Humans

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Received October 11, 1977, from the *Division of Biopharmaceutics and Pharmacokinetics, Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, TN 38163.* Accepted for publication January 12, 1978. *Present address: Clinical Pharmacology Department, A. H. Robins Co., Richmond, VA 23220.

Abstract □ The relative bioavailability of 400-mg meprobamate tablets manufactured by 11 different firms was evaluated in two groups of healthy male subjects. Each group of six subjects received a reference standard product and five test products given at 1-week intervals. Plasma meprobamate concentrations at 1, 2, 3, 4, 6, 8, 10, 24, and 32 hr after dosing were determined using a GLC assay. Analysis of variance of the plasma level–time profiles revealed no statistically significant differences between any of the products in terms of plasma levels at the various sample times, time of peak plasma level, peak plasma level, and area under the plasma level–time curve. It was concluded that the 11 400-mg products could be considered bioequivalent.

Keyphrases □ Meprobamate—bioavailability of 11 commercial products in humans □ Bioavailability—meprobamate, 11 commercial products in humans □ Sedatives—meprobamate, bioavailability of 11 commercial products in humans

At present, there are more than 60 manufacturers or distributors of meprobamate products in the United States. Several groups have evaluated the potential of meprobamate products to exhibit bioavailability inequivalence (1–3). However, the bioavailability of meprobamate from tablets obtained from a variety of manufac-

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Table I—*In Vitro* Test Results for 400-mg Meprobamate Tablets [a]

Product Code Number (Study Group)	Assay, % of Label	Mean Percent Dissolved in 30 min
1 (I, II)	102.7	>77.0
2 (I)	97.1	94.2
3 (I)	100.5	100.5
4 (I)	99.3	78.9
5 (I)	106.0	96.9
6 (I)	100.4	81.8
7 (II)	101.5	89.4
8 (II)	106.0	80.9
9 (II)	100.7	72.0
10 (II)	100.9	70.8
11 (II)	95.8	97.2

[a] Manufacturer and lot number are as follows: 1, Wyeth Laboratories, 1751101; 2, ICN Pharmaceuticals, 9031-4XP; 3, Towne, Paulsen and Co., 047544; 4, Stanley Drug Products, 086503; 5, Smith Kline and French Laboratories, 555134; 6, Heather Drug Co., 57023; 7, Lannett Co., 17288; 8, Zenith Laboratories, 3904-670; 9, Westward, 41682; 10, Wallace Laboratories, 5D1008; and 11, Danbury Pharmacal, 10686. All products were obtained from FDA regional offices.

turers has not been well documented. The present study was undertaken to determine the relative bioavailability of 11 meprobamate tablet products.

EXPERIMENTAL

Assay of Plasma Samples—The measurement of plasma meprobamate levels was based on a GLC method developed by Martis and Levy (4). A 0.4–1.5-ml plasma sample was added to 1.0 ml of 0.15 *N* NaOH and 1.0 ml of a 2.5-μg/ml tybamate internal standard solution. The mixture was extracted for 15 min with 5 ml of ether. After centrifugation, 4 ml of the ether phase was removed, evaporated to dryness, and stored at −18° until analysis.

The residue was dissolved in 15–25 μl of ether, and 2 μl was injected into a gas chromatograph[1] equipped with flame-ionization detectors. Glass U-shaped columns (180 mm × 2.5 mm) were packed with 3% SE-30 on 80–100-mesh Gas Chrom Q. Temperatures were 180, 175, and 250° for the injector, oven, and detectors, respectively. Plasma meprobamate concentrations were determined from standard curves of meprobamate to tybamate peak height ratio *versus* meprobamate concentration, prepared over a meprobamate concentration range of 0.5–5.0 μg/ml, using pooled human plasma.

***In Vitro* Tests**—The USP XIX (5) tablet weight variation, product assay, and dissolution tests were performed[2] on each product. Disintegration times also were determined[2] for eight products.

Meprobamate Products—Table I summarizes the meprobamate products evaluated. Eleven single lots of 400-mg tablets were selected.

Clinical Study Protocol—Twelve male volunteers[3] underwent urine analyses as well as hematologic and blood enzyme analyses[4] to ensure that they were in good health. They ranged in age from 22 to 27 years, in height from 175 to 188 cm, and in weight from 70.5 to 95.5 kg. All subjects were within 10% of the ideal weight for their age, sex, height, and build.

