Comparative Bioavailability of a Lipophilic Steroid

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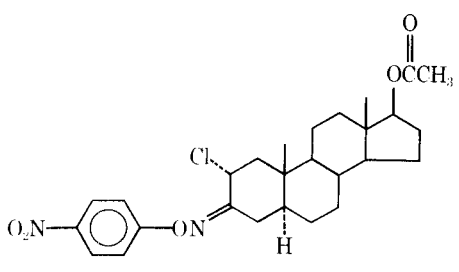
Abstract □ 17β-Acetoxy-2α-chloro-3-(*p*-nitrophenoxy)imino-5α-androstane (I) is a lipophilic steroid with postimplantive antifertility activity in laboratory animals. The bioavailability of micronized I from solutions and suspensions was compared in four groups of adult female Wistar rats. Each group received varying concentrations of micronized ^{3}H-I (specific activity of 0.38–8.94 μCi/mg) in sesame oil by oral gavage. Samples of whole blood and urine collected following drug administration were assayed for radioactive content. Calculation of the mean area under the blood radioactivity *versus* time curve, when corrected for the quantity of drug administered, indicated that a substantially larger fraction of the dose was absorbed in the two instances where I was present only in solution. A linear relationship between the amount of I absorbed based on whole blood radioactivity and urinary excretion and the administered dose was found primarily for groups receiving the drug in solution. Preliminary results in humans indicate that ^{3}H-I was absorbed to a much greater extent following oral administration of the drug in sesame oil than when admixed with lactose.

Keyphrases □ 17β-Acetoxy-2α-chloro-3-(*p*-nitrophenoxy)imino-5α-androstane—bioavailability from solutions and suspensions in rats and humans □ Bioavailability—substituted androstane from solutions and suspensions in rats and humans □ Steroids, lipophilic—substituted androstane, bioavailability from solutions and suspensions in rats and humans

17β-Acetoxy-2α-chloro-3-(*p*-nitrophenoxy)imino-5α-androstane[1] (I), an *O*-aryl oxime of 2α-chlorodihydrotestosterone, possesses postimplantive antifertility activity in the rat (1, 2) and other laboratory animals[2] following oral administration. The effects of various changes of physical–chemical properties of drug formulations on the bioavailability of drugs were studied for digoxin (3–9), tolbutamide (10), phenylbutazone (11), phenytoin (12, 13), oxytetracycline (14), and chloramphenicol (15). Examples of altered bioavailability due to specific physical–chemical changes include the effects of the particle size of griseofulvin (16, 17), of polymorphs of chloramphenicol (18), of water of hydration of ampicillin (19), and of the acid or salt form of phenylbutazone (20) or phenytoin (21).

Studies of the contragestational potency of I, administered in solution or suspension in various vehicles to animals, suggested that the majority of the biological activity of I resulted from drug in solution in sesame oil at the time of administration[2]. To confirm this hypothesis, a comparative bioavailability study employing solutions and suspensions of I in sesame oil was conducted in rats.

In addition, preliminary data on the comparative bioavailability of I from sesame oil and lactose formulations in normal adult female subjects and on the influence of vehicle on I absorption in Wistar rats are also presented.



I

EXPERIMENTAL

Comparative Bioavailability Study in Rats—*Preparation of Radiolabeled Suspensions and Solutions*—Unlabeled micronized I was prepared by micronization employing a high-velocity impact mill[3]. Micronized ^{3}H-I (specific activity of 8.94 μCi/mg) was prepared by precipitation of ^{3}H-I[1] (specific activity of 169.5 μCi/mg) and unlabeled micronized I from methylene chloride by the use of hexane.

The radiochemical purity of ^{3}H-I and micronized ^{3}H-I was determined by TLC [250-μm silica gel GF plates with hexane–ethyl acetate (8:2)] to be greater than 95%.

Portions of 2 mg of micronized ^{3}H-I were added to each of four vials containing various amounts of unlabeled micronized I. The powders were mixed gently in each vial, and sesame oil was added slowly with constant stirring to yield a final volume of 2.5 ml.

