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Pharmacokinetic study of low- versus high-dose medroxyprogesterone acetate (MPA) in women

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Abstract The present study was conducted to compare the pharmacokinetics (PK) of low-dose versus high-dose medroxyprogesterone (MPA) as a once-daily oral administration. Of 32 patients, all women, enrolled in this PK study, 18 received 600 mg MPA daily and 14 received 1200 mg daily. Detailed PK data were obtained on day 1 and after more than 4 weeks of MPA treatment. In addition, multiple data for the minimum steady-state concentration (Css min) were analyzed. The MPA serum concentrations were measured by high-performance liquid chromatography. Wide interpatient variability was found in the PK parameters obtained both on day 1 and after more than 4 weeks. There were no clear relationships between the oral dose and the MPA peak concentration (Cmax), area under the time versus concentration curve (AUC), or mean Css min. Weight gains of 10% or more were demonstrated more frequently in the high-dose group ($P < 0.01$). Liver dysfunction ($n = 5$) did not influence the PK of MPA. Five patients demonstrated extremely low AUC and Cmax (< 10 ng/ml) values on day 1. Phenobarbital, dexamethasone and betamethasone were being taken concomitantly with the MPA each by one patient. The serum MPA concentrations were markedly increased after the discontinuation of phenobarbital in that patient, suggesting a drug interaction. At present we cannot recommend the high dose of MPA, except in clinical studies, from a PK or a pharmacodynamic points of view.

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Introduction

Medroxyprogesterone acetate (MPA) is one of the drugs most commonly used in endocrine therapy for advanced or recurrent breast cancer and endometrial cancer. However, the optimal dose of MPA remains uncertain, with dosages ranging from 300 mg/day to 2000 mg/day accepted in various treatment protocols. It is also controversial as to whether there is a relationship between the dose of MPA and the response rate. Some clinical trials have indicated a higher response rate in patients receiving high MPA doses [1, 2], but others have found no association between response rates and the different dosages administered [3–5], although a higher frequency of toxicity has been seen at higher doses [3–5]. Moreover, a higher response rate with a higher dose does not always mean a better survival rate [2].

The conflicting results are considered to be a result of uncertainties as to the relationship between dose and blood concentration, and that between blood concentration and tumor response. It is known that the absorption of orally administered MPA is highly variable and erratic, showing a more than tenfold difference in the steady-state concentration at the same dose [5, 6]. One study has demonstrated a clear linear increase in the MPA level in the blood with increasing dosage [7], whereas others demonstrated no difference in MPA pharmacokinetic (PK) parameters at 500 mg/day and at 1000 mg/day given orally [8], or surprisingly, a lower MPA trough concentration at more than 1000 mg/day given orally [5]. Furthermore, some studies have found a correlation between the blood concentration and tumor response [5, 9, 10], while others have found no correlation [11–14].

Several methods of measuring MPA have been developed, and PK analyses have been conducted mostly using a radioimmunoassay (RIA) [6, 7, 10–14], gas chromatography (GC) [8, 9] or high-performance liquid

chromatography (HPLC) [5]. Some metabolites of MPA may crossreact with the antibody used in an RIA; therefore, it is important to detect MPA itself by GC or HPLC. Details of the PK analyses of oral MPA using HPLC, however, have not been reported [15].

Questions have been raised as to the rationale of using high-dose MPA in the treatment of breast cancer. In Japan, the Advanced Breast Cancer Study Group (ABCSG) of the Japan Clinical Oncology Group (JCOG) is currently conducting a large-scale randomized clinical trial of chemoendocrine therapy for advanced breast cancer, comparing low-dose (600 mg/day) with high-dose (1200 mg/day) oral MPA in combination with tamoxifen (TAM) and anticancer agents. The present investigation was undertaken to provide a pharmacological foundation for the interpretation of the results of the above-referenced clinical trial, which will be reported elsewhere. The purposes of the present study were to identify the detailed PK behavior of orally administered MPA using HPLC and to compare the PK of MPA at a low dose and at a high dose.

Table 1 Characteristics of the 32 patients receiving low- or high-dose oral MPA

Number of patients	32
Age (years) Median (range)	55 (38–77)
Sex, male/female	0/32
Performance Status 0/1/2/3	14/9/5/4
Menopausal state Pre/post	8/24
Disease	
Advanced breast cancer	30
Endometrial cancer	1
Adenocarcinoma of unknown origin	1
Prior chemotherapy	26
Prior hormone therapy	19
Dose of MPA (mg/day) 600/1200	18/14
Combination therapy with MPA	
Chemotherapy + tamoxifen	17
Chemotherapy	2
Tamoxifen	3
None	10
Liver dysfunction (GOT or GPT > normal)	5

Materials and methods

Patients

Between December 1993 and April 1995, 32 female patients who were being treated for cancer with oral MPA in a clinical trial or in clinical practice at the National Cancer Center Hospital East (NCCHE), Japan, were enrolled in this PK study of MPA. The protocol was accepted by the Institutional Review Board and the Institutional Ethics Committee. The eligibility criteria were as follows: (a) age between 15 and 80 years; (b) an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2 or 3; (c) an interval of at least 6 weeks between the start of the present MPA treatment and the end of any previous endocrine therapy; (d) full recovery from the toxic effects of prior therapy, if any; (e) adequate hematopoietic function (WBC $\geq 3500/mm^3$, hemoglobin ≥ 10.0 g/dl, and platelets $\geq 100\,000/mm^3$), renal function (normal creatinine and urea nitrogen), and hepatic function (total bilirubin ≤ 1.5 mg/dl and transaminases ≤ 80 IU/l except in patients with liver metastasis); (f) serum Ca ≤ 11 mg/dl and fasting blood sugar ≤ 115 mg/dl; and (g) normal cardiac function. Written informed consent was obtained from all patients according to the institutional guidelines.

