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The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone*†

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Objectives: To examine the effects of food ingestion and administered dose on the absorption of oral micronized P (Utrogestan; Besins-Iscovesco, Paris, France) and to compare the bioavailability of intramuscular versus oral routes of administration.

Design: Prospective, randomized, open label crossover protocol with 7 days between dosages.

Setting: Academic institution.

Participants: Fifteen normal postmenopausal women.

Interventions: All subjects participated in three separate protocols: [1] micronized P (200 mg) or placebo under fasting or nonfasting conditions once daily for 5 days; [2] micronized P (100, 200, or 300 mg) once daily under fasting conditions for 5 days; and [3] micronized P (200 mg) or intramuscular P (50 mg in oil) administered once daily for 2 days.

Main Outcome Measures: Serum P concentrations were measured in all groups.

Results: Concomitant food ingestion increased the area under the serum P concentration versus time curve ($AUC_{0\text{ to }24}$) and the maximum serum P concentration (C_{max}) without affecting time to maximum serum concentration (T_{max}) ($P < 0.05$). Micronized P absorption and elimination were first-order processes and exhibited dose-independent pharmacokinetics between 100 and 300 mg. After intramuscular P, C_{max} was higher and T_{max} occurred later compared with the oral P preparation. Oral P had lower relative bioavailability (8.6%) than intramuscular P.

Conclusions: Absorption of micronized P was enhanced twofold in the presence of food. Both absorption and elimination were dose-independent, dose proportionality being confirmed. Bioavailability of the oral P was approximately 10% compared with intramuscular P.

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Key Words: Oral micronized progesterone, pharmacokinetics, intramuscular, progesterone, bioavailability

Progesterone has been available for >50 years and has been used in the management of various gynecological disorders including endometrial hyperplasia, menopausal symptoms, dysfunctional uterine bleeding, amenorrhea, luteal phase inadequacy, and premenstrual syndrome (1, 2). Proges-

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terone has had limited clinical usefulness because of its poor absorption after oral administration and its susceptibility to first-pass metabolism by the liver. A number of synthetic progestogens have been developed to overcome this problem of low bioavailability. Their pharmacological effects, however, differ from native P and may result in increased androgenic effects, fluid retention, alterations in high-density lipoproteins (HDL), headaches, mood disturbances, and possible teratogenicity (3).

A new oral micronized P compound (Utrogestan; Besins-Iscovesco, Paris, France) has been developed to overcome the problems associated with the absorption of previously available oral P preparations and the adverse metabolic effects of the synthetic progestogens. Preliminary studies have indicated that micronization of P enhances absorption (4, 5). A natural P with improved bioavailability would provide a distinct advantage over other currently available therapies. These studies were designed to evaluate the influence of food ingestion on the absorption of oral micronized P, to examine the dose proportionality after oral administration of three different doses (100, 200, and 300 mg), and to compare the bioavailability between this new dosage formulation and intramuscular P in oil.

MATERIALS AND METHODS

Utrogestan (oral micronized P, 100-mg capsules) and placebo capsules were supplied by Besins-Iscovesco, Inc., Paris, France. Progesterone in sesame oil (50 mg; Rugby Pharmaceuticals, Inc., West Hempstead, New York) was purchased from a local pharmacy.

Subjects

Fifteen healthy postmenopausal female volunteers with a history of amenorrhea for 6 months or more, serum FSH concentrations > 40 mIU/mL, and serum E_2 concentrations < 30 pg/mL (110 pmol/L) completed each of the studies. A total of 21 subjects, ranging from 27 to 67 years of age, initially participated in the three studies. A baseline physical examination, medical history, and laboratory tests to rule out patients with significant disease were required before entry into the study. The patients had not been exposed to any steroid therapy for at least 30 days before the study. Additionally, they had not used other medications, with the exceptions of acetaminophen, ibuprofen, or aspirin, for at least 48 hours before the study. All patients signed informed consents approved by the Institutional Review Board of the Eastern Virginia Medical School, Norfolk, Virginia.

