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The Pharmacokinetics of High-dose Medroxyprogesterone Acetate (MPA) in the Therapy of Advanced Breast Cancer

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Summary. *Oral MPA 1.5 g/day leads to plasma concentrations between 1 and 12 μg/ml, with a broad intra- and interindividual variance. The plateau state is reached in between 4 and 16 days. Plasma concentrations in the plateau state are very sensitive to dose modifications. After cessation of administration, the decline in plasma levels seems to proceed in two phases, with half-times of about 20 h and 4 days. Extraction procedures reveal no benefit in discriminating between MPA and its metabolites.*

Introduction

The first trial with continuous high-dose MPA administration IM in advanced breast cancer was reported in 1974 [24]. Further studies confirmed the remarkable clinical results [5, 10, 20, 22, 23, 26, 27]. Later on, the oral route of administration was also used, with a comparable therapeutic effect [2, 25].

Some clinical and laboratory observations concerning pharmacodynamics were reported [23–26, 30] but no pharmacokinetic data are now available. The aim of the present communication is to give some insight into the pharmacokinetics of MPA in high dosages.

Patients, Materials, and Methods

Patients. Within the German association of medical oncology (AIO) a phase II study in advanced breast cancer was performed with the following therapy schedule:
1. Mitomycin C 4 mg/m^2 IV for 3 h on days 1–5 and 15–19; further cycles after intervals of 3–5 weeks.
2. Medroxyprogesterone acetate (Provera, the Upjohn Company; trade name in Germany, Clinovir) 1.5 g/day, PO, in three doses of 500 mg, 100 mg/tablet, continuous administration.

Further details of the study are published elsewhere [2].

Materials and Methods. For the determination of MPA plasma concentrations an RIA was established as previously described [9, 16] with the aid of an anti-MPA goat antibody kindly provided by Dr. K. T. Kirton (Upjohn Co., Kalamazoo). The lyophilized antibody (goat, no. 16, reference 9980-JCC-112) was dissolved in water and diluted in Tris-HCl 0.05 *M*, pH 8, 1 : 10,000.

^{3}H-MPA (New England Nuclear), specific activity 40.5 Ci/mMol, was evaporated, dissolved in ethanol, and diluted in Tris-HCl 0.05 *M*, pH 8, to 5,000 cpm/μl.

Assay tubes contained Tris-HCl 0.05 *M*, pH 8, 100 μl, patients' plasma 100 μl, antibody 100 μl, ^{3}H-MPA 100 μl. The assay was incubated overnight at 4° C, after which 800 μl Dextran-coated charcoal was added [16] and the 3,000 *g* supernatant was counted in 10 ml Instagel (Packard).

In extraction experiments 100 μl plasma was extracted with 2 ml diethylether, petroleumether, or benzene/isooctane 2 : 1 (v/v), evaporated to dryness, dissolved in Tris-HCl 0.05 *M*, pH 8, 100 μl, and assayed as described above.

For the estimation of extraction efficiency 50 μl ^{3}H-MPA was added to 200 μl free plasma. Of this solution, 50 μl was counted. The remaining 200 μl was extracted with 2 ml organic solvents mentioned above and after extraction 50 μl plasma and 500 μl solvent were counted as described.

Results

After oral administration of MPA 1.5 g/day a rapid increase in plasma concentrations is observed reaching a steady level in order of concentration level (μg/ml) (Fig. 1). In terms of kinetics, two groups of patients can be described in the initial phase, differing in the time needed to reach the plateau state: in the first group, the final steady plasma level is reached within the first 5 days, as shown by the range and the median given on the right-hand side of the panel (Fig. 1A). The shape of the curve is characterized by a peak for plasma levels in the first phase. In the second group of patients there seems to be a delayed

