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Bioavailability of a new oral formulation of medroxyprogesterone acetate compared with the standard formulation: a single dose randomized study

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Twenty-six female patients with breast cancer participated in an open, randomized, cross-over study comparing single dose bioavailability of a recently developed oral medroxyprogesterone acetate (MPA) formulation (200 mg sachet where MPA is loaded in a polyvinylpyrrolidone cross-linked polymer, MPA/PVP) with the standard formulation (500 mg tablet). Blood tests were performed under standardized conditions for 120 h in all patients and MPA plasma concentrations determined by means of HPLC. Dose-normalized AUC(0–t_z), AUC (0–∞) and C_{max} were all significantly higher for the MPA/PVP formulation than for the standard formulation. The relative bioavailability of the MPA/PVP formulation was on average three times superior to that of the standard formulation. This new MPA formulation might have important clinical implications for the treatment of hormone-sensitive cancer.

Key words: Breast cancer, MPA bioavailability, pharmacokinetics.

Introduction

Medroxyprogesterone acetate (MPA) is a synthetic steroid derived from progesterone. The molecule was synthesized by two independent research groups in 1958[1,2] and has been in clinical use since 1959.[3] It is a white crystalline powder practically insoluble in water, making i.v. administration of the drug impossible. The main clinical indications in oncology have been renal cell carcinoma,[3] endometrial cancer,[4] prostate cancer[5] and breast cancer.[6]

Controversies about doses and scheduling of MPA were predominant for many years mainly due to a lack of sensitive methods for determination of MPA plasma concentrations and, hence, little precise information about the pharmacokinetic and pharmacodynamic properties properties of the molecule. With the development of sensitive radioimmunological and chromatography techniques determination of low MPA concentrations became feasible and showed the following.[7]

(i) After oral administration. MPA absorption depends largely on the characteristics of the dosage form, especially the particle size of the drug preparation. The absorption is prompt but poor: <10% of the administered dose, with peak plasma concentrations detected between 2 and 4 h after a single dose and detectable plasma levels for more than 24 h after administration.
(ii) After intramuscular administration. The drug is absorbed and eliminated very slowly. Peak plasma levels after a single injection are detected within 2–4 days with a slow elimination rate after discontinuation.

Both routes of administration lead to large interindividual differences in plasma concentrations. Oral formulations are easier to handle and more convenient for the patients than parenteral ones. The poor oral bioavailability led some authors to use very high oral dosages of 1000–2000 mg daily, especially in breast cancer, in order to try to overcome this problem.[8] Gastrointestinal absorption might be improved by modification of the formulation. A new formulation of MPA loaded in a polyvinylpyrrolidone cross-linked polymer (PVP) has recently been developed. The aim of the present study was to evaluate the bioavailability after single dose administration of the 200 mg MPA/PVP sachets compared with that of standard 500 mg MPA tablets in an open randomized cross-over

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study in breast cancer patients. [MPA in tablets 500 mg Farlutal® (batch No. SF 1003) and sachets 200 mg (batch No. SF 1006) was supplied by Farmitalia Carlo Erba, Milan, Italy.]

Materials and methods

Protocol design

The study was an open, randomized cross-over single dose investigation in 26 post-menopausal patients with breast cancer. Following oral informed consent patients were given a single oral dose of the two MPA formulations in a randomized order with at least 2 weeks washout between dosing. Treatment A sachets contained 200 mg MPA/PVP. The content of one sachet presented as granules was poured into 120 ml of tap water and stirred until a complete suspension was obtained. Treatment B tablets containing 500 mg commercially available MPA was given with 100–120 ml of tap water. Each subject received both formulations after an overnight fast. Fasting was maintained for 2 h after dosing.

After either administration venous blood samples were drawn through an indwelling catheter in EDTA-containing tubes just prior to ($t = 0$), and then 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h after dosing. Blood samples were immediately cooled on ice and centrifuged in the cold. Plasma samples were stored at −20°C until analysis.

The study protocol was approved by the Danish Health Authorities and by the Ethical Committees for Northern Jutland and Viborg counties.

