Drug Development and Industrial Pharmacy, 26(5), 567–570 (2000)

COMMUNICATION

Improved Bioavailability of a Micronized Megestrol Acetate Tablet Formulation in Humans

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ABSTRACT

Megestrol acetate, a progestogen widely used in the palliative treatment of endometrial carcinoma and breast cancer, is currently administered orally as a solid dosage form. Bioavailability of the drug following oral administration is closely related to the effectiveness and safety profile of the drug in formulation. Improved immediate-release formulations should allow improved drug delivery into the systemic circulation and, at the end, to the site of action. The micronization of drugs is one of the technological procedures to achieve such a purpose. This paper reports the design and results obtained in an in vivo study of the bioavailability of a micronized megestrol acetate tablet formulation compared to a conventional form. A significant increase in the drug bioavailability was observed, in either the rate or the extent of absorption. In vitro dissolution data of the two study formulations reflected the in vivo findings.

INTRODUCTION

Megestrol acetate (Fig. 1) is a progestogen widely used in the palliative treatment of endometrial carcinoma and breast cancer in daily oral doses of 40 to 320 mg and 160 mg, respectively (1). Megestrol acetate is known to have an excellent safety profile. Clinical studies with administered doses up to 800 mg per day showed no serious side effects (2). Unlike progesterone, megestrol acetate has reduced hepatic metabolism.

Previous bioavailability/bioequivalence studies (3,4) following the administration of a 160 mg oral dose, as tablets and sachets containing the conventional form of the drug, showed an elimination half-life $t_{1/2}$ for meges-

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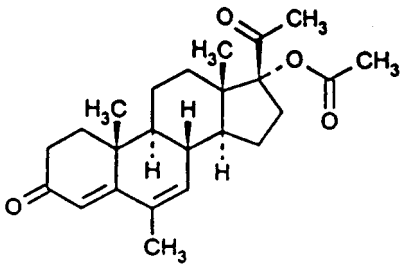

Figure 1. Molecular structure of megestrol acetate.

trol acetate of 32.2 (±11.7) hr and 33.8 (±13.6) hr. Maximum plasma concentrations of 136.2 (±71.2) ng/ml were observed between 1.0 and 4.0 hr postadministration.

Micronization of drugs is currently used to increase bioavailability, to provide higher dissolution rates, and to improve absorption. Gaver (2) compared the bioavailability of two 160-mg tablet formulations, one containing micronized megestrol acetate and the other a conventional tablet formulation of 40 mg administered four times a day. The author found a significant C_{max} mean difference between the two 160-mg doses ($p < .05$), with the micronized form revealing a higher rate of absorption. Relative bioavailability, as AUC_{inf} ratios, of the micronized form in relation to the conventional form was 1.25. According to the author, other pharmacokinetic parameters, such as t_{max} and $t_{1/2}$, did not differ significantly between the two formulations.

The objective of this study was to evaluate the relative bioavailability of a new tablet formulation containing 160 mg of micronized megestrol acetate by comparison with a regular 160-mg megestrol acetate tablet formulation.

EXPERIMENTAL

Study Design

The study was performed as a two-treatment, two-period, balanced, randomized crossover design. Twenty-four healthy male subjects were enrolled in the clinical investigations. Subjects were between 20 and 39 years old (mean 24 years), and their average body mass and height (mean ± SD) were 74.3 ± 9.1 kg and 176.8 ± 7.1 cm, respectively. None of the subjects had any relevant medical history or was on any other medication.

Subjects were assigned randomly to one of two sequences (TR, RT), taking either the test preparation or the reference preparation. After a 1-week washout period, the subjects were crossed over. Written informed consent was obtained from all subjects prior to the start of the study, which had the approval of the Ethics Committee of the clinical unit. All the subjects fasted overnight for at least 10 hr prior to the administration of the investigational products at 08:00. Each formulation was swallowed with 150 ml of water, after which the subjects remained in the upright position for at least 1 min. Standard meals were served 4.0, 8.0, and 11.0 hr after drug administration, and during the entire course of the study, all the subjects complied with the diet restrictions concerning the intake of xanthines, alcohol, quinine, and citrus fruits.

