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Effect of oral high-dose progestins on the disposition of antipyrine, digitoxin, and warfarin in patients with advanced breast cancer

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Summary. The influence of two progestins, medroxyprogesterone acetate (MPA) and megestrol acetate (MA), given orally in high doses, on the pharmacokinetics of antipyrine, digitoxin, and warfarin were studied in patients with advanced breast cancer. Antipyrine and warfarin were given as a single test dose before and after 5 weeks of progestin treatment. The pharmacokinetics of digitoxin was investigated at steady state in patients receiving this drug therapeutically before and during treatment with progestins. Small changes in clearance rates for antipyrine, warfarin, and digitoxin were found. A minor decrease observed in warfarin clearance however may be of clinical importance. Half-lives decreased by 13% for antipyrine and increased by 71% for warfarin. High-dose progestins given orally do not seem to have a major influence on drug metabolism, probably reflecting a minor effect on drug and steroid-metabolizing microsomal mono-oxygenases in the liver.

Introduction

High-dose progestin therapy seems to be as efficient as conventional endocrine therapy in the management of advanced breast cancer. This has been documented for intramuscular (IM) administration, but recently also for oral (PO) treatment [1, 16]. The mechanism of action of progestins as anticancer agents is unknown but may be related to suppression of adrenal steroid synthesis [1, 24], decrease in estrogen receptor synthesis [20], or alterations in steroid metabolism in target cells [21, 22].

There are recent reports on a possible influence of progestins on the mixed function oxidase system of the liver [3, 8, 15, 17]. This enzyme system is responsible for the metabolism of several drugs and some steroid hormones, including progestins themselves. Therefore, progestin administration may have a major impact on the metabolic fate and thereby dose schedules of these compounds.

No data exist on the possible effects of a high oral dose of progestins on the pharmacokinetics of drugs metabolized by the hepatic mixed function oxidase system. We therefore studied the kinetics of antipyrine, digitoxin, and warfarin before and during long-term oral dosage of two progestins, medroxyprogesterone acetate (MPA) and megestrol acetate (MA). These drugs were selected because their use as clinical probes for assessing the functional state of the mixed function oxidase system has been verified.

Materials and methods

Patients

All patients (13 females and 1 male) in this study were receiving progestins (MPA or MA) as treatment for their advanced breast cancer. MPA was given at a dose of 500 mg b.i.d. (5 × 100 mg tablets, Provera, Upjohn) and MA as 160 mg once daily (4 × 40 mg tablets, Megace, Bristol-Myers). All patients gave their informed concent to participate in the study. None of the patients were smokers, and other drugs known to be enzyme inducers or inhibitors were not used. Aminoglutethimide (AG), a known enzyme inducer [11], had been given to 3 of the patients, but this treatment was stopped 2–5 weeks before the first test situation. Other drugs were kept constant during the test period. During the investigation patients were on a standard hospital diet without charcoal broiled food and with a fixed amount of xanthine-containing beverages. Serum creatinine and BUN were within normal limits in all patients. Albumin, coagulation factors, and bilirubin were usually within normal limits; no changes were observed during the study.

Study protocols

Antipyrine study. Nine patients (eight females, one male) were used to test for an influence on antipyrine metabolism, four with MPA and five with MA. Their mean age was 69 years (range 43–85), and the mean body weight was 67 kg (range 45–88). One patient (KH) had liver metastases shown by ultrasonography, but these remained unchanged during the test period. None of the patients had thyroid dysfunction [18], episodes with fever [5]; both conditions which are known to influence drug metabolism. Three patients (KH, 0N, GRG) had stopped AG therapy 2, 2.5, and 5 weeks, respectively, before the first test situation.

The patients received a single dose of 1000 mg of antipyrine orally (two 500 mg tablets, Fenazon, "NAF", Oslo). The drug was given at 8 a. m. after an overnight fast.

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Food and medication was allowed 2 h after the dose. Blood samples were taken immediately before and 2, 4, 6, 8, 10, 12, 24, and 30 h after the test dose. Then the patients started progestin therapy (MPA or MA) and the study was repeated 5 weeks later, at a steady state blood level of progestins.

Digitoxin study. Three patients with mean age 76.3 years (range 74–80) and mean body weight 58 kg (range 54–63) were studied, two with MPA and one with MA. One patient (GRG) was tested at the same time both for digitoxin and antipyrine metabolism and one (OG) for both digitoxin and warfarin metabolism. One patient (GRG) had stopped AG therapy 5 weeks before the first test dose. Steady-state blood concentration of digitoxin was estimated in three patients from blood samples taken 6 h after medication on 3 consecutive days, before start and after 5 weeks on progestin treatment.