Aliquots of Solutions A and B were assayed for radioactive content by liquid scintillation spectrometry and for concentration of I using UV absorption spectrometry (at 312 nm). Aliquots of dosage forms C and D were centrifuged (1000 rpm for 5 min), and the resulting supernates were passed through a 0.45-μm filter[4] (cellulose) and then reassayed. The specific activity of ^{3}H-I present in solution in each preparation was determined from the results of the assays for radioactivity and for total I (Table I).

Comparative Absorption Studies—Three adult female Wistar rats[5], 250–275 g, in each of four groups, were fasted 18–22 hr before drug administration and then received 0.6 ml (3.69–3.98 μCi) of the corresponding dose preparation by oral gavage. The rats were placed in metabolism cages for urine and feces collection. Whole blood samples were removed from the tail vein or the orbital plexus at intervals up to 24 hr after drug administration. Aliquots (0.5 ml) of these samples were placed into tissue sample cups[6] immediately after each collection. The samples were subsequently combusted in a tissue oxidizer[7], dissolved in a scintillation cocktail[8], and assayed for radioactive content using a liquid scintillation spectrometer[9].

Internal standardization was used to correct for quenching. The area under the whole blood radioactivity concentration *versus* time curve (*AUC*), from 0 to 24 hr after drug administration to each rat, was then determined. The *AUC*'s were converted (through division by appropriate specific activity) to corrected areas representing mass concentration of I equivalents (I and/or metabolites) *versus* time.

Urine was collected for 48 hr after drug administration. Aliquots of urine (0.5 ml) were added to scintillation cocktail[10] and were assayed for radioactive content.

Influence of Vehicle on ^{3}H-I Absorption—The influence of vehicle on ^{3}H-I absorption was first studied by administering the drug either dissolved in sesame oil or as an aqueous suspension in 0.5% (w/v) methylcellulose and 0.4% (w/v) polysorbate 80. A solution of ^{3}H-I (3.7 μCi, 2.5 mg/kg) in sesame oil (0.4 ml) was orally administered to three rats. To

[1] Synthesized at Ortho Pharmaceutical Corp., Raritan, N.J.
[2] D. W. Hahn, Ortho Pharmaceutical Corp., Raritan, N.J., personal communication.
[3] Trost Inc., Hatboro, Pa.
[4] Millipore.
[5] Royal Heart Laboratories, New Hampton, N.Y.
[6] Combustocones, Packard Instrument Co., Downers Grove, Ill.
[7] Model 306, Packard Instrument Co., Downers Grove, Ill.
[8] Monophase 40, Packard Instrument Co., Downers Grove, Ill.
[9] Model SL-30, Teledyne-Intertechnique, Westwood, N.J.
[10] Scintisol-Complete, Isolab Inc., Akron, Ohio.

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Table I—Comparison of Solutions and Suspensions of ^{3}H-I

Preparation[a]	Micronized ^{3}H-I, mg	Micronized I, mg	Concentration, mg/ml	Activity of[b] Dissolved ^{3}H-I, μCi/ml
Solution A	1.997	0	0.8	6.42
Solution B	2.004	2	1.6	6.20
Suspension C	2.005	18	8	6.63
Suspension D	1.998	38	16	6.13

Group Comparison	Ratio of Activity	Ratio of Mean Area of ^{3}H Activity[c]
A/C	1.93	1.51
A/D	2.62	1.91
B/C	1.86	1.58
B/D	2.53	2.00[d]

[a] Three female Wistar rats per dose group were each administered micronized ^{3}H-I in sesame oil (3.68–3.98 μCi, 0.6 ml) by oral gavage. [b] Aliquots of Solutions A and B were assayed for concentration of radioactivity. Aliquots of Suspensions C and D were centrifuged (1000 rpm for 5 min), and the supernates were assayed. [c] Ratio of uncorrected mean *AUC* values. [d] Statistically significant ($p < 0.05$).

three additional rats, the same dose was administered orally as an aqueous suspension (0.4 ml). Finally, three rats were administered orally ^{3}H-I (9.5 μCi, 75 mg/kg) as an aqueous suspension (0.48 ml). The concentration of radioactivity in whole blood was determined, and the *AUC*, corrected for quantity of administered drug, was calculated.

