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Adrenal Steroids as Parameters of the Bioavailability of MA and MPA

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Abstract—*Serum levels of cortisol (C), androstenedione (A), dehydroepiandrosterone (D), estrone (E1) and estradiol (E2) were chosen as parameters to compare the bioavailability of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) in postmenopausal patients with advanced breast cancer. In 36 patients randomized to MPA, the levels of A (13% vs. 19%) and C (6% vs. 8%) were slightly lower than in 36 patients on MA, but D-levels (68% vs. 59%) and E1 or E2, were similar. The correlation between baseline C and A disappeared during treatment. Treatment levels of E1 and E2 were correlated. There was no correlation between individual drug levels and any steroid, indicating a maximal suppression.*

After ingestion of a single dose of MA or MPA, peak levels were found after 2–3 h for MA and 3–4 h for MPA. Four hours after ingestion, the levels of A and C were similar, 40–60% of baseline values, while D levels remained unaltered. Doubling the dose of either drug did not enhance hormone suppression, indicating that the drug dosage is maximally suppressive.

In conclusion, although the median serum MA levels are double those of MPA, suppression of A, C and D is usually similar, with correponding estrogen levels, demonstrating a comparable and maximal bioavailability. Higher dosages of MA or MPA will not increase their pharmacological effects any further.

INTRODUCTION

FOR THE hormonal treatment of patients with breast cancer, tamoxifen is usually the first choice due to its minor side-effects. As second-line treatment some authors prefer aminoglutethimide, others progestins. Of the latter, two compounds are presently available, megestrol acetate (MA) and medroxyprogesterone acetate (MPA). The first is used mostly in the U.S.A., while the second is preferred in Europe. Both are stated to be practically free of severe side-effects, but do have a number of steroid-like effects which may be cumbersome for the patient. Consequent to their steroid character, progestins are known to suppress adrenal steroids. In this study we wanted to compare the bioavailability of both drugs by measuring the levels of cortisol (C), androstenedione (A) and dehydroepiandrosterone (D) and the serum estrogens, estrone (E1) and estradiol (E2) during treatment with either MA or MPA.

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PATIENTS AND METHODS

For the determination of C, A, D, E1 and E2, blood samples were obtained before and during therapy in 36 patients treated with MA and in 30 patients treated with MPA. To account for eventual effects of drug accumulation, blood samples during therapy were taken when a steady state had been reached after at least 3 months of treatment.

The dosage for MA in this study was 80 mg b.i.d. and for MPA 500 mg b.i.d. Both dosages were chosen for their maximal clinical effects in breast cancer, as reported in previous studies by others and by our group [1, 2, 5].

In four smaller groups of six patients each, the serum levels of MA and MPA were followed hourly after ingestion of a single dose of respectively 80 and 160 mg MA and 500 or 1000 mg MPA to study pharmacodynamics and dose–level relations. Four hours after ingestion, the serum levels of C, A and D were measured to study the immediate effects.

All steroids were determined by commercially available RIA kits. All samples were pooled into mixed runs to account for interassay variability. Samples were taken preferably in the non-fasting patient between 9.00 and 10.00 a.m. to exclude diurnal variations. Pharmacokinetic studies with

single dose MA or MPA were performed in the fasting patient, to prevent any influence of food on the drug resorption. Steroid levels were compared by Wilcoxon's test, and the relation between different steroids determined by a Spearman rank test. The levels of MA and MPA were determined by GCMS [5, 6].

RESULTS

The pretreatment levels of A and C are depicted in Fig. 1. There is a close correlation between the baseline levels of steroids, which is lost after treatment. All steroids are suppressed during treatment (Table 1), to 13–19% (A), 6–8% (C) and 59–68% (D) of baseline levels. There was no overlap between baseline and treatment levels. Both the levels of A and C in the MPA group were slightly lower compared with those on MA. The difference does not result in lower estrogen levels in the MPA group; however, the levels of E1 and E2 being similar, indicating that this difference is only of statistical, but not of biological significance (Fig. 1). The levels of E1 and E2 during treatment are correlated (Fig. 2). The adrenal suppression by MPA evidently is somewhat more pronounced than that of MA.