The subjects were divided into two groups of six subjects. Each subject received a single 400-mg tablet once a week for 6 consecutive weeks. The administration sequence was based on a crossover matrix designed to minimize the influence of any residual or cumulative effects of the preceding doses (6). Each subject in each group was administered six different meprobamate products, with only Product 1 being common to both test groups as a reference standard.

Each subject was instructed to adhere to a standard protocol and to abstain from any medication during the study period. The tablets were administered in the morning following an overnight fast. No food or liquid, other than water, was permitted until 4 hr following drug ingestion. Blood samples of 10 ml were collected in heparinized containers prior to the dose and at 1, 2, 3, 4, 6, 8, 10, 24, and 32 hr. The blood samples were centrifuged, and the plasma fraction was removed and frozen until assayed.

Statistical Analysis—Four parameters were examined to evaluate the relative bioavailability of the 11 meprobamate products: plasma levels at each sampling time, time of peak plasma level, peak plasma level, and area under the plasma level–time curve (*AUC*). The data for each group were statistically analyzed for differences between products, subjects, and weeks using the *F* ratio test and the Newman–Keuls *a posteriori* test (7). The power of the study design was calculated (8) for $\alpha = 0.05$ and $\beta = 0.2$.

[1] Varian model 2100.
[2] In the laboratories of the U.S. Food and Drug Administration (FDA).
[3] Staff and students of the University of Tennessee Center for the Health Sciences. Each subject gave written informed consent.
[4] SMA 12/60.

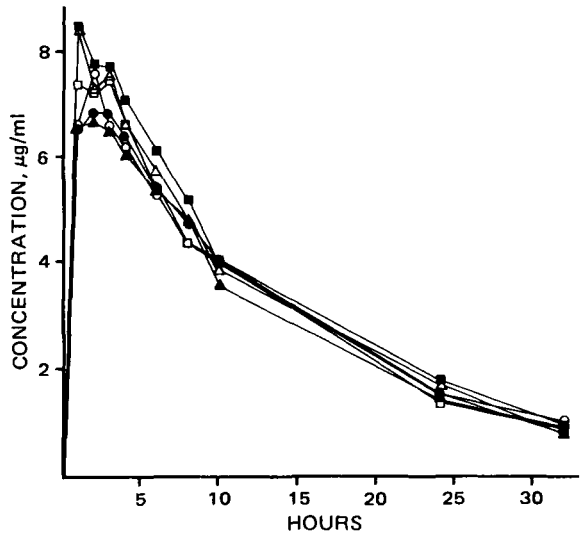

Figure 1—*Mean plasma meprobamate levels for Study Group I. Each data point represents the mean of six subjects. Key: ○, Product 1; ●, Product 2; □, Product 3; ■, Product 4; △, Product 5; and ▲, Product 6.*

RESULTS AND DISCUSSION

***In Vitro* Tests**—Table I summarizes the results of the *in vitro* tests. The meprobamate content of Product 5 (Group I) and Product 8 (Group II) was slightly in excess of the USP XIX (5) limits of 95–105% of labeled content. All 11 products met the USP XIX requirement of 60% dissolution within 30 min, with the mean percent dissolution in 30 min ranging from 71 to 101%. Tablets from eight lots also were tested for disintegration using the USP XIX apparatus. All products tested disintegrated within 5 min.

Plasma Levels—Tables II and III summarize the mean plasma meprobamate levels for each product at each sampling time. These results are shown graphically in Figs. 1 and 2. Analysis of variance for these data indicated no significant differences ($p > 0.05$) among the six products tested in each group in terms of mean plasma levels obtained at each sampling time.