Comparative Bioavailability Studies in Humans—*Materials*—Compound ^{3}H-I (specific activity of 275 μCi/mg) and unlabeled I were recrystallized together to yield ^{3}H-I with a specific activity of 100.8 μCi/mg. The radiochemical purity of this compound was determined by TLC to be greater than 95%.

The two dosage forms were prepared according to the following procedure. Capsule E, containing 1.0 mg of ^{3}H-I (100 μCi/mg), was prepared by triturating 13.0 mg of ^{3}H-I and 537.0 mg of lactose in a mortar. Aliquots of the resultant blend containing 1.0 mg of ^{3}H-I were then hand packed into white-opaque (No. 4) gelatin capsules.

Capsule F, containing 1.0 mg of ^{3}H-I (100 μCi/mg) dispersed in sesame oil, was prepared by adding 13 mg of ^{3}H-I, dissolved in chloroform, to 3.0 g of sesame oil. The chloroform was then evaporated by heating the mixture to 60° with constant stirring. A suitable volume of sesame oil, containing 1.0 mg of ^{3}H-I, was then injected into each 5-minim, clear, soft gelatin capsule. The capsules were sealed by means of an aqueous gelatin solution. Samples of both dosage formulations were assayed for drug content and tritium activity.

Samples of both formulations were reassayed immediately prior to use for radioactive content, radiochemical purity, and drug content.

Subjects—Two healthy female subjects, LD and MJ, were 40 and 33 years of age, respectively. Their heights were 157 and 168 cm, respectively, and their weights were 60.9 and 58.6 kg, respectively.

Methods—After a 12-hr fast, both subjects were hospitalized and each

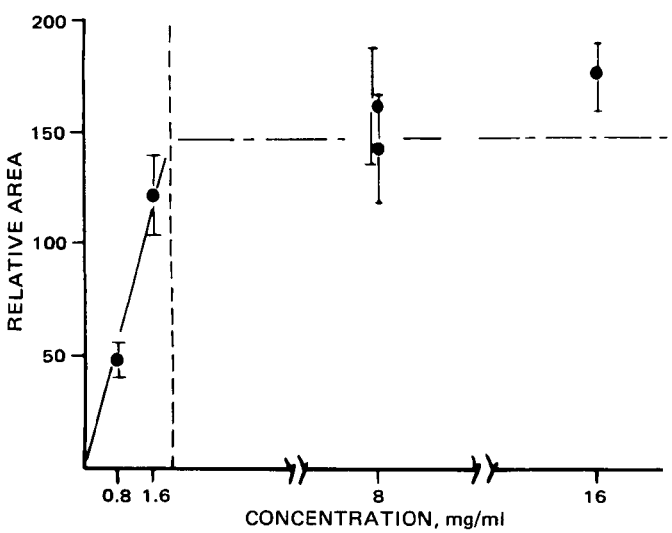

Figure 1—*Absorption of I* versus *concentration administered. Each point represents mean* AUC *converted to area representing mass concentration* versus *time* ± SE *for each group of three rats (Table II). Horizontal dashed line represents an extrapolated line.*

Table II—Absorption of I after Oral Administration in Sesame Oil

Dose Preparation	Concentration in Solution ^{3}H-I, μCi/ml	Concentration in Solution I[a], mg/ml	Concentration in Solution Specific Activity, μCi/mg (Calculated)	Area[b] Mass Concentration × *t*, mg, Mean ± *SE*
A	6.42	0.76	8.44	4.69 ± 8.7
B	6.20	1.83	3.39	122.1 ± 18.0
C	3.32	1.83–2.08[c]	1.60–1.81[c]	163.9 ± 25.3[c]
				144.9 ± 22.4[c]
D	2.45	2.08	1.18	174.9 ± 14.9

[a] Aliquots of Solutions A and B were assayed for concentration of I by UV absorption. Aliquots of Suspensions C and D were centrifuged (1000 rpm for 5 min), and the supernates were filtered and assayed. Filtrate C was lost, and the concentration range from Samples B to D was employed. Refer to footnote *c*. [b] The *AUC* for each rat (expressed in milligrams) was divided by the specific activity for the corresponding dose solution to yield area representing mass concentration *versus* time. [c] Value employed is range based upon results of assay of Solutions B and D. In all cases, the values agree with the known equilibrium solubility of I in sesame oil.

was given a different dosage formulation followed by 240 ml of water. Subject LD received Capsule F. Subject MJ received Capsule E. Water was permitted *ad libitum*, and a normal diet was permitted 6 hr after drug administration.

