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Comparative bioavailability of two medroxyprogesterone acetate suspensions

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Summary

The drug particle-size characteristics of two medroxyprogesterone acetate (MPA) sterile suspension products (Depo-Provera sterile aqueous suspension, DP, Upjohn; Farlutal Depot sterile aqueous suspension, FD, Farmitalia) were compared, followed by bioequivalence studies of these preparations in humans after both oral and intramuscular administration. By means of scanning electron microscopy, DP was shown to contain smaller drug particles than FD. After oral administration of the suspensions in a single-dose, randomized cross-over study involving 16 healthy males, DP-treated subjects exhibited a significantly higher mean individual peak serum MPA concentration (C_{max}) and a significantly larger mean area under the serum MPA concentration vs time curve compared with FD-treated subjects. In a separate single-dose, randomized, non-cross-over study involving 38 healthy males, log-transformed data showed the mean C_{max} to be significantly higher in DP-treated subjects than in FD-treated subjects after intramuscular administration of the drug. We conclude that the bio*in*equivalence of MPA formulations may be attributed largely to variations in the overall size of the component drug particles.

Introduction

Different brands of drug products containing a chemically equivalent active compound may exhibit inequivalent physicochemical behavior. This can sometimes be a result of interproduct differences in the ultrastructure of the active compound. In particular, interproduct particle size differences can lead to profound disparities in the rates of solution and, ultimately, the bioavailability of pharmaceutical compounds (Hoener and Benet, 1979; Higuchi et al., 1985). Such bioinequivalencies become important clinically when they result in an unexpected treatment response.

High-dose medroxyprogesterone acetate (MPA) therapy has been shown to produce improvements in the rate of induced remission of several types of carcinoma. The normal route of administration in such uses is intramuscular injection of a sterile aqueous suspension; however, this route is associated with a 14% incidence of abscess formation and a 15% incidence of infiltration at the injection

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site (Lober, 1983). As an alternative, *oral* MPA administration has been shown to induce an antiblastic activity in advanced breast cancer similar to that seen in objective remissions obtained after intramuscular injections (Pannuti et al., 1980).

Several companies have introduced MPA sterile aqueous suspension products into the market. It is unlikely that all of these products contain drug with identical particle characteristics, bringing to question the bioequivalency, or lack thereof, of these products.

The purposes of this study were to compare the drug particle-size characteristics of two internationally marketed brands of MPA sterile suspension (Depo-Provera™ sterile aqueous suspension, Upjohn; Farlutal Depot™ sterile aqueous suspension, Farmitalia) and to see if any observed particle size differences would result in differing absorption characteristics after either oral or intramuscular administration.

Materials and Methods

Analyses of drug samples

Depo-Provera source. Both lots of Depo-Provera sterile aqueous suspension (Upjohn), containing 150 mg MPA per ml, were obtained in-house from the manufacturer. Lot B914N was used in the oral administration study, and lot B774N was used in the intramuscular administration study. All Depo-Provera lots contain bulk drug that has been micronized.

Farlutal Depot source. The Farlutal Depot sterile aqueous suspension (Farmitalia) sample, containing 200 mg MPA per ml, was obtained on the open market in Italy. This lot (2012) was used in both the oral and intramuscular administration studies.

Scanning electron microscopy and elemental analysis. A 1 ml aliquot of each drug suspension was diluted with 2.0 ml of double-distilled water. The resulting dilution was mixed well, and an aliquot of less than 0.05 ml was placed on a carbon stub. The stub was sputter-coated with gold, and the drug samples were photographed with a Cambridge Stereoscan 150 Scanning Electron Microscope. The MPA content of these samples was confirmed via an analysis for elemental content using a Kevex Unispec 7000 System 77 Energy Dispersive Spectrometer.

Potency assay. The potency of each lot used in this study was confirmed by means of a high-performance liquid chromatographic assay specific for MPA.

Particle size analysis. Scanning electron micrographs of the samples were visually inspected, and the diameter of individual particles was measured with a graduated linear scale. While a statistical data design for measuring particle size and/or including a specific sample was not attempted with this general morphological inspection, the MPA samples and fields chosen for evaluation were consistent with what was observed overall.