Time of Peak Plasma Level—The mean times of peak plasma meprobamate concentration for the individual products, uncorrected

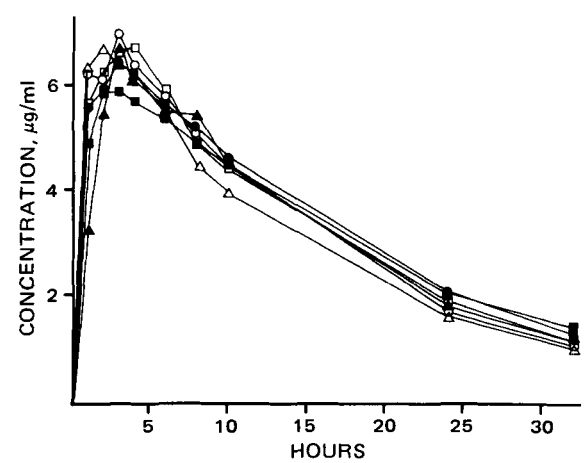

Figure 2—*Mean plasma meprobamate levels for Study Group II. Each data point represents the mean of six subjects. Key: ○, Product 1; ●, Product 7; □, Product 8; ■, Product 9; △, Product 10; and ▲, Product 11.*

Table II—Average Plasma Meprobamate Concentrations [a] of Group I

Product	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	24 hr	32 hr
1	6.68	7.65	6.63	6.25	5.32	4.42	4.03	1.58	1.08
	(20.9)	(7.2)	(7.3)	(12.7)	(14.6)	(11.8)	(14.5)	(23.1)	(17.9)
2	6.60	6.92	6.88	6.45	5.45	4.78	4.10	1.58	0.88
	(19.9)	(15.4)	(13.6)	(5.6)	(13.5)	(27.7)	(22.1)	(21.7)	(46.1)
3	7.48	7.33	7.55	6.73	5.55	4.47	4.13	1.47	1.02
	(12.0)	(18.7)	(14.8)	(18.9)	(28.6)	(32.5)	(29.9)	(38.2)	(36.0)
4	8.57	7.85	7.80	7.17	6.18	5.25	4.05	1.87	1.03
	(27.6)	(27.9)	(19.8)	(15.9)	(15.7)	(11.2)	(31.0)	(32.3)	(42.7)
5	8.50	7.40	7.60	6.67	5.80	4.87	3.93	1.78	0.85
	(19.5)	(24.0)	(19.1)	(21.1)	(19.0)	(25.9)	(27.8)	(39.4)	(41.3)
6	6.65	6.75	6.55	6.12	5.43	4.85	3.65	1.50	0.92
	(33.1)	(18.3)	(24.4)	(19.4)	(15.2)	(27.5)	(28.8)	(36.8)	(48.5)

[a] Average data for six subjects; concentration in micrograms per milliliter. The coefficient of variation in percent is given in parentheses.

Table III—Average Plasma Meprobamate Concentrations [a] of Group II

Product	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	24 hr	32 hr
1	6.25	6.13	7.03	6.43	5.82	5.12	4.52	1.75	1.10
	(45.3)	(39.9)	(37.7)	(27.9)	(22.2)	(21.7)	(17.3)	(32.5)	(28.2)
7	5.62	5.98	6.50	6.28	5.68	5.23	4.68	2.13	1.38
	(36.3)	(32.3)	(23.7)	(19.0)	(22.5)	(17.8)	(27.0)	(26.0)	(37.8)
8	5.70	6.33	6.67	6.77	5.97	4.92	4.42	1.95	1.18
	(41.5)	(37.0)	(32.2)	(22.2)	(26.4)	(35.9)	(40.7)	(35.5)	(19.6)
9	4.90	5.90	5.92	5.73	5.38	4.95	4.43	2.08	1.45
	(43.9)	(32.1)	(21.0)	(26.1)	(25.4)	(39.9)	(49.9)	(42.2)	(50.1)
10	6.40	6.77	6.45	6.33	5.45	4.55	4.00	1.65	1.05
	(33.4)	(21.8)	(24.5)	(26.8)	(28.8)	(28.3)	(27.9)	(38.5)	(30.0)
11	3.27	5.43	6.75	6.20	5.57	5.48	4.57	1.87	1.18
	(28.8)	(33.1)	(27.7)	(26.3)	(17.5)	(22.2)	(19.7)	(31.7)	(36.8)

[a] Average data for six subjects; concentration in micrograms per milliliter. The coefficient of variation in percent is given in parentheses.

for any lag time, are summarized in Table IV. Because the time interval between individual samples was at least 1 hr, the actual peak time may have been overestimated.

In Group I, the time of peak concentration ranged from 1.5 to 2.3 hr. The times of peak concentration in Group II were generally greater, ranging from 1.8 to 3.8 hr. These values are in agreement with other studies that reported peak levels at 1–3 hr after dosing (9). Because of the large coefficient of variation for these mean parameters, no statistically significant differences ($p > 0.05$) were found among products in either test group.