Warfarin study. Four patients were included; two received MPA and two MA. Mean age was 71.0 years (range 58–80) and mean body weight was 66 kg (range 46–95). One patient increased her body weight by 2.5 kg during the test period.

Warfarin was administered as a single test dose of 0.30 mg/kg BW using racemic warfarin dissolved in water. Parameters of coagulation (NT, TT, Cephotest, platelet count, and bleeding time) were measured and found normal in all patients before the two test situations. Blood samples were taken immediately before and 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 h after the test dose and repeated after 5 weeks on progestin treatment.

Progestins. Progestin serum levels were measured in all our patients at steady state, using blood samples taken immediately before and 2, 4, 6, 8, 10, 12 (MPA) and also 24 (MA) h after the morning dose of progestin. For one patient (HF) only the 6-h sample on 3 consecutive days was used.

Radioimmunoassay of progestins

[^{3}H] MPA (NET-480:6 α methyl-17α-hydroxy-progesterone acetate, [1,2-^{3}H(N)], 60.0 Ci/mmol was obtained from New England Nuclear (Boston, Mass.). Crystalline nonradioactive MPA, 6-α-methyl-17α-hydroxy-progesterone acetate (No.M-1629) and MA, megestrol acetate (No.M-0513) were from Sigma Chemical Co. (St. Louis, Mo.). All solvents, of analytical grade, were from Merck. Opti-Fluor from Packard Instruments was used as liquid scintillation cocktail.

Antiserum against MPA-3-O-carboxymethyl-oxime-BSA conjugate; Anti-Provera, ≠ 15698-Fak-53 was a gift from the Upjohn Co. (Kalamazoo, Mich.). All blood samples, drawn as venipuncture, were allowed to coagulate for 1 h at 4 °C, and then centrifugated at 3000 rpm for 15 min. Serum was separated and stored at −20 °C until analysis.

MPA and MA were measured by a radioimmunoassay (RIA) carried out as described by Ortiz et al. [13] with some modifications. Phosphate-BSA buffer (PBSA) with pH 7.5 (0.05 *M* potassium phosphate, 0.1 *M* sodium chloride, 0.2% BSA, and 0.05% sodium azide) was used in the assay.

[^{3}H]MPA (1000 cpm) was added in 300 µl buffer to 300 µl serum and extracted once with 5 ml hexane for 20 min. The extract was evaporated at 40 °C with N_2 and the residue dissolved in 1 ml PBSA. To correct for extraction loss, an aliquot (400 µl) was obtained for scintillation counting. Aliquots of 50 µl adjusted to 200 µl with PBSA and seven different standard solutions, containing 62.5 to 4000 pg MPA or MA in each assay tube, were used. [^{3}H]MPA (5000 cpm) in 100 µl buffer and 100 µl antiserum diluted 1:16000 in buffer were added to the incubation tubes. Samples and standards were run in duplicate and incubated overnight at 4 °C. Then 750 µl ice-cold dextran-coated charcoal solution (0.25% charcoal Norit A and 0.025% dextran) were added and the antibody-bound [^{3}H]MPA in the supernatant was obtained for liquid scintillation counting after centrifugation at 2000 *g*. A nonlinear fit was used to construct standard curves and calculate MPA or MA concentrations in the unknown samples. The antiserum did not cross-react with progesterone, 17-hydroxy-progesterone or medroxyprogesterone, but showed a high affinity for MPA ($K_a = 10^9$ l/mol) and a 45% cross reaction with MA ($K_a = 10^8$ l/mol).

Measurements of the test substances

Antipyrine concentration was measured as described by Frazer et al. [6]. The series of antipyrine from each patient were analyzed at the same time, each sample in duplicate, with an intraassay coefficient of variation (Cv) of 2.8%. *Serum digitoxin concentration* was measured by a commercially available RIA Kit (Diagnostic Products Corporation, California) used routinely in this hospital. Drug analyses were done in duplicate with an intraassay coefficient of variation of 4.1%. *Warfarin concentration* was measured, using a HPLC method published previously [23], all samples from each patient were analyzed in a single run.