Study Designs

Study I: Effects of Food Ingestion

Study I compared the absorption of a single daily dose of micronized P administered either 2 hours before or immediately after a standardized breakfast for 5 days. The study was an open label, placebo-controlled crossover protocol in which 15 postmenopausal women received specific preparations under each of the following conditions for a period of 5 days: placebo or micronized P (200 mg) immediately after a standardized breakfast containing 300 to 800 calories with 12 to 26 g of protein; and placebo or micronized P (200 mg) on a fasting stomach, followed in 2 hours by the standardized breakfast noted above. A washout period of 7 days was required between dosages. Blood specimens for the determination of serum P concentrations were drawn at the following times: 0, 1, 2, 3, 4, 6, 10, and 24 hours after administration of the study drug on day 1 and at 0, 1, 2, 3, 4, 6, and 10 hours after drug administration on day 5.

Study II: Effects of Dose

Study II was an open label, three-way crossover dose proportionality investigation conducted on 15 postmenopausal women each receiving micronized P in a fasting state in doses of 100, 200, and 300 mg. The doses were administered in a random order, once daily, in the early morning for a period of 5 days. A washout period of 7 days was required between dosages. Blood specimens for the determination of serum P concentrations were drawn at the following times: 0, 1, 2, 3, 4, 6, 10, and 24 hours after administration of the study drug on day 1 and at 0, 1, 2, 3, 4, 6, and 10 hours after drug administration on day 5.

Study III: Comparison of Oral and Intramuscular Routes of Administration

Study III was an open label, two-way crossover design in which 15 postmenopausal women received each of the following dosages: micronized P (200 mg), administered orally in the fasting state, once daily for a period of 2 days; and P in oil (50 mg, Rugby Pharmaceuticals, Inc.), intramuscular ad-

ministration, once daily for a period of 2 days. Subject assignment to the initial treatment (oral or intramuscular) was determined by random order. A washout period of 7 days was required between dosages. Blood specimens for the determination of serum P concentrations were drawn at 0, 1, 2, 3, 4, 6, and 10 hours after administration on days 1 and 2, and at 24, 48 and 72 hours after drug administration on day 2.

P Assays

Serum P levels were determined using a commercially available solid-phase RIA kit (DPC Corporation, Los Angeles, CA). Intra-assay and interassay coefficients of variation were 5.6 and 9.0%, respectively. The assay sensitivity was 0.1 ng/mL.

Pharmacokinetic Analyses

The following pharmacokinetic parameters were determined.

1. Area under the curve (AUC) (ng · h/mL): the area under the serum concentration versus time curve during the specified time intervals. The AUC values were calculated according to the linear trapezoidal rule. The $AUC_{0\text{ to }24}$ was calculated for day 1 of each study. The $AUC_{0\text{ to }10}$ was calculated for day 5 of studies I and II. The $AUC_{24\text{ to }96}$ was determined for days 2–4 of study III. The AUC values were not extrapolated past the last measured serum concentration versus time values because insufficient data existed in most serum concentration versus time profiles to accurately characterize the elimination rate constant.

2. $t_{\frac{1}{2}}$ (h): terminal half-life. Data from the terminal phase of serum P concentration versus time curves were used to calculate half-lives through linear regression of the unweighted data. These values are referred to as "apparent" $t_{\frac{1}{2}}$ values and are estimates of the actual elimination $t_{\frac{1}{2}}$ values because intravenous data were not available to distinguish the relative contributions of absorption, distribution, and elimination processes to the serum profile. Also, insufficient data existed in most serum concentration versus time profiles to accurately characterize the elimination rate constant.

3. C_{max} (ng/mL): maximum serum concentration values. Each C_{max} was obtained from individual serum P concentration versus time profiles by visual inspection.