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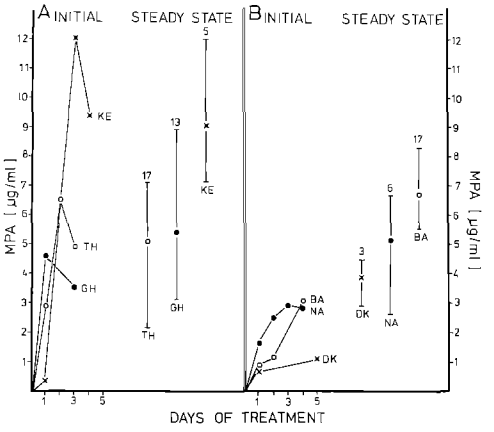

Fig. 1A and B. Initial phase, ranges, and medians of MPA plasma concentrations in a 'fast' (**A**) and a 'slow' (**B**) group of patients. The number of determinations in the plateau state is given on the top of the ranges

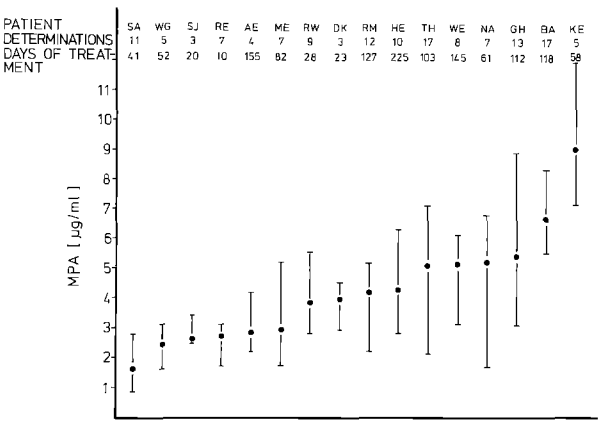

Fig. 3. Ranges and medians of MPA plasma concentrations in 16 patients. Determinations were carried out in the plateau state throughout

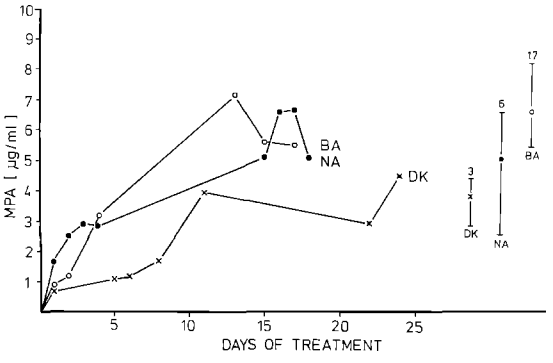

Fig. 2. Time-course of MPA plasma concentrations in the slow group (see also Fig. 1B)

Fig. 4. MPA plasma concentrations in the plateau state, monitored hourly

increase in MPA plasma levels (Fig. 1B). After 5 days of treatment the lower borderline of the range may be reached but the median under steady-state conditions is markedly higher (Fig. 1B). From the shape of the curves it may be concluded that the plateau state is reached after about 2 weeks of treatment (Fig. 2). It is not clear whether these different kinetic characteristics represent two distinct groups of patients or just the extremes of a continuous variation. Four other patients – initially not monitored as well – could be attached retrospectively to one of these kinetic characteristics.

Figure 3 shows a remarkable intra- and interindividual variation of MPA plasma levels in 16 patients under steady-state conditions. These variations are apparently dependent neither on the frequency of MPA determinations nor on the duration of observation. The differences between the individual ranges