Patients

Twenty-six post-menopausal female patients with histologically proven breast cancer were included in the study from November 1990 to May 1991. One patient was eliminated from the study without blood sampling because she developed progressive disease during the study period and was excluded from all analysis. The following evaluation was performed in all patients prior to study entry and repeated before the second study period: medical history, physical examination including performance status, height, weight, temperature, pulse rate and systolic and diastolic blood pressure. Blood tests included hemoglobin, WBC, thrombocytes, creatinine, urea, bilirubin, alanine aminotransferase, lactate dehydrogenase and glucose.

Table 1. Patient characteristics

	Group AB	Group BA
N	12	13
Age (years)		
mean	62	59
range	52–74	44–69
Weight (kg)		
mean	69	71
range	49–108	54–112
Height (cm)		
mean	164	166
range	153–170	154–181

All patients included had a good performance status (≤2 according to WHO criteria) with no history of hypertension (unless well controlled with therapy), extreme obesity, diabetes or heavy smoking (≥10 cigarettes per day).

Main characteristics of importance for the pharmacokinetic calculations are shown in Table 1. There were no significant differences concerning any of the patient characteristics between the two sequence groups.

Determination of MPA in plasma

The concentration of MPA in plasma was measured using the HPLC method described by Milano *et al.*,[9] slightly modified in order to obtain an improved sensitivity. MPA and the internal standard, 19-norprogesterone, were extracted from 2 ml of plasma by solid phase extraction. The extracts dissolved in the chromatographic eluent were chromatographed on a 25 cm × 4.6 mm i.d. stainless steel column slurry packed with Nucleosil 300-5 C_{18} reverse phase material.

The chromatographic eluent consisted of 50% acetonitrile in 0.01 M acetate buffer, pH 4. Detection was carried out by UV absorption at a wavelength of 240 nm. The limit of quantification was 2 ng/ml with a coefficient of variation of 10.4%.

Pharmacokinetic data analysis

Pharmacokinetic calculations were carried out with the aid of the Siphar pharmacokinetics package (Simed, Créteil, France). C_{max} and T_{max} in each patient were read as the coordinates of the highest plasma level points measured. Terminal half-life $t_{1/2}$

was estimated by linear regression of natural log concentrations versus time; $t_{1/2}$ = ln2/slope, using a terminal phase selected by eye. AUC(0-t_z) was estimated by the trapezoidal rule up to the last detectable concentration $C(t_z)$ at the time t_z, and AUC(0–∞) was estimated by adding $C(t_z) \times t_{1/2}$/ln2 to AUC(0–t_z). In many patients, accuracy of half-life determination was limited due to a small number of terminal phase points and the proportion of AUC(0–∞) obtained by extrapolation, $\%EXT_{AUC}$ exceeded 20% in some cases. This was mainly due to decay of levels below the quantification limit rather than insufficient sampling time. Relative bioavailability analysis thus includes a comparison of both AUC(0–t_z) and AUC(0–∞).

Pharmacokinetic parameters for the two formulations were compared by ANOVA, using the CSS program (Statsoft, Tulsa, OK), with sequence and formulation, respectively, specified as between- and within-subject factors. AUC, C_{max} and $t_{1/2}$ were analyzed as log transforms and, correspondingly, are also described by geometric means. Relative bioavilability is expressed as dose-normalized ratios of AUC and C_{max} parameters. A 90% confidence interval about the geometric mean was constructed both for dose-normalized and non-normalized parameters, using a two-tailed t-distribution for the mean difference of log transforms (unweighted averaging of cell means over sequence grouping) and standard error $MSE(1/n_1 + 1/n_2)/2$, where MSE is the ANOVA mean square error, and n_1 and n_2 are the numbers of patients in each sequence. The difference between t_{max} values for the two formulations was analyzed non-parametrically: a 90% confidence interval was constructed about the Hodges–Lehmann point estimate, according to a procedure attributed to Moses:[10,11] in this approach, Walsh means are constructed for all possible pairs of t_{max} differences between the two sequence groups; these are ordered and the distribution compared with expectation for Wilcoxon rank sum statistics.