4. T_{max} (h): time to maximum serum concentration. T_{max} was taken at the time at which C_{max} occurred.

5. The AUC food:AUC fasting and AUC oral:AUC intramuscular ratios: The relative bioavailability (F) of micronized P was calculated for study I (day 1) by dividing the $AUC_{0\text{ to }24}$ values obtained after a meal by the $AUC_{0\text{ to }24}$ values derived under fasting conditions. In study III, the relative bioavailability (F) was calculated by dividing AUC values obtained after oral administration by AUC values obtained after intramuscular administration and correcting for dose:

$$F = \frac{\text{AUC oral}}{\text{AUC IM}} \cdot \frac{\text{Dose IM}}{\text{Dose oral}}$$

Statistical Analyses

Potential differences in the pharmacokinetic parameters from each study were evaluated using a commercially available computerized statistical package (Statistical Analysis Software, SAS Institute Inc., Cary, NC). Paired *t*-tests were performed to assess differences between the treatment conditions for study I and study III. A repeated measurements ANOVA was used to evaluate differences among the different dose groups in study II. A P value ≤ 0.05 was required for rejection of the null hypothesis. All pharmacokinetic parameters have been expressed as the mean ± SEM.

RESULTS

Study I: Effects of Food

The serum P profiles for fasting and nonfasting subject groups during the 1st day of micronized P administration are shown in Figure 1. Baseline

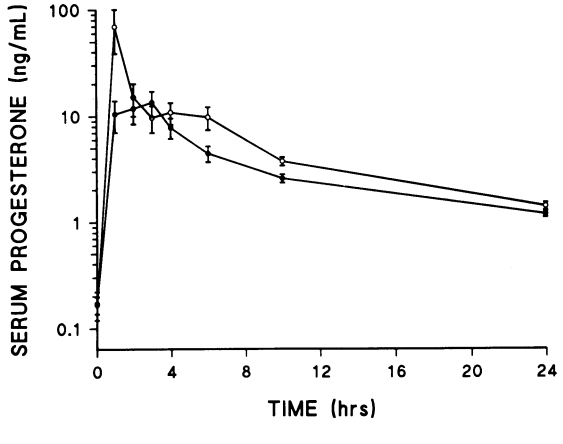

Figure 1 Time course of P serum concentrations (ng/mL) after administration of a single 200-mg oral dose of Utrogestan during fasting or nonfasting conditions for day 1 of a 5-day dosing regimen. Each point is the mean ± SEM for 15 subjects. ●, Fasting condition. ○, Nonfasting condition.

Table 1 Pharmacokinetic Parameters for Fasting and Nonfasting Conditions of Utrogestan Administration for Day 1 of a 5-Day Regimen

	Fasting condition	Nonfasting condition
C_{max} (ng/mL)	13.4 ± 3.6	69.5 ± 31.0*
T_{max} (h)	2.7 ± 2.2	3.1 ± 2.7
AUC_{0to24} (ng · h/mL)	91.5 ± 11.8	182.5 ± 38.9*

* Significantly different from fasting condition ($P < 0.05$). Each value is the mean ± SEM of data from 15 subjects.

serum levels of P averaged 0.17 ng/mL for both treatment groups. After the administration of micronized P, P concentrations were greater for the nonfasting group, most notably at time points immediately after dosing, suggesting that the presence of food enhanced absorption.

Differences in $AUC_{0\text{ to }24}$, C_{max}, and T_{max} values between the nonfasting and fasting groups were evaluated for day 1 of the study (Table 1). C_{max} and $AUC_{0\text{ to }24}$ values were significantly increased when micronized P was administered with food. The mean $AUC_{0\text{ to }24}$ for day 1 was increased by a factor of 2.0, indicating a doubling in the relative bioavailability of micronized P when the dose was administered with food. The mean time to reach peak serum P levels (T_{max}) was similar for both conditions, indicating that the presence of food influenced the extent of P absorption rather than the rate of absorption.

The results from day 1 corresponded to the data from day 5 (data not shown). No significant differences in C_{max} or T_{max} values were observed between days 1 and 5 within each group. Even though serum P did not completely return to baseline levels within the dosing interval of 24 hours, the similarity in C_{max} between days 1 and 5 suggested that no substantial accumulation occurred and that a single dose had no apparent effect on subsequent doses.

