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SHORT COMMUNICATION

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Pharmacokinetic evaluation of two different formulations of megestrol acetate in patients with advanced malignancies

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Abstract The bioequivalence of two megestrol acetate formulations, 160-mg "tablets" and 160-mg "sachets," was investigated in a single-dose, open-label, balanced-for-sequence cross-over study involving 12 advanced-cancer patients. The observed plasma megestrol-acetate time course obtained with both formulations was consistent with the literature data. The main source of variability in the pharmacokinetic parameters was intersubject variability; drug formulation played only a minor (and nonsignificant) role. The width of the 90% confidence interval of the area-under-the-curve (AUC) ratio (sachets: tablets) computed according to Schuirmann (0.9–1.4) was mainly due to the presence of a single outlier, showing an AUC ratio of 2.7. The trend to higher bioavailability of the new formulation was not significant, especially as compared with the dose-response data reported in the literature.

Key words Megestrol acetate · Pharmacokinetics · Bioequivalence

Introduction

Megestrol acetate is widely used in the palliative treatment of advanced breast cancer and endometrial cancer because of its clinical efficacy and excellent safety profile. In single-agent therapy, the average overall response rate to megestrol acetate therapy in advanced breast cancer is 30% [12, 15, 21]. The response rate is equivalent to that reported for tamoxifen, another hormonal agent widely used in treatment of breast cancer [16]. The weight gain associated with the use of megestrol acetate may be beneficial in patients who also have cancer anorexia. Several randomized, placebo-controlled trials demonstrate that megestrol acetate therapy improves appetite and food intake in such patients [5, 11]. Data regarding the use of megestrol acetate in the treatment of cachexia related to human immunodeficiency virus (HIV) infection also indicate its effectiveness in treating HIV-related anorexia and cachexia [9, 14].

From the compliance point of view, in advanced neoplastic patients it is easier to give liquid formulations rather than tablets and capsules. Thus, a new 160-mg "sachet" formulation has been developed; the aim of the present study was to determine the bioequivalence of the new oral formulations of megestrol acetate relative to the commercially available 160-mg "tablets.".

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Patients and methods

Patients

The subjects of this study were 12 advanced-cancer patients with normal hepatic and renal function who were aged between 40 and 70 years, had a performance status (Karnofski) of >70% and a body weight of 45–90 kg, and were within ±10% of normal for height and body frame. The characteristics of the patients are described in Table 1.

The exclusion criteria were concomitant treatment with cytostatics, corticosteroids, or other hormonal therapies; concomitant treatment with phenobarbital or any other metabolic inducer drug; positive anamnesis for thrombosis, hypertension, diabetes, or cardiovascular disease; any of the following parameters higher than 25% of the upper normal range: SGOT, SGPT, serum bilirubin, blood urea nitrogen (BUN), and serum creatinine; serum albumin levels lower than 25% of the lowest normal range; and the receipt of an investigational drug within 30 days of the study.

Drugs

The megestrol acetate tablets used as a reference in this study are commercially available as Megestil 160-mg tablets, obtained from

Table 1 Megestrol acetate pharmacokinetics: characteristics of the patients (*NH* Non-Hodgkin's, *ca.* carcinoma, *LFN* lymph-nodes, *Creat. Cl.* creatinine clearance)

Patient number	Sex	Age (years)	Primary tumor	Metastases	Weight (kg)	BUN (mg/dl)	Creatinine (mg/dl)	Creat. Cl. (ml/min)	Bilirubin (mg/dl)	SGOT (U/l)	SGPT (U/l)
1	M	68.5	Melanoma	LFN	92.00	48	1.20	76.13	0.3	19	16
2	M	69.0	NH lymphoma	LFN	68.00	25	1.10	60.96	0.6	28	15
3	M	67.5	Leukemia	LFN	83.00	60	1.40	59.70	0.9	22	15
4	M	62.0	Kidney	LFN	51.70	14	0.90	62.23	0.5	23	9
5	M	64.0	Bladder	Bones, lung	85.00	41	1.10	81.57	0.5	29	17
6	M	59.0	Bladder	LFN peritoneum	55.00	40	1.10	56.25	0.4	14	10
7	M	69.5	Bladder	Pelvis	45.50	29	0.90	49.50	0.4	11	7
8	M	60.5	Colorectal ca.	Liver	58.50	19	0.80	80.74	0.5	21	21
9	M	51.0	Colorectal ca.	Liver (removed)	69.50	19	0.80	107.39	0.7	20	38
10	M	64.0	Lung	Bones	57.00	42	1.00	60.17	0.8	19	10
11	M	61.0	Mesothelioma	\	71.40	10	1.00	80.33	0.3	2	6
12	M	70.0	Lung	\	64.00	12	0.80	77.78	0.8	21	27