The course of serum drug levels after ingestion of a single dose of MA is depicted in Fig. 3. Peak levels are reached after 2–3 h and the maximal serum concentration is almost three times as high after ingestion of double the amount of drug, indicating that resorption is quick and apparently not limited by a transport maximum in this dose range (Table 2). For the two dosages of MPA the findings are similar. The area under the curve of MA is also three-fold higher while that for MPA almost doubles. The levels of A, C and D measured 4 h after ingestion are given in Table 2. A and C are suppressed to about 50–60% of their baseline values, but their decrement after doubling the amount ingested is not enhanced, indicating that a

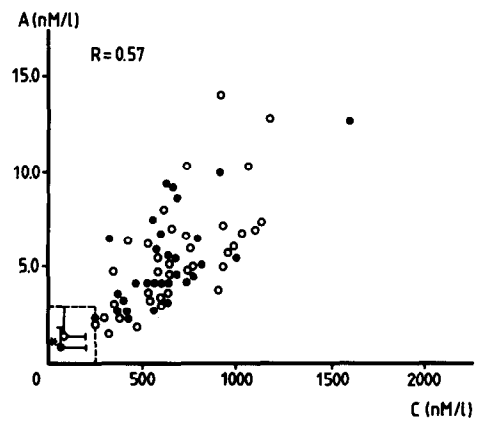

Fig. 1. Baseline serum levels of androstenedione (A) and cortisol (C) and in patients on MA (○) and MPA (●) (mean ± 2 S.D.).

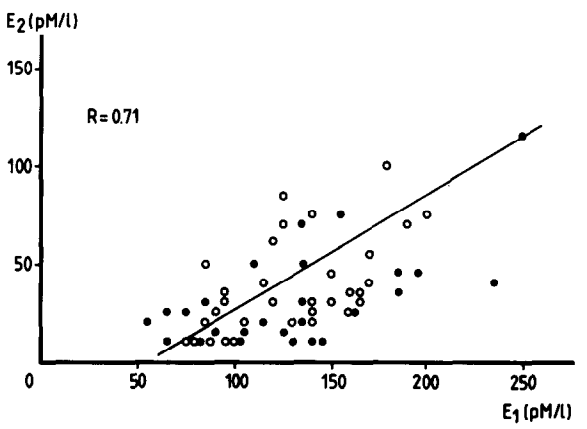

Fig. 2. Serum levels of estrone (E1) and estradiol (E2) in patients on MA (○) and MPA (●).

Table 1. Treatment levels of A, C, D, E1, E2 and MA or MPA, median, percentage of baseline and range

Daily dose	MA 160 mg	MPA 1000 mg
A(nmol/l)		
median(%)	1.35 (19)	0.89* (13)
range	0.27–3.02	0.07–1.89
C(nmol/l)		
median(%)	65 (8)	50* (6)
range	10–225	30–290
D(μmol/l)		
median(%)	179 (59)	220 (68)
range	60–700	50–800
E1(pmol/l)	125	130
range	80–180	55–250
E2(pmol/l)	35	25
range	20–100	20–115
Drug level (ng/ml)	227	126
range	102–348	38–364

*$P < 0.05$ vs. MA.

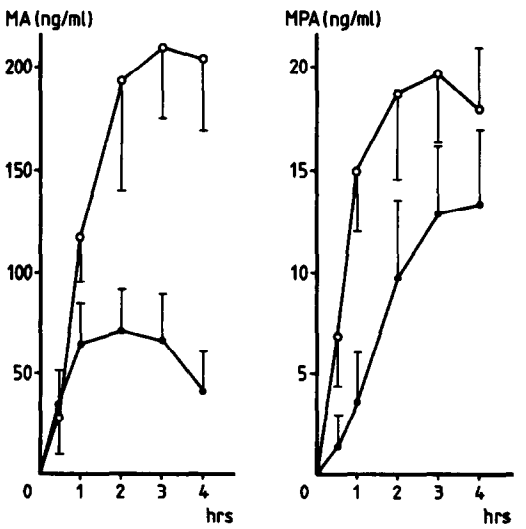

Fig. 3. Serum levels of MA and MPA after single (80 resp. 500 mg) (●) or double (160 resp. 1000 mg) (○) dose (mean ± S.D.).