Serum P levels in the placebo group were stable and consistent with the initial P levels from the treatment groups before micronized P administration. The AUC estimates were not performed for the placebo group because P levels were below the limits of detection of the assay (<0.1 ng/mL) for a number of the measured time points.

Study II: Effects of Dose

Single doses of 100, 200, and 300 mg of micronized P were administered daily for 5 days. Mean serum concentrations of P for day 1 of the study are shown in Figure 2. Mean $AUC_{0\text{ to }24}$, C_{max}, and T_{max} values for day 1 are presented in Table 2. Increases in the $AUC_{0\text{ to }24}$ values were proportional to the increases in micronized P dose. When the $AUC_{0\text{ to }24}$ values were normalized for the administered dose, there were no significant differences in the computed values. C_{max} also increased proportionally with dose. When normalized for the dose administered, the C_{max} after the 300 mg dose was significantly different from the normalized values after the 100 and 200 mg doses. The reason for this difference is unclear; however, no such difference was observed for the C_{max} values from day 5 of the study. T_{max} values were not significantly different among the various doses. Half-life values were estimated

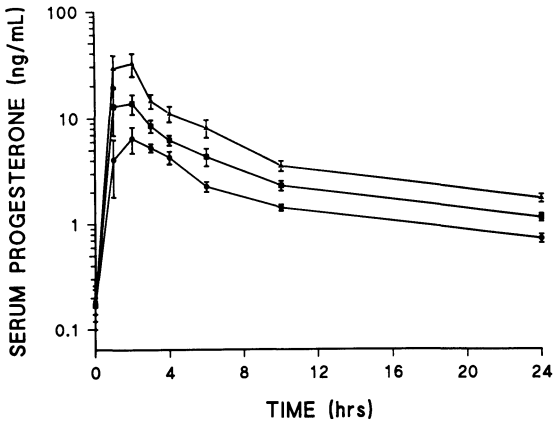

Figure 2 Time course of P serum concentrations after administration of Utrogestan in the indicated doses to fasting subjects. Data are from day 1 of a 5-day dosing regimen. Each point is the mean ± SEM for 15 subjects. ●, 100-mg Utrogestan. ■, 200-mg Utrogestan. ▲, 300-mg Utrogestan.

Table 2 Comparison of Pharmacokinetic Parameters for Utrogestan 100 mg, 200 mg, and 300 mg for Day 1 of a 5-Day Regimen

	Dose of utrogestan administered		
	100 mg	200 mg	300 mg
AUC_{0to24} (ng · h/mL)	45.2 ± 4.4	86.9 ± 11.5*	148.4 ± 15.6*
AUC_{0to24} (ng · h/mL)	0.45 ± 0.04	0.43 ± 0.12	0.49 ± 0.16
C_{max} (ng/mL)	6.5 ± 1.8	13.8 ± 2.9*	32.3 ± 7.8*
C_{max} (ng/mL) (dose-normalized)	0.07 ± 0.02	0.07 ± 0.03	0.11 ± 0.08*
T_{max} (h)	2.7 ± 1.0	2.2 ± 1.4	2.0 ± 1.4

* Values are significantly different from those at other dose levels ($P < 0.05$). Each value is the mean ± SEM of data from 15 subjects.