Boehringer-Mannheim Italia. Megestrol acetate "sachets," batch number F088-03A, were obtained from Boehringer-Mannheim Italia. Each sachet contained white granulated material whose composition was as follows: megestrol acetate, 160 mg; Cetomacrogol 100,5 mg; and sorbitol, 2335 mg.

Treatment modalities

A randomized, balanced crossover design was used to determine the bioequivalence of the two oral formulations of megestrol acetate. Patients received single oral administrations of 160 mg of megestrol acetate according to the crossover design. The two treatments were scheduled with an interval of 7 ± 2 days. The formulations were given early in the morning after an overnight fast as follows. For 160-mg tablets, each tablet was swallowed together with 100 ml of water. For 160-mg sachets, the contents of one sachet were poured into a disposable glass containing 50 ml of tap water and thoroughly stirred with a teaspoon for 30 s. The reconstituted suspension was then given and the patient was asked to ingest a further 50 ml of tap water, rinsing the glass and the mouth.

A predose blood sample was collected for megestrol determinations. The patients than received the test medication according to the randomization schedule. Blood samples (2 ml) were then drawn at 1, 2, 3, 4, 6, 8, and 10 h after drug administration; 3-ml samples were obtained at 24, 48, 72, and 96 h after drug administration. The blood samples were immediately centrifuged (2500 *g* for 5 min). Each plasma sample was divided into two tubes and stored at –20 °C until analysis.

Analytical method

A specific, sensitive, and reliable high-performance liquid chromatographic method for the determination of megestrol acetate in human plasma has been developed and validated for this study. The complete method description and validation data have been reported elsewhere (Camaggi et al. submitted for publication). Briefly, plasma samples were extracted with cyclohexane in a vortex mixer. Chromatographic analysis was performed with a cyanopropyl chromatographic column (Supelcosil LC-CN; 25 cm × 4.6 mm inside diameter; particle size, 5 µm) and UV detection (wavelength, 290 nm). The sensitivity, defined in terms of minimal detectable concentration, was better than 2 ng/ml; the mean recovery of the unchanged drug was better than 90%. The interassay coefficient of variation was 7.68%. The mean intraassay precision was 4.47% for sample concentrations above 5 ng/ml.

Pharmacokinetic analysis

Computations were carried out with the BMDP package of statistical programs [6] running on a Digital VAX GPX-II computer under the VMS version 5.3 operating system. Two one-sided *t*-tests (Schuirmann) and Westlake's symmetrical confidence intervals (CI) were computed by programming Westlake's [20] and Schuirmann's [18] formulae in MATHEMATICA language on a Macintosh IIx computer using the MATHEMATICA version 2.1 program [22].

The peak concentration (C_{max}) and the corresponding peak time (t_{max}) were obtained directly from the experimental data. The experimental area under the plasma concentration-time curve (AUC_{96}) was calculated by the trapezoidal rule from time zero to 96 h after treatment. The total (time = 0 to infinity) AUC was computed as follows:

$$AUC = AUC_{96} + C96_{int}/\lambda,$$

where λ is the rate constant calculated by log-linear regression analysis of the plasma concentration-time curve in the apparent terminal phase and $C96_{int}$ is the concentration at $t = 96$ h as estimated by the same regression equation. The mean residence time (MRT) was calculated as the ratio of the area under the first moment curve (AUMC) and the AUC.

Estimated plasma megestrol pharmacokinetic parameters were analyzed both in the linear scale and after log transformation. Analysis of variance (ANOVA) was carried out according to the crossover design of the study, taking into account the *sequence* effect, the *subject* effect, and the *formulation* effect.