Table 2. Suppression of A, C and D 4 h after a single or double oral dose of MA (80 and 160 mg) or MPA (500 and 1000 mg)

Steroid	Baseline	4 h after a single dose (%)	4 h after a double dose (%)
Androstenedione (nmol/l)			
MA	7.3 ± 3.1	3.0 ± 1.0* (41)	3.4 ± 1.4* (46)
MPA	7.9 ± 4.7	4.4 ± 2.3* (56)	4.0 ± 1.0* (51)
Cortisol (nmol/l)			
MA	793 ± 161	435 ± 146* (55)	448 ± 139* (56)
MPA	670 ± 223	358 ± 158* (53)	425 ± 203* (63)
D (μmol/l)			
MA	289 ± 156	279 ± 136 (96)	283 ± 161 (98)
MPA	324 ± 88	336 ± 113 (104)	296 ± 77 (91)
AUC (mg/l.h)			
MA		323	722 (223)
MPA		228	665 (292)

*$P < 0.05$ vs. baseline.

maximal effect is already obtained by the lowest dose taken. There are no changes in the levels of D after ingestion of either compound.

DISCUSSION

In this study we have found that the serum levels of the adrenal steroids A, C and D are suppressed slightly more by MPA than by MA. This, however, does not result in lower estrogen levels for MPA. In the menopause estrogens are mainly derived from androstenedione, by conversion in peripheral tissues like fat and muscle [7, 8]. Suppression of the estrogen levels by progestins in postmenopausal women has been reported by others [1, 2]. A concomitant fall of SHBG levels was seen also [1, 2]. During chronic treatment with MA or MPA, D levels are not suppressed to the same extent as those of C or A. In a previous study on the progestin cyproterone acetate, D was the only steroid which was suppressed in a dose-dependent way [15]. Evidently, the sulfotransferase system is influenced variably by the individual progestins [14].

After ingestion of a single dose of either drug, there is a dose-related increase in their serum levels, reaching a peak after 2–4 h, indicating that resorption generally is good. The peak serum levels of MPA are reached somewhat later than for MA. Ingestion of 160 mg MA, however, gives 10-fold higher plasma peak levels than 1000 mg MPA, but the reason for this difference is not quite clear. As the plasma peak levels are reached almost simultaneously, it will not be caused by different resorption rates. Giving MPA parenterally (i.m.) instead of orally does not result in higher serum levels [9]. Others have reported nearly the same serum half-life for MA as for MPA, 10–12 h [12]. Therefore, the metabolic rate does not seem to be a significant factor in their bioavailability either. It is surprising that a five-fold higher dosage of MPA is needed to reach similar effects as MA. It may be that MPA is metabolized within the gut to a greater extent than MA [13], or that there is a substantial first-pass effect, part of the compound being metabolized by the liver after oral ingestion [12]. To some extent, serum levels may depend on the preparation used [10, 11]. Four hours after ingestion, both A and C are suppressed to about 60% by each compound, and their decrement is the same after the double amount of each drug. This means that the production of steroids by the adrenal is already blocked completely by the lowest dosage, and the rate of decrease will therefore be determined by the serum half-life of each steroid. D is not lowered acutely by either drug, as its serum half-life is considerably longer than that of A or C [14]. Its decrease therefore will take more time than the 4 h interval we measured. In view of these prompt effects, the action of progestins on the adrenal appears to be a direct one and not mediated by a metabolite of the drug. It also shows that the dosage used is sufficient to give a maximal adrenal suppression. In other papers we have shown that MPA induces a shut-off of ACTH release as well as a direct blockade of steroid synthesis by the adrenals themselves [3, 4].

Increasing the dosage of MA does result in higher serum levels, but not in enhanced suppression of adrenal steroids [16]. It is not quite clear therefore what exact mechanism underlies the dose difference, necessary to obtain a similar biological effect. Further studies are also indicated to understand the cause of the large individual variation of progestin levels [16].

We have shown in this study that a daily dosage of 160 mg MA induces a maximal suppressive effect on the adrenals which is similar to the effects of 1000 mg MPA after a single as well as chronic exposure. No additional effect should be expected from a further increase in the dosage.

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