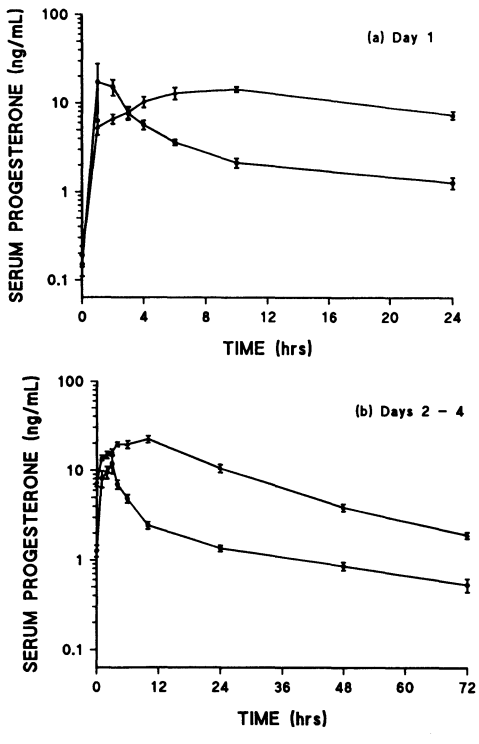

Figure 3 Time course of P serum levels after the oral administration of 200-mg Utrogestan or the intramuscular administration of 50 mg P in oil. (**A**), Data from day 1. (**B**), Data from days 1 to 4 with dosing occurring at 0 and 24 hours as indicated. Each point is the mean ± SEM for 15 subjects. ●, Utrogestan. ▲, P in oil.

from the terminal phase of the serum P concentration versus time curves for each dose. The mean terminal $t_{\frac{1}{2}}$ values were: 18.3 ± 3.5 hour for the 100-mg dose, 16.8 ± 2.3 hour for the 200-mg dose, and 16.2 ± 2.7 hour for the 300-mg dose; none of these values were significantly different from each other. The lack of difference among the dose-normalized $AUC_{0\text{ to }24}$ values, t_{max}, and terminal $t_{\frac{1}{2}}$ values among the dose groups (with the exception of C_{max} for the 300-mg dose) indicated that the absorption and elimination of micronized P were dose-independent processes, i.e., the administration of different doses did not produce significant variations in the pharmacokinetics of micronized P, dose proportionality confirmed.

The data from day 5 corresponded to the results from day 1, although the day 5 data were limited by the fact that serum concentrations were only measured for 10 hours after the micronized P dose (data not shown). No significant differences in the dose-normalized AUC and C_{max} or T_{max} values among the dose groups were found for day 5, supporting the evidence that the pharmacokinetics of micronized P were independent of dose when administered to fasting subjects in doses between 100 and 300 mg.

Study III: Comparison of Oral and Intramuscular Routes of Administration

In each of the two dosage forms P was administered as a single dose on 2 consecutive days. Serum P levels were measured through the 2 days of dosing as well as for 72 hours after the second dose. Figure 3A shows the mean P levels after the administration of 200 mg of micronized P orally or 50 mg IM P in oil for day 1 of the study. Mean values for $AUC_{0\text{ to }24}$, C_{max}, and T_{max} for day 1 of the 2-day regimen are presented in Table 3 as well as the dose-normalized values for these parameters. Intramuscular administration of P resulted in significantly higher $AUC_{0\text{ to }24}$ values than were found after orally administered micronized P. This relationship persisted even after the $AUC_{0\text{ to }24}$ values were adjusted to account for the difference in administered dose. The relative bioavailability of micronized P was 8.6% compared with intramuscular P. Mean normalized C_{max} values for oral micronized P were 30.0% of those measured after intramuscular administration. In addition, T_{max} occurred significantly earlier after oral micronized P than following intramuscular P.

The serum P concentration profiles after the 2nd day of dosing (days 2 to 4 of the study) are shown in Figure 3B for each of the dosage forms. The mean normalized AUC values for days 2 through 4 indicated that the relative bioavailability of oral micronized P was 6.2% compared with intramuscular P in oil, in close agreement with the relative availability calculated after a single day of dosing. The

Table 3 Comparison of Pharmacokinetic Parameters for Utrogestan Administered Orally and P in Oil Administered Intramuscularly for Day 1 of a 2-Day Regimen

	Utrogestan*	Intramuscular P†
AUC_{0to24} (ng·h/mL)	87.4 ± 17.2	254.6 ± 18.2‡
AUC_{0to24} (ng·h/mL) (dose-normalized)	21.9 ± 4.3	254.6 ± 18.2‡
C_{max} (ng/mL)	17.1 ± 10.7	14.3 ± 1.0
C_{max} (ng/mL) (dose-normalized)	4.3 ± 2.7	14.3 ± 1.0‡
T_{max} (h)	2.5 ± 1.6	8.7 ± 2.0‡

* 200 mg.
† 50 mg in oil.
‡ Values after intramuscular P significantly different from corresponding values after Utrogestan treatment ($P < 0.05$). Each value is the mean ± SEM of data from 15 subjects.