Comparative bioavailability studies

After oral administration. Sixteen healthy males (mean age: 26.8 ± 8.1 years; mean weight: 74.3 ± 6.1 kg) took single 500-mg oral doses of MPA in a randomized cross-over study. Subjects took either Depo-Provera or Farlutal Depot (mixed in 50 ml of orange juice and followed by 6 oz of water) and, after a minimum of 28 days, crossed over and took the other brand. Blood samples were drawn just before drug administration (time 0) and at the following hours after administration: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144. The time 0 blood sample was 10 ml in volume; the remaining samples were each 7 ml. Serum was harvested from all samples as soon as possible after allowing 40 min for clot formation. Serum samples were frozen until they were radioimmunoassayed for MPA-like material, using the method of Cornette et al. (1971). This method is non-specific for both MPA and its metabolites.

After intramuscular administration. Thirty-eight healthy males (mean age: 33.0 ± 7.5 years; mean weight: 77.4 ± 12.9 kg) were given single 500-mg intramuscular doses of MPA in a randomized non-cross-over study. Subjects received either Depo-Provera ($n = 20$) or Farlutal Depot ($n = 18$); injections were made deeply into the gluteal muscle in the upper outer quadrant of the buttock. Blood samples were drawn just before drug administration (time 0) and at the following hours after administration: 1, 2, 4, 6, 8, 10, 12, 16,