Pharmacokinetic calculations (2)

Clearance for antipyrine and warfarin were obtained using the formula:

$$\mathrm{Cl} = \frac{f \times D}{\mathrm{AUC}},$$

where f is the fraction of dose absorbed, D is the dose of drug, and AUC is the area under the serum concentration curve from time zero to infinity. Since these drugs have been shown to be nearly completely absorbed with no detectable first pass metabolism [10, 18], f was considered to be 1 in our calculations. AUC was measured by the trapezoidal rule from time zero until the last serum value obtained. The total area was found by adding the residual area calculated by extrapolation to infinity after log linear least-square regression analysis. Since antipyrine elimination is described by a first-order, one-compartment model, all concentrations after peak were used to estimate $t_{½}$. For warfarin all concentrations after $t = 12$ were used.

Apparent volume of distribution (V_Z) was calculated by the equation:

$$V_Z = \frac{f \times D}{\lambda_Z \times \mathrm{AUC}}$$

λ_Z = the disposition rate constant

Clearance of digitoxin was calculated using the formula:

$$\mathrm{Cl} = \frac{f \times \mathrm{DM}}{C_{aV}^{SS} \times \tau},$$

where DM is the maintenance dose size, C_{aV}^{SS} is the average steady-state concentration and τ is the dosing interval.

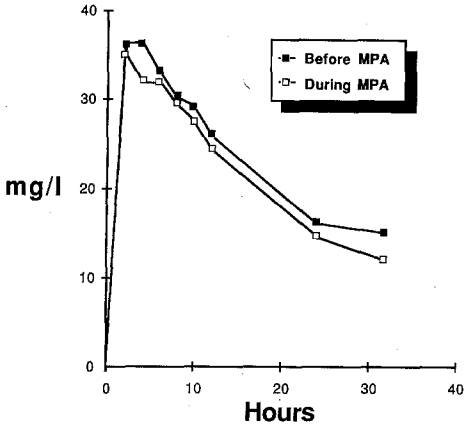

Fig. 1. Antipyrine serum concentration profiles in one patient before and after medroxyprogesterone acetate (MPA) therapy. Antipyrine serum concentration is expressed as mg/l

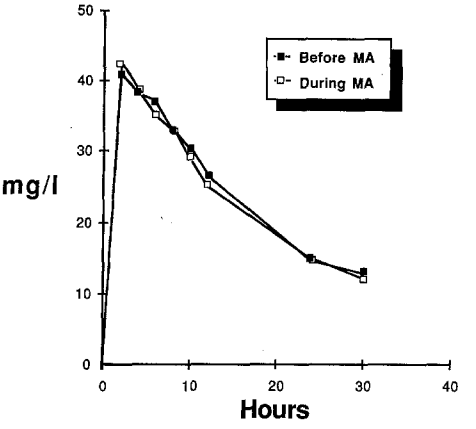

Fig. 2. Antipyrine serum concentration profiles in one patient before and after megestrol acetate (MA) therapy. Antipyrine serum concentration is expressed as mg/l

Digitoxin is known to be well absorbed [14] and f in the formula was considered to be equal to 1. AUC_{ss} (at steady state calculations) for the progestins were measured by the trapezoidal rule using all measurements during the dosing interval.

Results

Antipyrine serum concentration profiles in two patients are shown in Fig. 1 (MPA) and Fig. 2 (MA). The half-life, apparent volume of distribution, and clearance values for each patient before and during progestin treatment are shown in Table 1. Log linear regression analysis of antipyrine elimination curves gave r values between 0.949 to 0.999. No difference in the pharmacological parameters were observed after progestin treatment. The clearance values for digitoxin are shown in Table 2. Only small differences were observed following progestin treatment.

The warfarin serum concentration profile in one patient is shown in Fig. 3. Log linear regression analysis of warfarin elimination curves gave r values between 0.873 to 0.995. The clearance values for individual patients before and during progestin treatment are shown in Table 3, which also gives distribution volume and half-lives. No differences in distribution volumes were observed, but all patients showed a consistent decrease in clearance from 2.3 to 1.5 ml/h kg BW (34.8%). A mean increase in half-lives from 43.4 to 74.4 h (71.4%) was observed.

Individual progestin values of concentrations immediately before (C_{min}) and 6 h (C_{6h}) after the morning dose, with AUC at steady state, are given in Table 4. Mean values found for MPA and MA were 85.3 ng/ml and 162.4 ng/ml for C_{min} and 143.1 ng/ml and 221.1 ng/ml for $C_{6\,h}$.

Discussion

Antipyrine, digitoxin, and warfarin are all drugs, which are well absorbed after PO administration, and they do not undergo significant first-pass metabolism [10, 14, 18]. The pharmacokinetic calculations [2], based on the assumption that the absorption fraction is equal to 1, therefore, seem justified.