Venous blood samples were collected into heparinized tubes at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, 72, 96, and 120 hr, at 7, 12, and 14 days, and at selected intervals thereafter. Urine and feces were collected during the day prior to drug administration and daily for 2 weeks thereafter and were frozen immediately.

Two 0.5-ml aliquots of whole blood from each sample were placed into tissue sample cups[6] immediately after each collection. The aliquots were subsequently combusted and assayed for radioactive content. Plasma was separated from the remainder of each whole blood sample and was frozen. Two 0.5-ml aliquots of plasma were subsequently combusted and assayed for radioactive content.

Urine was assayed for radioactive content by the procedure described previously. Each fecal specimen was diluted to a constant volume (500 ml) with methanol–water (1:1 v/v) and homogenized in a blender[11], and aliquots (0.5 ml) were transferred to tissue sample cups[6] and assayed for radioactive content.

RESULTS

Comparative Bioavailability Studies in Rats—For each rat, the concentration of radioactivity determined in samples of whole blood was plotted as a function of time. Radioactivity in whole blood represented the sum of I and/or all of its metabolites at any time. The ratios of the mean area under these curves for any dosage group when compared to the mean for any other group (Table I) were similar to the corresponding ratios of the radioactivity of I dissolved in sesame oil for each dosage form comparison. However, the values obtained for dissolved radioactivity were not proportional to the total amount of I in solution in sesame oil (Table II) and indicated a preferential solubilization of ^{3}H-I.

Calculation of the mean *AUC*, when corrected for the quantity of drug administered (Table II), indicated that a substantially larger fraction of the dose was absorbed in the two instances where I was present only in solution than where I was present in suspension. A linear relationship (Fig. 1) existed between the quantity of I absorbed and the amount of drug present in solution for Solutions A and B (true solutions). This relationship was not apparent for the dosage forms containing I in suspension.

This observation was confirmed upon examination of the total amount of radioactivity excreted in the urine of each group of animals in the first 48 hr after administration of the various dosage forms (Table III). Figure 2 shows the mean mass of I equivalents (I and/or metabolites) excreted for each group of rats as a function of the concentration of I in the dosage forms. A linear relationship was found to exist between the total mass excreted and the concentration of I for dosage forms that were true solutions (A and B) but did not hold where some I was in suspension (C and D).

The relative bioavailability of I following oral drug administration either in solution in sesame oil or in aqueous suspension is presented in

[11] Waring Products Corp., Winstead, Conn.

Table III—Urinary Excretion of I after Oral Administration in Sesame Oil

Dose Preparation	Total Disintegrations per Minute Excreted in 48 hr, Mean ± *SE*	Specific Activity, μCi/mg	Total Micrograms Excreted[a] in 48 hr, Mean ± *SE*	Mean Percent Dose Excreted
A	472,883 ± 58,050	8.44	25.2 ± 3.1	5.2
B	665,000 ± 87,619	3.39	88.4 ± 11.6	9.2
C	595,050 ± 101,416	1.60–1.81[b]	167.5 ± 28.6 148.1 ± 25.2	3.1–3.5[b]
D	318,767 ± 41,128	1.18	121.7 ± 15.7	1.3

[a] Total micrograms excreted in 48 hr for each rat was calculated by the following formula: total dpm excreted × [1000/2,200,000 (specific activity)] = total μg excreted. [b] Theoretical value employed; refer to Table II footnotes *a* and *c* for details.