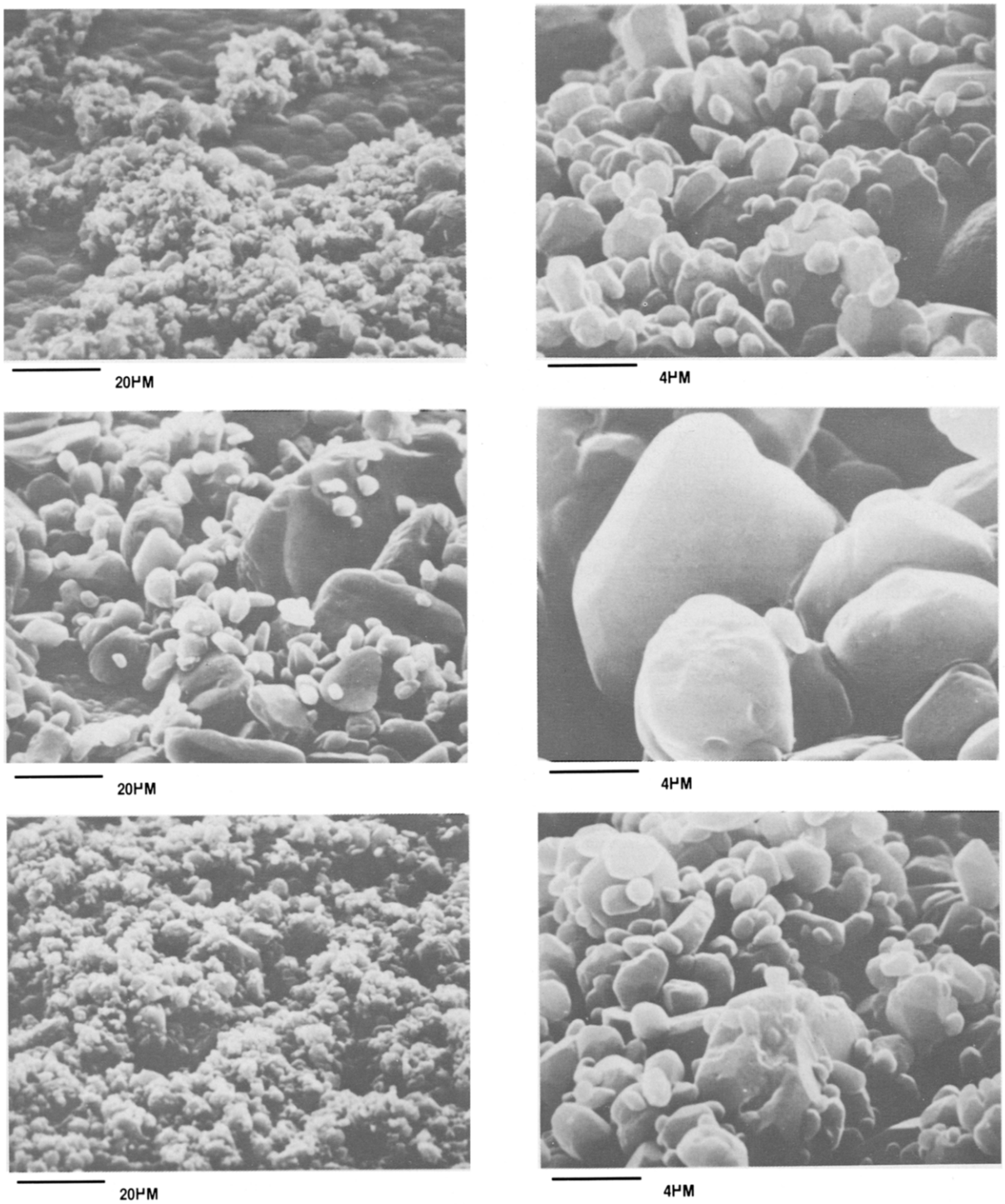

Fig. 1. Scanning electron micrographs of MPA drug particles. Depo-Provera lots B914N (top row) and B774N (bottom row), Farlutal Depot lot 2012 (middle row).

24, 28, 36 and 48; in addition, samples were collected each morning on the following days after drug administration: 3, 4, 5, 7, 9, 11, 14, 17, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112 and 119. All blood samples were 7 ml in volume. Serum was harvested from all samples within 45 min after sampling and then stored and assayed as in the oral administration study.

Pharmacokinetic calculations and statistical methods

Serum levels of MPA and the resultant bioavailability parameters were statistically compared between treatments by means of analysis of variance for cross-over design (oral administration study) or unpaired *t*-test analysis (intramuscular administration study). AUCs were determined using the trapezoidal rule. All doses were normalized to 500 mg, based upon assayed potency. Individual maximum serum MPA concentration data from the intramuscular administration study were subjected to log transformation for statistical analysis because the original values were found to be non-normally distributed and heteroscedastic by Bartlett's test analysis. Unless otherwise indicated, "statistically significant" and similar phrases imply $P < 0.05$.

Results

MPA particle characteristics

The ultrastructures of representative MPA particles (taken from the lots used in the bioavailability studies) can be seen in the scanning electron

TABLE 1

Bioavailability parameters following oral administration of 500 mg medroxyprogesterone acetate (n = 16, cross-over)

Bioavailability parameter	Depo-Provera	Farlutal Depot	*P*-Value (ANOVA)
Individual peak serum MPA concentration, C_{max}, (ng/ml)	106 (44.9) *	75.4 (30.1)	0.002
Time of peak serum MPA concentration, t_{max}, (h)	5.1 (6.2)	10.3 (23.5)	NS **
AUC serum MPA concentration vs time, 0–144 h, AUC, (ng·h/ml)	5733 (1996)	4675 (1602)	0.02

* Standard deviations are given in parentheses.
** Not significant ($P > 0.05$).