Results

Figure 1 shows the (arithmetic) mean concentration versus time curves for the 25 patients treated with the two formulations. The vertical bars represent standard errors of the mean. Table 2 presents the individual pharmacokinetic parameters calculated for the 200 mg MPA PVP dose and the 500 mg standard formulation. Statistical comparisons are summarized in Table 3.

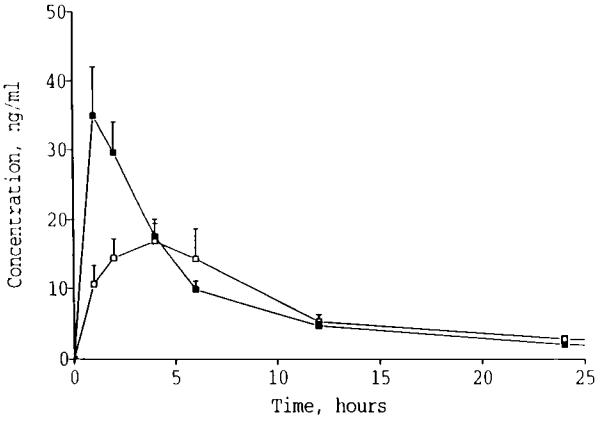

Figure 1. MPA plasma concentration time curves (mean + SEM) for the two MPA formulations: ■, MPA/PVP 200 mg; □, MPA standard formulation 500 mg.

The new lower-dose formulation gave AUC values quite close to those of the standard formulation, but clearly higher C_{max} and shorter t_{max}. No significant alteration in $t_{1/2}$ was found. No significant carry-over effect was detected. Dose-normalized ratios of AUC(0–t_z), AUC(0–∞) and C_{max} were all significantly larger for the MPA/PVP formulation by a wide margin, the observed 90% confidence intervals being 2.5–3.9, 2.3–3.5 and 4.0–6.0.

Discussion

Oral treatment with MPA has been hampered by the very large interindividual differences in rate of absorption and bioavailability leading to the use of massive doses by some authors.[8]

The relative bioavailability found in this study is in good agreement with the 2.2–4.8 90% confidence interval reported previously for the same formulations at the end of a 15 day twice-daily dosing regimen.[12] However, the reported values for AUC_{SS} in that study are approximately three times higher than AUC(0–∞) in this study. Some of this difference might be attributable to variability between patient populations, but a considerable proportion is likely to reflect an underestimation of AUC(0–∞) in the present study. As has been previously indicated, accurate estimation of terminal half-lives for MPA is very difficult except at high doses, where a value of the order of 50 h is expected. The current half-life estimates are mostly shorter than this value. The effect of this on the relative bioavailability estimates is minor, however, since the administered doses are close to bioequivalence and

Table 2. Individual pharmacokinetic parameters for treatments A (MPA/PVP 200 mg) and B (standard 500 mg MPA tablet)