Table IV—Effect of Different Vehicles on I Bioavailability following Oral Administration in Rats

Vehicle	Dose, mg/kg	Mean *AUC* ± *SE*[a], μg equivalents/ml × hr	Mean *AUC* per Dose ± *SE*
Sesame oil (solution)	2.5[b]	3.92 ± 0.27	1.57 ± 0.11 [c]
0.5% (w/v) methylcellulose and 0.4% (w/v) polysorbate 80 (suspension)	2.5[b]	1.33 ± 0.14	0.53 ± 0.05 [c]
	75[b]	6.53 ± 1.54	0.09 ± 0.02 [d]

[a] *AUC* = area under whole blood drug equivalent concentration (I and/or metabolites) *versus* time curve, determined from the following formula: [*AUC* (μg equivalents/ml × hr)] = [*AUC* (dpm/μl × hr) determined by cut and weight method × 1000 μl/ml]/specific activity of administered I in dpm/μg. [b] $n = 3$. [c] Statistically significant difference ($p < 0.001$) by Student t test (two tail). [d] Statistically significant difference ($p < 0.005$) by Student t test (two tail).

Table IV. Following administration of I in solution in sesame oil, the mean *AUC*, when corrected for the quantity of drug administered, was threefold greater than that following administration of the same dose of I in aqueous suspension ($p < 0.001$). The bioavailability of a 75-mg/kg dose of I was compared with that of a 2.5-mg/kg dose following oral administration of I in aqueous suspension at both doses. The mean *AUC*, when corrected for the quantity of drug administered, was significantly lower ($p < 0.001$) following administration of the 75-mg/kg dose than following administration of the 2.5-mg/kg dose (Table IV).

Comparative Bioavailability Studies in Humans—Absorption of radioactivity was fairly rapid following oral administration of ^{3}H-I in sesame oil to Subject LD. Peak blood levels of total radioactivity occurred within 2 hr after drug administration (Fig. 3). The radioactivity in blood then rapidly decreased to a low level that persisted for more than 120 hr. The apparent half-life of radioactivity in whole blood was estimated to be 63 hr, and the elimination rate constant was calculated to be 0.011 hr^{-1}.

Cumulative elimination of radioactivity in the urine and feces of this subject is shown in Fig. 4. Approximately 45% of the administered dose was eliminated within the 14-day study period, 30% within the first 3 days. Approximately 29% of the administered dose appeared in the urine within the 14-day study period. These calculations were based on an administered dose of 90.2 μCi, the average value obtained from analysis of two similar capsules just prior to the study. By 96 days after drug administration, radioactivity corresponding to approximately 76% of the dose was recovered, with about 49% in the urine. After the initial 2 weeks following drug administration, ~0.5 μCi/day was excreted between Days 15 and 41 and ~0.3 μCi/day was excreted between Days 41 and 60 (Fig. 4).

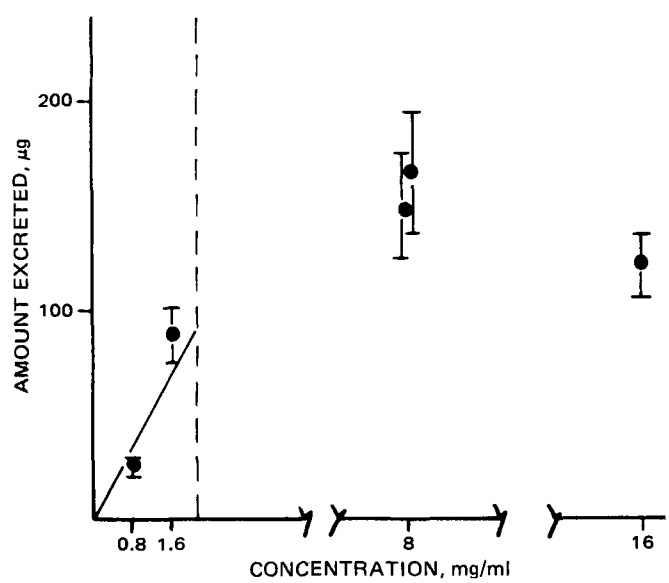

Figure 2—*Urinary excretion of I* versus *concentration administered. Each point represents the mean amount of I and/or metabolites* ± SE *excreted into the urine by 48 hr after drug administration to each group of three rats (Table III).*

Absorption of radioactivity following oral administration of ^{3}H-I, mixed with lactose, to Subject MJ occurred more slowly than in the first subject (Fig. 3). Peak blood levels of radioactivity occurred approximately 10 hr after administration. Furthermore, only low levels of radioactivity were found at all time intervals, *i.e.*, less than 400 dpm/ml.