Results

The mean plasma levels of megestrol acetate recorded during this study are shown in Fig. 1. Single-patient data are reported in Table 2. ANOVA (latin-square design; log-transformed data) failed to reveal any statistically significant difference between the mean AUC values with regard to sachet or tablet administration; intersubject variability was the main source of data spread (Table 3). Similar results were obtained from the matched-pair *t*-test ($P = 0.28$) and from the corresponding nonparametric tests (Wilcoxon, $P = 0.48$; signed, $P = 1.00$).

The width of 90% CIs computed according Schuirmann or Westlake (0.9–1.4 and 0.7–1.3, respectively) was mainly due to the presence of a single outlier (patient 1), showing a 2.7 AUC ratio (sachets : tablets). In a repeat of the statistical analysis without the data relative to this patient, Schuirmann's CI (AUC ratio, sachets : tablets) was

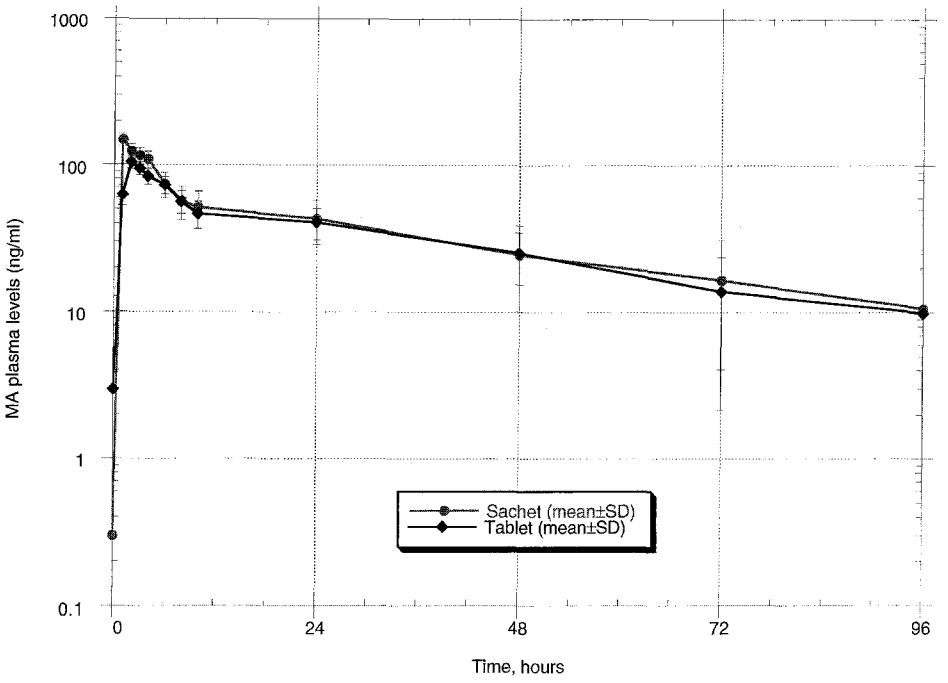

Fig. 1 Mean megestrol acetate (*MA*) plasma concentration-time curves (±SD) generated for the two MA formulations (single administration of 160 mg)

Table 2 Megestrol acetate pharmacokinetics: patients' data

Patient number	Sequence		AUC (ng h ml^{-1})		C_{max} (ng h ml^{-1})		t_{max} (ng/ml)		$t_{1/2}$ (h)		MRT (h)	
	Sachet	Tablet	Sachet	Tablet	Sachet	Tablet	Sachet	Tablet	Sachet	Tablet	Sachet	Tablet
1	1	2	5287	1932	227.6	63.1	1	4	35.9	38.5	48.1	52.7
2	1	2	3312	3526	184.8	119.7	4	1	30.1	51.1	35.2	76.3
3	2	1	1607	1979	122.4	97.4	1	3	33.2	35.6	38.9	47.3
4	2	1	4608	4731	253.2	289.7	1	2	24.4	24.4	34.2	33.4
5	1	2	3309	1940	180.1	75.5	1	1	37.4	35.1	49.4	48.4
6	2	1	2153	2418	232.2	209.3	1	1	10.2	7.2	13.3	19.1
7	2	1	3956	4798	179.9	188.5	1	2	24.0	29.9	31.5	43.2
8	1	2	5636	4623	193.1	91.3	2	1	34.9	32.2	51.0	53.0
9	2	1	2507	1590	162.0	76.5	4	4	30.1	21.1	41.2	28.4
10	2	1	2899	2596	102.3	99.0	2	3	40.8	36.3	55.8	50.7
11	1	2	2100	2917	110.7	212.0	4	6	35.8	26.6	47.5	30.7
12	1	2	8149	7249	107.7	111.9	3	4	68.1	47.4	105.9	72.9