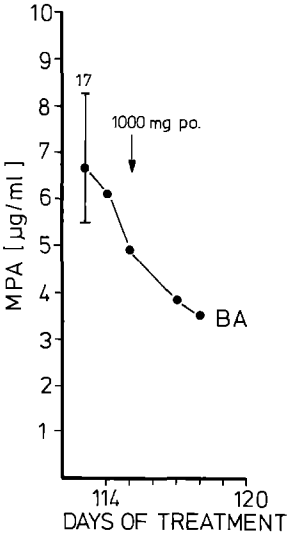

Fig. 5. Dose reduction from 1,500 to 1,000 mg/day

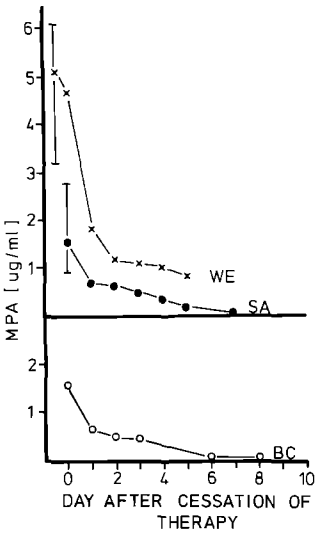

Fig. 6. Elimination kinetics after cessation of MPA administration. Day 0 is the last day of application

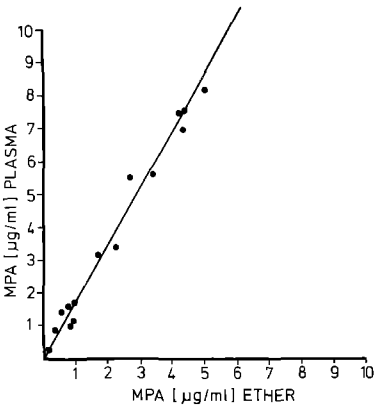

Fig. 7. MPA concentrations in plasma and after extraction with diethylether. The *line* was inserted by hand

Table 1. Extraction efficiency for MPA with various organic solvents in the absence of MPA metabolites. The values reflect ^{3}H-MPA in cpm

	Organic solvent		
	Diethyl-ether	Petroleum-ether	Benzene : isooctane 2 : 1 (v/v)
Plasma before extraction	5,300	5,300	5,250
Plasma after extraction	3,100	4,200	3,300
Extraction phase	2,400	900	1,950

and medians are larger than could be expected to result from random variations.

Figure 4 shows the influence of ingestion of MPA 500 mg on the actual plasma concentrations under steady-state conditions. The slope of MPA concentrations in patient RM seems to reflect the oral medication, whereas in patients GH and BA no correlation can be seen. It should be emphasized that the periodic administration of mitomycin C had no influence on MPA plasma concentrations at any time.

For patient BA the dose was reduced from 1,500 to 1,000 mg due to a change in the therapeutic regimen. Figure 5 shows the immediate reduction in the level of MPA plasma concentrations.

Three patients were monitored after the cessation of MPA therapy (Fig. 6). Regardless of the level of the foregoing range and median there is a dramatic decrease of MPA plasma concentrations at day 1. In terms of kinetics, the half-time of MPA in this phase is about 20 h. The elimination kinetics seems then to switch to a second phase, where half-time seems to be 3–4 days.

The methodological approach to the determination of MPA plasma concentrations by RIA has been different [9, 16–18, 28, 31]. Some extraction methods were claimed to discriminate between MPA and its metabolites [21, 34]. Table 1 shows that the ether extraction is the most effective of the methods tested but the efficiency, at least in our hands, was about 40% in the absence of metabolites. Patients' plasmas were also extracted, and Fig. 7 shows an excellent linear correlation between determinations in plasma and ether extracts over a wide range of concentrations. The relation is not exactly 6 : 4, so MPA metabolites may play a perhaps marginal role in the determination of MPA plasma concentrations.

Discussion

The continuous oral administration of MPA 1.5 g/day leads to an accumulation of the drug in plasma (Figs. 1–3). The different time courses before the plateau state is reached may be explained by differences in absorption, distribution, and metabolism. It is interesting to note that the two time-courses in the initial phase have some relation with the two half-times observed in elimination kinetics (Figs. 1 and 6). Underlying a one-compartment model, the plateau state should be reached after four half-times, i.e., in this case after 4 or 16 days. This is exactly what was found in the initial phase. As MPA is highly lipophilic a multi-compartment model must be discussed, but

the kinetic data described here are at least compatible with a one-compartment model.