Peak Plasma Level—Table IV summarizes the mean peak concentrations found for the products in each group. These mean levels ranged from 7.4 (Product 6) to 8.9 (Product 4) μg/ml in Group I and from 6.8 (Product 9) to 7.8 (Product 10) μg/ml in Group II. The true peak plasma levels may have been underestimated because of the time interval between successive samples.

Previous studies employing 400-mg single doses of meprobamate reported mean peak plasma levels of 6.0–10.8 μg/ml (9). Blood levels of 5–20 μg/ml usually result during chronic administration of therapeutic doses (10). When expressed as a percentage of the reference standard (Product 1), the peak concentrations ranged from 94.9 to 114.1% in Group I and from 88.3 to 101.3% in Group II. There were no statistically significant differences among the products in either group in terms of peak plasma levels.

Area under Plasma Level–Time Curve (*AUC*)—The trapezoidal rule was used to obtain the individual *AUC* values from 0 to 32 hr. In those instances where plasma concentrations were still measurable at 32 hr, the extrapolated *AUC* was estimated from the following equation:

$$(AUC)_{0-\infty} = (AUC)_{0-32\ hr} + (C_p)_{32\ hr}/K_e \qquad \text{(Eq. 1)}$$

where $(C_p)_{32\ hr}$ is the plasma level at the 32-hr sampling time, and K_e is the elimination rate constant determined from the slope of the terminal portion of the semilog plot of plasma concentration *versus* time.

Table IV summarizes the mean $(AUC)_{0-32\ hr}$ as well as the mean $(AUC)_{0-\infty}$ values for each product. In both groups, neither area showed statistically significant differences ($p > 0.05$) between products. The $(AUC)_{0-\infty}$ values, expressed relative to Product 1, ranged from 94 to 108% in Group I and from 95 to 109% in Group II.

Differences between Subjects and between Weeks—Analysis of variance indicated statistically significant differences ($p < 0.05$) between subjects within each group at all but the 1- and 2-hr sampling times. In Group I, there was also a statistically significant difference ($p < 0.05$) between subjects for the $(AUC)_{0-32\ hr}$ as well as the $(AUC)_{0-\infty}$ but not for the time of peak plasma level or peak level. Group II showed no differences between subjects for time of peak concentration but did for the *AUC* values and peak concentration.

Calculation of individual half-lives following administration of six

Table IV—Mean Peak Concentration, Time of Peak Concentration, and *AUC* for Each Product [a]

Product	Peak Concentration, μg/ml	Time of Peak Concentration, hr	$(AUC)_{0-32\ hr}$, (μg/ml) (hr)	$(AUC)_{0-\infty}$, (μg/ml) (hr)
		Group I		
1	7.8 (6.1)	2.2 (45.4)	103.2 (11.2)	120.2 (12.3)
2	7.6 (11.4)	2.3 (44.3)	103.8 (11.5)	115.0 (13.5)
3	7.9 (12.2)	1.7 (49.0)	105.2 (25.7)	120.5 (26.4)
4	8.9 (20.8)	1.7 (72.7)	114.8 (22.2)	131.2 (26.0)
5	8.8 (17.9)	1.5 (55.8)	109.0 (24.9)	121.7 (25.7)
6	7.4 (18.6)	1.5 (55.8)	98.7 (23.0)	112.5 (26.0)
		Group II		
1	7.7 (24.1)	3.5 (23.9)	110.4 (23.6)	127.2 (26.3)
7	7.3 (14.6)	3.0 (47.1)	115.7 (20.5)	138.9 (21.6)
8	7.4 (18.4)	3.0 (42.2)	112.3 (31.8)	131.9 (28.9)
9	6.8 (24.5)	2.7 (45.4)	110.1 (34.9)	139.0 (37.5)
10	7.8 (16.6)	1.8 (72.5)	103.6 (22.9)	121.0 (24.2)
11	6.9 (23.7)	3.8 (34.7)	108.6 (20.0)	129.1 (24.1)

[a] Average data for six subjects. The coefficient of variation in percent is given in parentheses.