Blood samples (8 ml) were obtained by an indwelling cannula or by venipuncture immediately prior to and at the following times after administration of each formulation: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 14.0, 16.0, 24.0, 35.0, 48.0, 72.0, and 96.0 hr. Blood samples were withdrawn into a Luer Monovette (Sarstedt, Portugal) tube containing lithium heparin as the anticoagulant. Plasma samples were obtained by centrifugation at 5°C for 10 min at 2500 rpm and stored frozen, at or below −20°C, in polypropylene screw-capped tubes pending analysis. After the 24-hr blood-sampling period, subjects were allowed to leave the clinical unit, returning for the subsequent samplings until 96 hr postdose.

Drug Formulations

Both study formulations, 160-mg conventional tablets and micronized megestrol acetate tablets, were thoroughly investigated in our institute with respect to the biopharmaceutical quality. USP 23 (5) includes a product monograph for megestrol acetate tablets, which was generally followed. Assay for the contents of megestrol acetate in both preparations showed a difference of 1.5%. Dissolution profiles (Fig. 2) revealed a higher dissolution rate for the micronized form, reaching 100% dissolution after 10 min. After 1 hr of dissolution, there was still a 6.9% difference in the amount of drug dissolved between

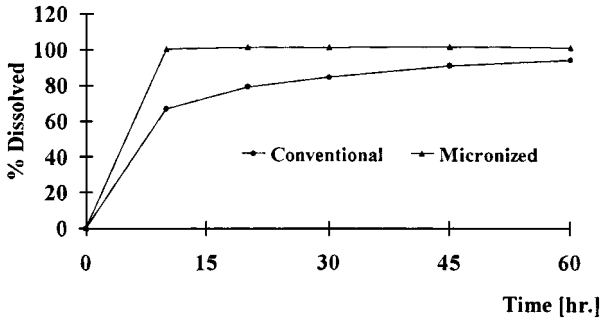

Figure 2. Dissolution profiles of both products.

the two formulations. All other tested pharmaceutical characteristics conform to the specifications. These in vitro results anticipated a different in vivo behavior of the two study formulations.

Sample Analysis

Megestrol acetate concentrations in plasma samples were determined using a specific and sensitive reverse-phase high-performance liquid chromatography (HPLC) procedure with UV detection based on that proposed by Gaver (2) and Camaggi (3).

Plasma samples were thawed at room temperature, after which a 1-ml sample was spiked with beclamethasone (internal standard, IS) and extracted with *n*-hexane for 15 min in a glass screw-capped tube. The organic layer was transferred to a clean glass tube and evaporated to dryness at 40°C under a stream of nitrogen. The dry residue was reconstituted with 100 µl of methanol. Samples of 20 µl were injected into a HiChrom HiRPB column (250 × 4.6 mm, 4 µm). The mobile phase, a mixture of acetonitrile, methanol, and 6% acetic acid solution (42:23:34), was pumped at 1.5 ml/min, and the column effluent was monitored at 290 nm.

Quantification

Calibration and quality control samples were prepared by spiking drug-free plasma with megestrol acetate and the IS. The weighted ($1/conc^2$) regression of the peak height ratios of megestrol acetate and the IS were calculated by least-square linear regression. The limit of quantification was set at 5 ng/ml. All samples with predicted concentrations below the limit of quantification (lowest standard) were reported as ''blq'' (below the limit of quantification) and entered as a zero concentration for the calculations.

Pharmacokinetic Analysis

All pharmacokinetic parameters were determined by noncompartmental models or were taken directly from the curves of plasma concentration versus time. Maximum plasma concentration C_{max} and t_{max}, time to reach C_{max}, were taken from the observed profiles of megestrol acetate plasma concentration versus time. The elimination rate constant K_e is the slope of the terminal log-linear portion of the pharmacokinetic profile and was determined by least-square regression analysis. The apparent elimination half-life $t_{1/2}$ was determined as $\ln 2/K_e$. The curve of the area under the plasma concentration versus time from time zero to t_{max} was determined by the linear trapezoidal rule and from t_{max} to the last quantifiable time point C_t by the log-linear trapezoidal rule. The extrapolated area under the curve from C_t to infinity was determined as C_t/K_e. The total area under the curve AUC_{o-inf} was the sum of AUC_{o-t} and AUC_{t-inf}.