C_{max} and T_{max} values for days 2 to 4 supported the results from day 1, further evidence of the delayed rate of absorption but greater availability of the intramuscular dosage form.

Comparison of the $AUC_{0\text{ to }24}$ for days 1 and 2 of the study revealed a nearly twofold increase in $AUC_{0\text{ to }24}$ from day 1 to day 2 for the intramuscular P dosage form. This increase in AUC demonstrated that P was accumulating after multiple intramuscular doses. No such increase was seen following oral administration. Half-life values were calculated from the terminal phase of the serum concentration versus time curves after the second dose for each of the dosage forms. The $t_{\frac{1}{2}}$ for micronized P was 18.0 ± 2.3 hours, significantly different from the $t_{\frac{1}{2}}$ of 25.6 ± 2.2 hours for intramuscular P ($P < 0.05$). As defined, these terminal $t_{\frac{1}{2}}$ values are considered to be estimates of the elimination $t_{\frac{1}{2}}$ for each dosage form because elimination rate constants were unable to be accurately calculated.

DISCUSSION

Oral micronized P was first developed in Europe (Utrogestan; Besins-Iscovesco Laboratories, Paris, France) to provide an orally active form of natural P. Results from early studies indicated that micronized P was effective in producing increases in the serum concentration of P and evoking end organ responses (6–8). These findings have been confirmed in a recent study by Hargrove et al. (8), using a different preparation. Furthermore, this later investigation demonstrated that absorption of oral P could be significantly influenced by the physical characteristics of the P preparation, in particular, the particle sizes as well as the vehicle used with oral administration.

It is known that food intake can increase or decrease the bioavailability of drugs through a variety of different mechanisms (9–11). Food may influence the rate and extent of drug absorption by reducing the rate of gastric emptying, decreasing gastrointestinal motility, increasing gastrointestinal secretions, and increasing splanchnic blood flow (11). The effects of food on the absorption and bioavailability of micronized P were investigated in study I.

In study I, maximal serum P levels (C_{max}) were significantly greater when micronized P was administered after a standardized breakfast as compared with administration in the fasting state. The relative bioavailability of the oral preparation was twice as high when micronized P administration followed food intake. There are a number of possible explanations for the increases in serum P levels, including an increase in the absorption or a decrease in the elimination of micronized P. For example, a drug-food interaction in the gastrointestinal tract could act to enhance its absorption. Alternatively, the effect of food on blood flow to the liver could decrease presystemic clearance by allowing a larger fraction of the absorbed dose to evade first-pass metabolism and, thus, increase bioavailability. It was not possible to differentiate among these potential mechanisms.

The pharmacokinetics of micronized P were compared for three different doses in study II. Dose proportionality was demonstrated, as shown by the increase in serum P concentrations after the administration of increasing doses of micronized P. Mean peak serum levels achieved after oral administration of 100, 200, and 300 mg of micronized P were 6.5, 13.8, and 32.3 ng/mL (20.7, 43.9, and 103 nmol/L), respectively. These values meet or exceed the mean levels experienced in the midluteal phase of the spontaneous menstrual cycle, indicating that such doses would be expected to reach supplemental or therapeutic levels. The $AUC_{0\text{ to }24}$ after 100-, 200-, and 300-mg doses of micronized P were also roughly proportional to the increasing dose administered (1.0:1.9:3.3) and, when normalized for the administered dose, were not significantly different. In addition, the dose-normalized C_{max}, T_{max}, and $t_{\frac{1}{2}}$ values for the three dose groups were similar. Based on the lack of difference among these parameters, the dose-normalized serum concentration versus time curves were superimposable. The superimposability of dose-normalized data indicated that the pharmacokinetic processes of absorption, distribution, and elimination for micronized P were not altered with changes in the administered dose. Therefore, the pharmacokinetics of micronized P can be said to be independent of dose, in the range of 100 to 300 mg, in fasting subjects.