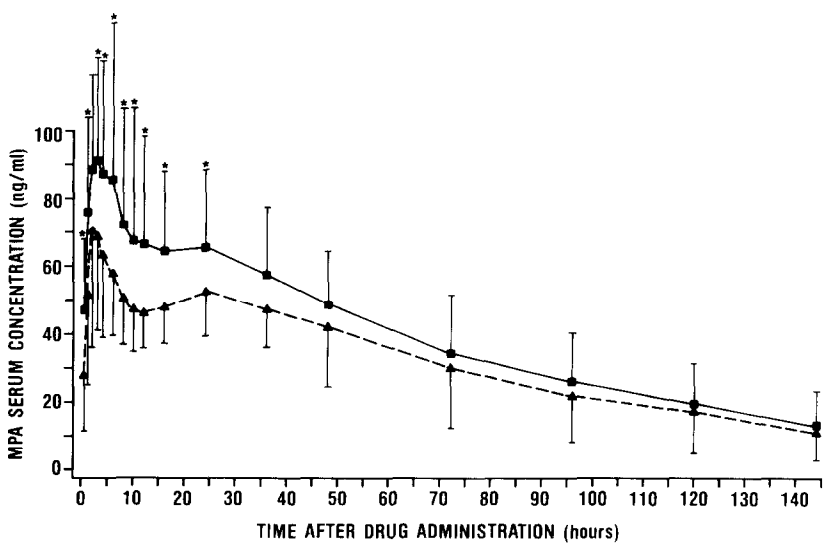

Fig. 2. Serum MPA concentrations following oral administration of two MPA suspensions ■, Depo-Provera; ▲, Farlutal Depot; (n – 16, crossover). *, Significantly different ($P < 0.05$). Doses have been normalized to 500 mg.

micrographs shown in Fig. 1. It is readily apparent that the two Depo-Provera drug samples had overall MPA particle-sizes similar to one another and smaller than those of the Farlutal Depot sample. Indeed, the MPA particles in Depo-Provera had diameters between 0.5 and 4.0 μm, while those in Farlutal Depot had diameters between 1.0 and 47 μm. In addition, the MPA particles in Depo-Provera were of a uniform, spherical shape in contrast to the irregularly shaped particles in Farlutal Depot.

Bioavailability

Table 1 contains statistical information concerning the pharmacokinetic data gathered after oral administration of the two preparations, and Fig. 2 graphically presents mean serum MPA concentrations throughout the study after oral administration. Both the individual peak serum MPA concentration (C_{max}) and area under the serum MPA concentration vs time curve (AUC) were significantly higher for Depo-Provera than for Farlutal Depot. The time of peak serum MPA concentration (t_{max}) occurred earlier with Depo-Provera than with Farlutal Depot but not significantly so. Statistically significant between-group differences in serum MPA concentrations were

TABLE 2

Bioavailability parameters following intramuscular administration of 500 mg MPA

Bioavailability parameter	Depo-Provera ($n = 20$)	Farlutal Depot ($n = 18$)	P-Value (t-Test)
Individual peak serum MPA concentration, C_{max} (ng/ml)	26.0 (25.0) *	15.7 (8.3)	0.03
Time of peak serum MPA concentration, t_{max} (days)	14.0 (22.1)	26.8 (29.8)	NS *
AUC Serum MPA Concentration vs Time, 0–14 days, AUC (μg·h/ml)	5.1 (1.9)	3.7 (2.4)	0.05
AUC Serum MPA Concentration vs Time, 0–119 days, AUC, (μg·h/ml)	26.77 (8.6)	25.54 (15.4)	NS

Values are means ± S.D.
* Not significant ($P > 0.05$).

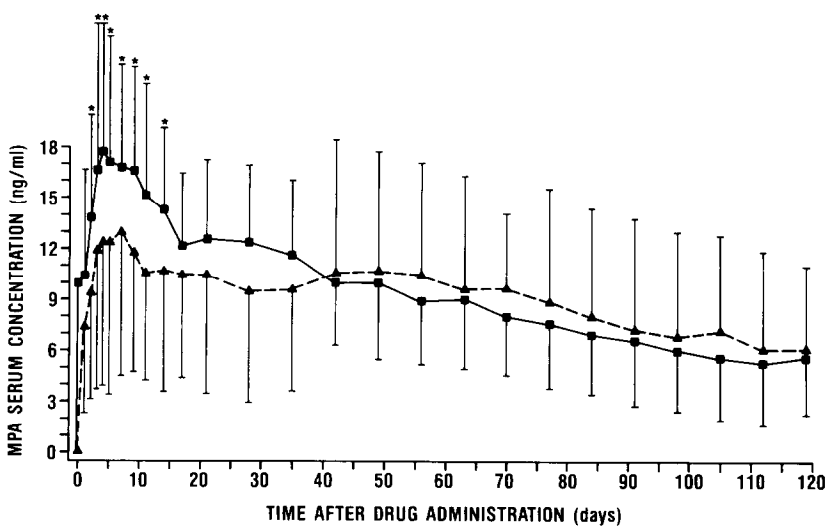

Fig. 3. Serum MPA concentrations following intramuscular administration of two MPA suspensions. ■, Depo-Provera™ ($n = 20$); ▲, Farlutal Depot™ ($n = 18$). *, Marginally significantly different ($P < 0.1$). Doses have been normalized to 500 mg.

observed at the 0.5, 1, 3, 4, 6, 8, 10, 12, 16, and 24-h post-dosing sampling times, with Depo-Provera producing the higher concentrations. The terminal phase half-life of both products was approximately 40 h.