Only a small fraction of plasma antipyrine is bound to

Table 1. Antipyrine kinetics

Patients	Age (years)	BW[c] (kg)	Distribution volume (% BW)		Clearance (ml h^{-1} kg^{-1})		Half-lives (h)	
			Before	During	Before	During	Before	During
GRG[a]	74	58	45.5	46.2	15.2	17.6	20.8	18.2
KH[a]	75	73	57.0	40.5	18.2	15.8	21.7	17.8
DE[a]	73	49	44.3	56.5	23.7	29.4	12.9	13.3
LH[a]	67	70	52.1	46.9	23.5	24.4	15.2	13.2
MM[b]	85	58	39.3	40.5	17.4	18.5	15.6	15.2
ØN[b]	71	45	56.4	58.0	51.6	35.8	7.6	11.2
OS[b]	72	88	43.4	43.5	28.5	32.5	10.6	9.3
EP[b]	43	79	33.5	33.3	9.8	16.5	23.6	14.0
SL[b]	59	83	39.7	39.8	19.1	23.1	14.0	12.0
$\bar{X}$	68.7	67.0	45.6	45.0	23.0	23.7	15.8	13.8
SD	11.9	15.2	8.1	8.0	12.0	7.4	5.3	2.9

[a] MPA
[b] MA
[c] No change in BW during progestin treatment

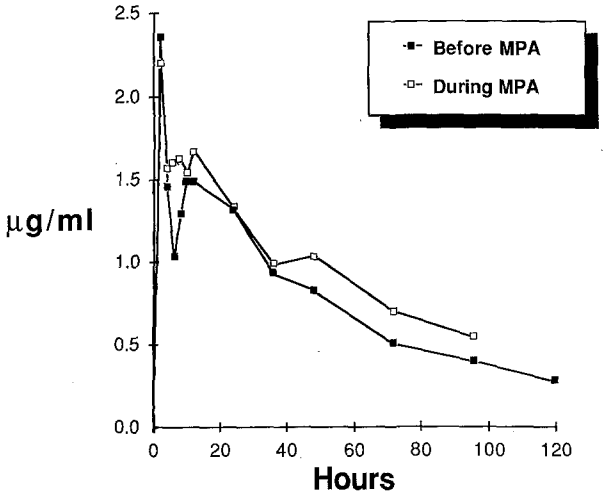

Fig. 3. Warfarin serum concentration profiles in one patient before and after medroxyprogesterone acetate (MPA) therapy. Warfarin serum concentration is expressed as µg/ml

albumin (< 10%) [18], whereas both digitoxin [14] and warfarine [10] are highly protein bound (> 90%). MPA does not bind to specific sites on plasma proteins and is only to a small extent associated with plasma albumin [12]. Therefore, MPA probably does not interfere with plasma protein binding of antipyrine, digitoxin, or warfarin, and interaction between MPA and these test drugs involving displacement seems unlikely. Besides, MPA did not affect protein binding of these drugs by alteration in the plasma albumin level.

The pharmacokinetic parameters, half-lives, apparent volume of distribution, and clearance, obtained for the test drugs during the present study were within the ranges reported by others [10, 14, 18]. We have previously obtained similar pharmacokinetic data for advanced breast cancer patients [11]. The time interval between the test before and during chronic progestin treatment (5 weeks) allowed a steady-state progestin concentration in plasma to be attained (Table 4). This concentration was in the range reported by others [19], when progestins were administered at the same dose as endocrine therapy for advanced breast cancer. The lack of major influences of progestins on mixed function oxidase activity does not seem to be due to low levels of progestins in our patients.

The antipyrine clearance is decreased following intake of an oral contraceptive containing estrogens in combination with small amounts of progestins [9]. However, when low oral dose (5–10 mg MPA daily) of progestin alone was given to patients with liver cirrhosis [17], an increase in antipyrine clearance was observed. This finding was in accordance with increased mixed function oxidase activity in liver biopsies from these patients [17].