Statistical Analysis

The AUC_{o-inf} and C_{max} values were analyzed after log transformation. Analysis of variance (ANOVA) was carried out according to the crossover design for both AUC_{o-inf} and C_{max}. The statistical model included formulation, period, sequence, and subject nested within sequence as fixed effects (6). Parametric and nonparametric $(1-2\alpha)$ confidence intervals (7,8) were determined for the estimates test/reference, and t_{max} was analyzed relative to the therapeutic relevance of the products difference. All statistical calculations were performed at the $\alpha = .05$ significance level.

RESULTS AND DISCUSSION

Figure 3 shows the mean plasma levels of megestrol acetate for both study formulations. Formulation A, containing the micronized drug, exhibits higher bioavailability than formulation B. Geometric mean AUC values of 3552 and 1678 $ng \cdot hr \cdot ml^{-1}$ were observed, respectively, for products A and B, with a geometric mean ratio of 2.1. This result, although in accordance with that reported by Gaver (2), shows a much better in vivo performance of the micronized megestrol acetate tablet formulation. The 90% $(1-2\alpha)$ parametric and nonparametric confidence intervals (1.93–2.32 and 2.44–3.19) confirm these findings.

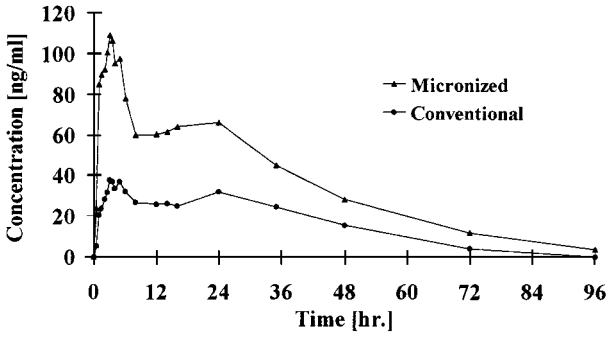

Figure 3. Mean plasma concentration-versus-time profiles for both products.

The C_{max} mean values of 125 ng/ml and 45 ng/ml for products A and B resulted in a geometric mean ratio of 2.8, confirming the improved performance of the micronized form regarding the absorption rate of the drug. Again, the 90% $(1 - 2\alpha)$ parametric and nonparametric confidence intervals of 1.87–2.30 and 2.42–3.03, respectively, clearly showed evidence of the improved in vivo performance of the micronized form.

Interindividual variability in drug plasma levels and in the main pharmacokinetic parameters was rather high. ANOVA results for AUC and C_{max} showed a significant subject effect ($p = .00$). Intrasubject coefficients of variation from $ANOVA_{log}$ (9) for AUC and C_{max} values were, respectively, 18.7% and 27.6%. It seems that megestrol acetate, with respect to C_{max}, behaves as a highly variable drug. This should be carefully considered when planning in vivo studies for bioequivalence purposes.

The t_{max} mean values for both formulations, 6.3 hr for the micronized form and 8.0 hr for the conventional formulation, were not significantly different. Very similar elimination half-lives were found, 22.3 hr for formulation A and 23.9 hr for formulation B, although the values are lower than those previously reported by other authors.

Overall in vivo results are in good agreement with data obtained with the in vitro dissolution test. Early differences in the in vitro dissolution profile seem to correlate with the in vivo findings. Although both study formulations are intended to behave as immediate-release products, making quantitative and meaningful in vitro/in vivo correlations difficult to obtain, a rank and qualitative relationship between both products is evident. The micronized formulation containing megestrol acetate represents a significant improvement in the bioavailability of the drug, beyond that reported by other authors. In fact, both the total amount of drug absorbed and its rate of absorption had a more than twofold increase when compared to the conventional formulation, representing a potential therapeutic advantage over the nonmicronized form.

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