Formulation	Sequence	Subject	AUC (0–t_z) (ng h/ml)	AUC (0–∞) (ng h/ml)	%EXT$_{AUC}$	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	Terminal phase (h)
A	AB	2	174	284	39	1	24.1	41.2	12–48
		3	354	372	5	1	126.2	3.0	4–12
		4	316	445	29	2	22.7	47.3	12–72
		7	146	202	28	2	30.2	16.3	6–24
		10	456	570	20	1	94.0	27.9	12–48
		12	163	183	11	1	25.0	6.8	4–24
		13	658	867	24	2	54.0	45.0	6–24
		16	75	122	39	1	11.0	21.1	6–24
		18	256	275	7	2	73.3	3.0	4–12
		21	137	153	11	1	21.7	3.3	4–12
		24	116	127	9	1	39.5	3.8	4–12
		25	172	254	32	4	14.6	12.3	4–24
	BA	1	197	233	15	4	24.3	8.7	6–24
		6	77	88	12	2	20.6	4.2	4–12
		8	325	359	9	1	64.3	8.4	6–24
		9	421	504	17	1	78.5	24.4	12–48
		11	384	455	16	1	87.9	9.8	6–24
		14	75	110	31	1	15.0	7.0	4–12
		15	52	74	29	1	23.4	3.5	2–6
		17	72	83	14	2	13.3	3.8	4–12
		19	39	45	14	2	10.8	1.4	4–6
		20	320	380	16	1	78.3	12.4	6–24
		22	229	386	41	1	32.6	23.4	6–24
		23	120	151	21	4	14.9	4.3	6–12
		26	340	396	14	4	30.2	18.9	12–48
B	AB	2	52	74	30	2	11.1	7.6	4–12
		3	377	431	13	2	53.0	8.0	6–24
		4	368	858	57	12	5.4	125.8	12–96
		7	150	204	26	2	27.5	14.0	6–24
		10	196	242	19	2	25.9	10.6	6–24
		12	280	302	7	4	30.5	5.8	6–24
		13	1235	1353	9	6	121.2	26.1	24–72
		16	41	97	58	2	5.6	12.5	2–12
		18	339	374	10	4	50.4	6.6	6–24
		21	47	57	17	4	11.3	1.5	4–6
		24	120	159	24	6	10.9	10.0	6–24
		25	190	386	51	1	10.2	49.9	12–48
	BA	1	293	463	37	4	18.1	56.1	24–72
		6	170	202	16	2	15.9	8.3	6–24
		8	154	217	29	2	22.1	15.2	4–24
		9	293	356	18	2	53.4	11.3	6–24
		11	248	281	12	4	24.1	7.4	6–24
		14	25	47	47	2	6.4	4.4	2–6
		15	33	47	29	4	6.1	5.2	4–12
		17	30	41	27	4	6.0	4.8	4–12
		19	14	17	19	4	4.6	1.4	4–6
		20	176	239	27	6	13.1	11.1	6–24
		22	423	503	16	4	27.9	18.4	6–48
		23	88	143	38	1	6.1	17.2	6–24
		26	506	566	11	4	35.2	24.6	12.72

the error will be similar for both formulations; hence, the similarity in comparisons based on AUC(0–t_z), AUC(0–∞) and AUC$_{SS}$.

Clinical data support the opinion that there exists a critical threshold plasma level that needs to be exceeded for prolonged periods of time in order to obtain therapeutic activity.[7] This is probably somewhere between 70 and 100 ng MPA/ml. Such plasma concentrations might be achieved more easily with MPA/PVP than with the standard

Table 3. Statistical analysis

Treatment	Statistics	AUC (0–t_z)	AUC (0–∞)	C_{max}	$t_{1/2}$	Statistics	t_{max}
A	Mean (arithmetic) ±SEM	227 ±31	285 ±38	41.2 ±6.3	14.5 ±2.7	mean (arithmetic) ±SEM	1.8 ±0.2
	Geometric mean ($10^{mean-SEM}$, $10^{mean+SEM}$; log data)	178 154–207	225 194–261	31.7 27.4–36.7	9.3 7.7–11.4	median range	1 1–4
B	Mean (arithmetic) (±SEM)	234 ±50	306 ±59	24.1 ±5.0	18.6 ±5.2	mean (arithmetic) ±SEM	3.6 ±0.5
	Geometric mean ($10^{mean-SEM}$, $10^{Mean+SEM}$; log data)	142 114–178	196 159–242	16.3 13.7–19.5	10.9 8.9–13.3	median range	4 1–12
	Non-normalized parameter ratio A/B					parameter difference A − B	
	Geometric mean	1.25	1.14	1.94	0.86	Hodges–Lehmann estimate	−1.75
	90% confidence interval	1.01–1.55	0.92–1.41	1.58–2.38	0.64–1.16	90% confidence interval	−2.5–1.0
	Dose-normalized parameter ratio A/B						
	Geometric mean	3.1	2.9	4.9			
	90% confidence interval	2.5–3.9	2.3–3.5	4.0–6.0			

formulation. This might translate into a greater therapeutic benefit than the currently commercially available tablets. However, only future prospective randomized clinical trials with detailed evaluation of effect and side-effects can address this issue.

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