0.9–1.2 and Westlake's 90% CI interval was 0.8–1.2. No significant difference was observed in t_{max}, $t_{1/2}$, or MRT values with regard to the two formulations (Table 3).

Discussion

The plasma megestrol acetate concentrations recorded during this trial are consistent with those previously determined by several other authors [1, 2, 7, 8, 10]. The variability in drug plasma levels and pharmacokinetic parameters was rather high (coefficient of variation in AUC, 50%). This variability is consistent with data reported by other authors [2, 7, 8]. As shown by the ANOVA procedure, the main variability factor in the pharmacokinetic parameters was the *subject*; the *drug formulation* played only a minor (and nonsignificant) role.

Although it was not significant when analyzed with the ANOVA, matched-pair *t*-test, and nonparametric procedures, a trend to a better absorption – and, consequently, to higher bioavailability – of the new formulation can be inferred from the C_{max} values. This trend is better documented by the Schuirmann and Westlake tests. Due to subsequent distribution factors, the increased peak level does not, however, significantly influence the overall bioavailability of the drug; as can be observed in Fig. 1, the terminal-phase plasma levels almost overlap. It is also noteworthy that the coefficient of variation (CV) in peak concentration was particularly high after the administration of standard megestrol acetate tablets (CV, 52%). The new sachet formulation exhibited more reproducibility with respect to this parameter (CV, 30%).

Two preparations can be considered bioequivalent if their bioavailabilities after administration are similar to such a degree that their effects with respect to both efficacy

Table 3 Crossover study: main pharmacokinetic parameters

	AUC (ng h ml^{-1})		C_{max} (ng/ml)		$t_{1/2}$ (h)		MRT (h)	
	Sachets	Tablets	Sachets	Tablets	Sachets	Tablets	Sachets	Tablets
Mean	3784	3359	171.4	136.2	33.8	32.2	46.0	46.4
SD	1872	1691	51.7	71.2	13.6	11.7	22.0	17.1
90% CI (Schuirmann)[a]	0.93–1.38		1.02–1.79		0.92–1.23		0.80–1.17	
90% CI (Westlake)[b]	0.69–1.31		0.33–1.67		0.81–1.19		0.81–1.19	
ANOVA[c]:								
Period	$P = 0.28$		$P = 0.38$		$P = 0.73$		$P = 0.81$	
Subject	$P = 0.01$		$P = 0.32$		$P = 0.00$		$P = 0.01$	
Formulation	$P = 0.28$		$P = 0.08$		$P = 0.46$		$P = 0.73$	

[a] Sachet/tablet ratio, Schuirmann's two one-sided *t*-test (log-transformed data)

[b] Sachet/tablet ratio, Westlake's 90% CI (log-transformed data)

[c] Latin-square design, log-transformed data

and safety are essentially the same [4, 19]. The intersubject spread of megestrol acetate plasma concentration is known to be rather high [1, 2, 7, 8, 10]; it has also been reported that the intersubject variability in plasma concentrations reached after 160-mg doses does not correlate with clinical response or toxicity [13]. Both the safety and the efficacy of megestrol acetate are hardly affected by the delivered dose in the 160- to 320-mg range (1:2 dose ratio) [17], and a clear-cut dose-response correlation exists only if the dose is increased to 800–1600 mg/day [3, 9, 15].

For these reasons, the trend to a higher bioavailability of the new formulation indicated by the two one-sided *t*-tests is practically nonsignificant, and the experimental data reported herein are in agreement with the bioequivalence of megestrol acetate 160-mg sachets and 160-mg tablets.

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