This subject eliminated approximately 77% of the administered dose within the 9-day study period, 74% within the first 3 days (Fig. 4). Approximately 71% of the total administered dose appeared in feces during the first 10 days. These calculations were based on a dose of 96.2 μCi, the average value obtained from analysis of two similar capsules just prior to the study.

After the first 2 weeks, only trace amounts of radioactivity, slightly above background, were found in the excreta (Fig. 4).

DISCUSSION

Results of the bioavailability study in rats indicated that, for doses of I in sesame oil where all drug was in solution at the time of administration, absorption of radioactivity from ^{3}H-I was proportional to the concentration of the drug present (Fig. 1). When the concentration of I exceeded its equilibrium solubility in sesame oil (2 mg/ml), this relationship was not maintained. If absorption were limited to only that portion of the drug in solution at the time of administration, doses of drug in suspension would yield *AUC* values equivalent to that for Solution B (assuming a constant volume is administered), depicted by the horizontal hatched line in Fig. 1. There appeared to be only a negligible amount of absorption of drug in suspension at the time of administration. Similar conclusions were obtained from a plot of the total mass of I equivalents excreted in the urine *versus* administered dose (Fig. 2).

Studies of the effect of the vehicle employed on I bioavailability indicated that considerably less drug was absorbed from aqueous suspension in methylcellulose than from solution in sesame oil and that absorption of radioactivity following oral administration of aqueous suspensions of ^{3}H-I was not proportional to the administered dose.

The data obtained in humans, although preliminary, indicated that ^{3}H-I absorption from the sesame oil formulation was much greater than that from the lactose formulation. Peak blood levels of radioactivity generated by the oil formulation were 12 times those generated by the

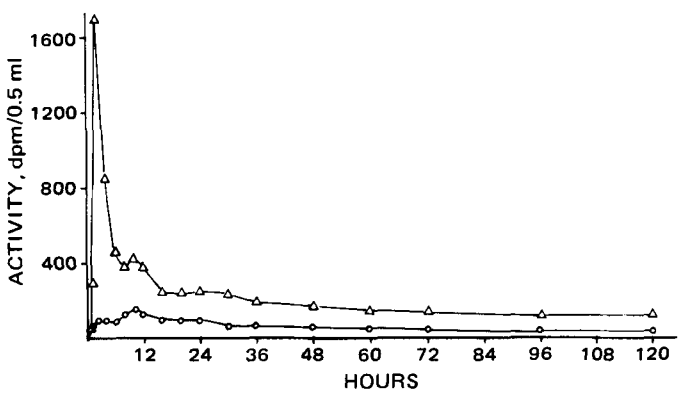

Figure 3—*Radioactivity found at various time intervals in the blood of Subject LD (Δ), who received ^{3}H-I (90.2 μCi, 1.0 mg) dispersed in sesame oil, and Subject MJ (○), who received ^{3}H-I (96.2 μCi, 0.97 mg) admixed with lactose.*

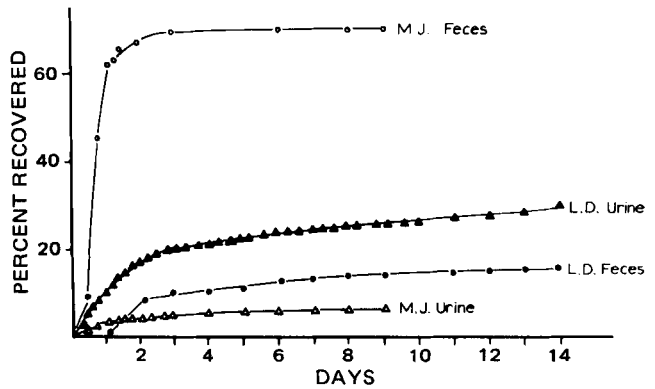

Figure 4—*Cumulative elimination of radioactivity in urine and feces from Subjects LD and MJ.*

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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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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