Table 2 contains statistical information concerning the pharmacokinetic data gathered after intramuscular administration of the two MPA preparations; mean serum MPA concentrations after intramuscular administration are presented graphically in Fig. 3. Log-transformed data yielded mean C_{max} significantly higher for Depo-Provera than for Farlutal Depot. Upon visual inspection of Fig. 3, it is apparent that both products produced large intersubject variability in serum MPA concentration. Marginally significant ($P < 0.1$) between-group differences were observed at the 48 h and 3, 4, 5, 7, 9, 11, and 14-day post-dosing sampling times, with Depo-Provera producing the higher concentrations. AUCs from 0 to 336 h (day 14) were significantly different, although those from 0 to 119 days were not. t_{max} occurred earlier with Depo-Provera than with Farlutal Depot, but the difference was not statistically significant. The terminal phase half-life of both products was approximately 50 days.

Discussion

Depo-Provera and Farlutal Depot were shown to have absorption characteristics clearly different from one another after both oral and intramuscular administration. While other formulation dissimilarities may have influenced the results to some extent, we attribute these differences to the smaller overall size of the drug particles in Depo-Provera.

We found that after oral administration, both rate and extent of absorption appeared to be affected by particle size difference, based upon the resultant significant differences in serum MPA concentrations at early (through 24 h) sampling times, as well as C_{max} and $AUC_{0-144\ h}$.

After intramuscular administration, differences in serum MPA concentrations appeared to be limited to relatively early sampling timepoints. Marginally significant or significant differences were found in serum MPA concentrations and AUC values calculated up to 14 days; C_{max} also differed significantly between the two treatments. As time progressed, serum MPA concentration differences decreased, resulting in similar concentration profiles. This could be the result of physicochemical or host-originated factors, such as encapsulation of the injection site, limited availability of dissolution media, or aggregation of drug particles, that would negate the effect of the original MPA surface-area differences over time.

The MPA used in manufacturing Depo-Provera is subjected to a controlled micronization process. It is well-known that reducing the particle size of a drug increases its total surface area and often its dissolution rate. A faster dissolution rate, in turn, can lead to a more rapid and, occasionally, greater extent of absorption. As early as the mid-1960s, it was shown that MPA particle size had an inverse relationship to MPA bioavailability after oral tablet administration (Helmreich and Huseby, 1965; Smith et al., 1966). Since drug in an aqueous suspension is analogous to the dispersion of tablet particles that exists after disintegration, it was not surprising to find similar results in our study.

High doses of MPA have been associated with much variability in pharmacokinetic parameters. Blossey et al. (1982) reported that oral (tablet) MPA doses of 1.5 mg/day produced a broad range of plasma MPA concentrations in patients with advanced breast cancer. In a study conducted in postmenopausal patients with metastatic breast cancer, the interpatient variability of plasma MPA levels in the plateau state increased significantly with oral dose (Blossey et al., 1984). Such interpatient differences can only by magnified by interproduct formulation differences of the kind found in this investigation. As a result, the therapeutic activity of the drug may, in theory, be greatly exaggerated or depressed. Since our data indicate that clinicians most likely see varying responses to MPA among their patients regardless of the drug brand, indiscriminately prescribing or dispensing bioinequivalent MPA products would possibly introduce additional variability and unpredictability of patient response. Because drug-band selection is a controllable variable, it seems prudent for

clinicians to limit their prescribing and dispensing practices to one MPA brand when possible.

We conclude that there is apparently a difference in the overall rate and extent of absorption of Depo-Provera compared with that of Farlutal Depot after oral administration and a difference in the rate (but not extent) of absorption after intramuscular administration. It is likely that the dissimilarities of the two suspensions can largely be attributed to the smaller overall size of the MPA particles in Depo-Provera and, further, appear to be dependent upon the route of administration and time after dosing. The clinical consequences of these observations are unknown.

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