In good agreement with previous studies [16], a broad intra- and interindividual variation of plasma concentrations is observed in the plateau state (Fig. 3). These variations appear not only with oral but also with IM administration [9, 19, 21, 33]. The basis for this phenomenon is not clear. Again different influences of the individual patients on drug absorption, distribution, and metabolism should be discussed. Recently the elevation of plasma estrogens during ampicillin therapy was reported [1]. In this context the modification of MPA plasma concentrations by other drugs should be considered. Mitomycin C, which was part of the therapy schedule in this study, had no influence either on the actual plasma concentrations or on the plateau state. It is important to note that oral administration was followed by much higher MPA plasma levels than was IM administration [9, 19, 31, 32], with a clear relation between dosage and plasma level [31].

Plasma levels monitored hourly were relatively stable within a day (Fig. 4). Methodological problems depending on laboratory techniques could thus be excluded. Interindividual differences were also observed in the reaction to the daily oral administrations. In one patient the plasma concentrations reflected the oral doses, whereas in other patients the reaction of plasma levels on oral medication was poor to say the least (Fig. 4).

The plateau concentrations were revealed to be very sensitive to dose reduction (Fig. 5). Apparently there is not a buffered system in which plasma concentrations can be kept constant for a while by redistribution from a drug reservoir. This sensitivity of the plateau state is more pronounced after the cessation of therapy (Fig. 6). The rapid decline in MPA plasma concentrations is clinically very important. The dose-related 'adequate' MPA plasma levels are not known, but for maintenance of the individual plateau concentrations continuous oral administration is crucial.

Previous investigations revealed some problems in the determination of the 'absolute' levels of MPA plasma concentrations [16, 18, 19, 21, 28, 31, 34]. It was shown by gas liquid chromatography that in RIA determinations plasma concentrations were overestimated five to ten times [18], and interference from MPA metabolites was discussed. The metabolism of MPA is not completely clear [1]. The major pathway seems to be the modification of the side chains at C_{17} and C_{21} [3, 7, 8, 11–15, 28, 29, 35]. These types of metabolites are not recognized by the antibody used here [9, 34]. Minor metabolites were found to be modified at C_3 and C_6 [3, 29]. Metabolites of this type might be readily bound by the antibody [9, 34], leading to overestimation of MPA plasma concentrations. Some extraction procedures were suggested to overcome this problem of the RIA technique [16, 34]. As not all MPA metabolites have yet been identified [1] and consequently their solubility in organic solvents is unknown, the results of these experiments are difficult to interpret.

When diethylether was used for extraction experiments only a marginal difference in the extraction effectivity could be observed in the presence and absence of metabolites (Table 1 and Fig. 7). Theoretically the different relation of MPA and its metabolites in the initial phase and after cessation of administration could be expected to give rise to some kind of hysteresis when plasma levels with and without extraction are compared. The absolute linear relation of RIA determinations with and without ether extraction seems to reflect only the methodological difference between the two procedures (Fig. 7 and Table 1). It may therefore be justified to use the direct plasma RIA without extraction, as described elsewhere [9, 17].

Keeping in mind that gas liquid chromatography reveals lower values, MPA plasma concentrations found in this study were nevertheless extraordinarily high. This may reflect a good bioavailability of the drug.

Clinically, high-dose MPA treatment was remarkably well tolerated as already observed in previous studies [23–25]. In terms of pharmacodynamics the intrinsic glucocorticoid activity of MPA has a predominant significance [6].

The complete suppression of ACTH and the gonadotropins in the sense of a partial 'pharmacological hypophysectomy' may be one of the main mechanisms of tumor regression achieved with MPA [2, 6]. The selective binding of MPA to the gestagen and androgen receptors suggests another more cytostatic mechanism of action [4, 5]. The function of MPA metabolites in this context is not clear. The plasma level related therapeutic efficiency is now under investigation. The pharmacokinetics of high-dose MPA administration will be only the beginning of the evaluation of the significance of gestagens in the therapy of advanced breast cancer.

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