Table V—Power Analysis Table[a]

Parameter	N for 20% Difference		Minimum Detectable Difference, %	
	Group I	Group II	Group I	Group II
1 hr	25	70	44.0	77.3
2 hr	18	50	37.0	60.9
3 hr	10	40	26.8	54.4
4 hr	8	22	23.7	40.8
6 hr	13	20	29.9	38.3
8 hr	22	28	36.3	46.7
10 hr	6	28	19.7	46.3
24 hr	16	24	34.2	42.8
32 hr	45	35	51.9	52.5
Peak level	11	17	27.0	35.5
Time of peak	>150	80	104.7	80.4
$AUC_{0-32\ hr}$	5	14	16.5	32.6
$AUC_{0-\infty}$	6	13	18.3	31.2

[a] Calculated for $\alpha = 0.05$ and $\beta = 0.2$.

products to each subject indicated mean half-lives ranging from 8.9 (*SD* 1.8) to 10.8 (*SD* 1.2) hr for Group I subjects and from 9.7 (*SD* 2.5) to 14.1 (*SD* 4.1) hr for Group II subjects. These data are in agreement with a previous study in which the half-life of meprobamate ranged from 6.4 to 16.6 hr with a mean of 11.3 hr (11). No trends were apparent in half-lives determined for each subject over the 6-week study period, indicating that the weekly administration of the drug had no progressive influence on its metabolism in a given subject.

Statistically significant differences ($p < 0.05$) were also found among study weeks in Group I for the 4-, 10-, and 24-hr sampling times as well as for the *AUC* values. The cause of these differences was not known, but they did not appear to result from any cumulative effect of repeated drug administration. For example, the $(AUC)_{0-32\ hr}$ calculated by week for Group I ranged from 92 to 117 (μg/ml) (hr), with the ranking of the weeks, from lowest *AUC* to highest, being Week 2, 6, 4, 5, 1, and 3.

Data Variability and Power Analysis—To maintain the study design within manageable limits, two groups of six subjects were employed. With the exception of the *AUC* and the drug level at 10 hr for Group I, more than six subjects would have been required to permit a difference of 20% or less to be statistically significant ($p < 0.05$) (Table V). A 20% difference in parameters was selected as the maximum difference allowable and still have the products be considered bioequivalent. For most parameters evaluated, the difference between the reference product and the other products was less than 15%.

There was considerable intersubject variability in the absorption and/or disposition of meprobamate, as may be seen from the coefficients of variation given in Tables II–IV. There was no clear trend to this variability among individual products. In Group I, the reference product (Product 1) was less variable than the other five products tested at several sampling times. However, in Group II, the variability of the data for Product 1 was similar to that of the other five products.

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New Drug Metabolism Inhibitor of Marine Origin

PUSHKAR N. KAUL ˣ and SHRINIVAS K. KULKARNI

Received November 4, 1977, from the *Marine Pharmacology Laboratories, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190.* Accepted for publication January 13, 1978.

Abstract □ Dactylyne, an acetylenic dibromochloro ether, was isolated from the sea hare *Aplysia dactylomela* and characterized pharmacologically. It had no direct effect on the cardiovascular, respiratory, and central nervous systems of mice, rats, and guinea pigs. However, a 25-mg/kg ip dose of dactylyne prolonged pentobarbital sleep time in mice by more than 10 hr. This potentiation was subsequently determined to be due to the inhibition of pentobarbital metabolism by dactylyne since the elimination half-life of pentobarbital in the dactylyne-treated mice increased several folds. Dactylyne was nontoxic up to 200 mg/kg iv. The unique structure, high potency, and relatively nontoxic nature of dactylyne make it an interesting pharmacological substance of marine origin.

Keyphrases □ Dactylyne—isolated from *Aplysia dactylomela* sea hare, pharmacological activity in mice, rats, and guinea pigs, effect on drug metabolism in mice □ *Aplysia dactylomela*—sea hare, dactylyne isolated, pharmacological activity in mice, rats, and guinea pigs, effect on drug metabolism in mice □ Metabolism, drug—effect of dactylyne isolated from *Aplysia dactylomela* sea hare

Exploration of the sea as a source of potential drugs is relatively recent. Over the past several years, cardioactive substances (1, 2), anticancer agents (3), and toxins (4) have been isolated from marine invertebrates. Moreover, the extracts of some marine organisms possess potent central nervous system (CNS) depressant activity in laboratory animals (2).

The followup study of bioassay-guided isolation and

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