In an earlier investigation, Nillius and Johansson (12) found that an injection of 25 mg intramuscular of P in oil achieved serum P levels equivalent to those seen during the luteal phase. This study also demonstrated significant absorption of P from rectal and vaginal administration; 100-mg dose two times per day was necessary to achieve and maintain luteal phase P plasma levels. Although these routes have been shown to be effective, they are not always therapeutically practical. Other options would be desirable.

The intramuscular route of P administration was

compared with oral micronized P in search of a better alternative (study III). The oral administration of micronized P resulted in a peak serum concentration of P that was 30% of the level obtained after intramuscular injection when adjusted for differences in the administered dose. In addition, the time to maximum serum P concentration (T_{max}) was much shorter for the oral route of administration as compared to the intramuscular route. The $AUC_{0\text{ to }24}$ was significantly lower after micronized P, yielding a bioavailability of 8.6% for the oral micronized form of P relative to the intramuscular dosage form. Although the bioavailability of micronized P appears to be low, it is almost equal to the bioavailability of other orally administered micronized steroids. For example, a 10% bioavailability is found with oral micronized E_2 (Estrace; Mead Johnson, Evansville, IN) (13).

A comparison of the pharmacokinetics of micronized P with other orally administered P preparations was complicated by the lack of published literature on the effects of food ingestion and dose proportionality for synthetic progestogens. Data from unpublished studies, however, were provided by the UpJohn Company for purposes of comparison with our data on micronized P absorption. These in-house documents (Clinical Services Study No. 038 and Clinical Services Study No. 030; the UpJohn Company, Kalamazoo, MI) pertained to pharmacokinetic studies on Provera (medroxyprogesterone acetate [MPA]; UpJohn) a synthetic progestational agent, and suggested an enhanced extent of absorption when Provera was administered in proximity to meals, similar to the effects of food on the absorption of micronized P. In contrast to micronized P, the rate of absorption of Depo-Provera (MPA formulated for intramuscular injection; UpJohn) was significantly influenced by the size of the dose. Studies designed to evaluate the dose proportionality following the intramuscular administration of Depo-Provera (100 mg/mL) suggested that the rate, but not extent of absorption, was enhanced by increasing the injection volume from 1 mL to 4 mL.

A study done by Salimtschik et al. (14) in a group of breast cancer patients compared the absorption of single doses of oral and intramuscular MPA at several dosage levels. The results showed a dose-dependent increase in serum MPA concentrations for both routes of administration. Similar to our results with oral versus intramuscular P, the T_{max} occurred significantly later, and the $t_{\frac{1}{2}}$ was significantly longer after intramuscular administration. In contrast to micronized P, however, the peak levels of MPA appeared similar between the oral and intramuscular dosage forms, suggesting that the bioavailability was similar for the two dosage forms.

In conclusion, these findings on the bioavailability, dose proportionality, effects of food on absorption, and our comparisons with intramuscular P and MPA suggest that micronized P may have advantages over intramuscular P and MPA. It has been reported that this oral P preparation has no detectable suppressive effects on HDL_2 cholesterol, in contrast to MPA and 19-nortestosterone progestins (15–17). It does not appear to affect aldosterone synthesis (18), blood pressure (19), or mood (20). It is presumed safe for early use in pregnancy as demonstrated by its ability to support implantation in a surrogate ET program (21), while avoiding the potential medico-legal liability of other progestins (22). Finally, this preparation has recently been demonstrated to have a protective effect on endometrium in postmenopausal women using estrogen replacement therapy (23).

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