Rautio et al. [15] reported that high-dose MPA (250 mg/day) treatment given as IM injections to patients

Table 2. Digitoxin kinetics

Patients	Age (years)	BW (kg)	Dose (mg)	Digitoxin concentration (nmol/l; $x \pm SD$)[e]		Clearance (ml h^{-1} kg^{-1})	
				Before	During	Before	During
GRG[a]	74	58.0	0.1[c]	14.2 ± 1.5	21.7 ± 2.0	6.6	4.3
HF[a]	75	53.5	0.05[d]	18.5 ± 1.5	16.5 ± 1.5	2.8	3.1
OG[b]	80	63.5	0.1[c]	19.7 ± 1.6	18.2 ± 1.5	4.4	4.8
$\bar{X}$	76.3	58.3		17.5	18.8	4.6	4.1
SD	3.2	5.0		2.9	2.7	1.9	0.9

[a] MPA [b] MA
[c] 5d/w [d] 7d/w
[e] Mean of measurements on 3 consecutive days

Table 3. Warfarin kinetics

Patients	Age (years)	BW[c] (kg)	Distribution volume l (% BW)		Clearance (ml h^{-1} kg^{-1})		Half-lives (h)	
			Before	During	Before	During	Before	During
MG[a]	58	95.0	13.5 (14.2)	14.6 (15.0)	2.4	1.6	40.5	66.4
OG[a]	80	63.5	8.4 (13.2)	7.5 (11.9)	2.1	0.9	44.6	96.3
IN[bx]	70	61.0	8.2 (13.4)	10.5 (17.1)	2.0	1.4	45.8	81.8
AC[b]	76	45.5	7.8 (17.1)	7.3 (16.2)	2.8	2.1	42.5	53.0
$\bar{X}$	71	66.3	9.5 (14.5)	10.0 (15.1)	2.3	1.5	43.4	74.4
SD	9.6	20.8	2.7 (1.8)	3.1 (2.3)	0.4	0.5	2.3	18.8

[a] MA
[b] MPA
[c] No change in BW during progestin treatment
[x] tested during steady-state progestin treatment, then 5 weeks after progestin had been stopped

Table 4. Plasma levels & AUC_{SS} of progestins

Patients	Concentration (ng/ml) C_{min}		C_{6h}		AUC_{SS} (ng ml^{-1} h^{-1})	
	MPA	MA	MPA	MA	MPA_{0-12}	MA_{0-24}
GRG	103		130		1555	
LH	72		63		795	
KH	82		151		1396	
DE	92		124		1461	
IN	54		77		1058	
AC	109		306		2912	
HF	–		151[a]		–	
OS		36		50		1171
ØN		264		325		5939
SL		80		146		2775
EP		244		383		8106
MM		211		220		4755
OG		153		223		4976
MG		149		201		4731
$\bar{X}$	85.3	162.4	143.1	221.1	1529.5	4636.1
SD	20.4	84.0	79.6	109.8	734.3	2211.6

[a] Mean of 3 measurements

with endometrial cancer, decreased the antipyrine half-life after 6 days. When the MPA exposure was continued in these patients by giving a low oral dose (50 mg/day), the antipyrine half-lives increased after 4 months to values observed prior to IM administration. A lack of induction of antipyrine metabolism during oral treatment was explained by the low dose used, but no data on serum progestin levels were given in this report [15].

Our data, showing that high oral dose of MPA or MA did not increase the clearance of three test drugs, including antipyrine, are difficult to reconcile with the finding of Rautio et al. [15]. The different conclusion reached by us is probably not related to different routes of administration (PO vs IM). Tamassia et al. [19] have shown that after daily IM injection of MPA, the serum concentration of this compound increases very slowly to reach steady state after several weeks. Therefore, within 6 days, i.e., the time period between the first and second test dose with antipyrine [15], only a low MPA serum level has probably been obtained.

We observed a small decrease in warfarin clearance following high-dose oral administration of MPA (Table 3). It is conceivable that high-dose MPA may function as a weak *inhibitor* of isozyme(s) of the mixed function oxidase system, participating in the metabolism of warfarin. This may, however, be of clinical importance as even a slight decrease in warfarin clearance can result in serious bleeding disturbances.

Progestins have been shown to increase the activity of some enzymes involved in the metabolism of steroids. These include hepatic 5-α reductase [7], estradiol dehydrogenase [21], and arylsulfotransferase [22]. This stimulatory effect may decrease the amount of estrogens available to the target tissues and has been assigned a role in the mechanism of action of MPA.

In conclusion, although progestins seem to influence the activity of some important enzymes in steroid metabolism, oral administration of high-dose MPA or MA did not have a significant stimulatory effect on the metabolism of antipyrine, digitoxin, and warfarin. Therefore, the results reported here give no reason to suggest that oral dosing with MPA or MA may increase the metabolism and thereby the dosing of these drugs or of other xenobiotics.

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