The patients' characteristics are given in Table 1. Of the 32 patients, 30 had advanced breast cancer. The median age was 55 years, with a range of 38 to 77 years. Almost all patients had already received chemotherapy and/or endocrine therapy for their advanced disease or as adjuvant therapy. Of the 32 patients, 18 were treated with 600 mg/day of MPA and 14 were treated with 1200 mg/day, and 22 received concomitant therapy including TAM and/or chemotherapy that consisted of doxorubicin and cyclophosphamide with or without 5-FU. MPA in combination with doxorubicin, oral cyclophosphamide and TAM was administered as the first-line therapy for advanced disease in 14 patients according to the protocol of the ABCSG-JCOG. Five patients with liver dysfunction were included, but the liver transaminase levels were less than 80 IU/l in all of these patients except one with extensive liver metastasis who showed a GOT/GPT level of 159/65 IU/l and a total bilirubin level of 1.7 mg/dl.

Pharmacokinetic sampling

Each patient received a single oral dose of MPA (200 mg tablets, Pharmacia Co., Tokyo) with adequate water once daily before breakfast. Venous blood samples for MPA analysis were withdrawn immediately before the administration of MPA and 1, 2, 3, 6, 12 and 24 h later on day 1 and after the attainment of the steady-state concentration, i.e. at least 4 weeks after the start of MPA treatment. Blood samples were also taken regularly just before the daily MPA administration whenever possible every month. Immediately separated serum samples were frozen at −40 °C until assay. Among all the 32 enrolled patients, a detailed PK analysis was performed on day 1 for 27 patients, and after 4 weeks of MPA administration for 15 patients.

Analytical techniques

The concentration of MPA in serum was determined by HPLC using megestrol acetate (MA) (Sigma-Aldrich Japan, Tokyo) as an internal standard. The HPLC system consisted of an SCL-6B chromatograph system (Shimadzu, Kyoto, Japan), an SIL-6B autoinjector, an SPD 10A UV detector at 240 nm, and a Chromatopac C-R4A data processor. Each serum sample (0.5 ml) was deproteinized with 7 ml *n*-hexane after the addition of water (1 ml) and 100 µl internal standard solution diluted with methanol (5 µg/ml). After centrifugation, the supernatant was filtered through a cartridge filled with 500 mg silica gel (Wakogel C-200®, Wako Junyaku Kogyo Co., Osaka, Japan) previously washed with 9 ml methanol, 9 ml ethyl acetate and 10 ml *n*-hexane. The cartridge was then eluted with 3 ml *n*-hexane and 5 ml ethyl acetate/*n*-hexane (1:3). These eluates were discarded, and MPA and internal standard were finally eluted from the cartridge with 6 ml ethyl acetate/*n*-hexane (1:3). The solution was vacuum-evaporated at 50 °C for 30 min. The residue was reconstituted with 0.5 ml 0.01 *N* H_3PO_4/acetonitrile (2:3), and 100 µl of the reconstituted sample was injected onto the HPLC column. HPLC was performed on a YMC-Pack A-312 (6 mm ø × 150 mm, Y.M.C. Co., Kyoto). The mobile phase was 0.01 *N* H_3PO_4/acetonitrile (2:3) at a flow rate of 1 ml/min. The retention times of MPA and the internal standard were 15.5 and 14.5 min, respectively. The recovery of MPA was 80%, and the interday reliabilities (coefficients of variation CV) of the assay for MPA at 30 ng/ml, 50 ng/ml and 100 ng/ml were 5.2%, 6.0% and 4.4%, respectively. The MPA concentration was quantified by linear regression analysis of the peak height ratio (MPA/internal standard) versus the standard curve generated from the solution of MPA with methanol, and the detection limit was 2 ng/ml.

Pharmacokinetic analysis

The area under the concentration versus time curve from time 0 to 24 h (AUC_{0-24}) was obtained by a noncompartmental moment method, computed by trapezoidal integration. The peak plasma concentration (Cmax) was the peak concentration actually observed. The mean minimum steady-state concentration (Css min) was calculated as the average of multiple trough measurements, taken after at least 2 weeks of daily MPA administration.

Statistical analysis

Statistical analysis was performed with STATVIEW 4.02 software (Abacus Concepts, Berkeley, Calif.). Because the Css min values for the patients did not fit a normal distribution curve, nonparametric tests were used. Comparisons between the 600 mg/day and 1200 mg/day groups were conducted using the Mann-Whitney *U*-test. Linear regression analysis was used and Pearson's correlation coefficients were obtained to test the relationship between the AUC for day 1 with each of the steady-state AUC values and the Css min. The proportional weight gains at different dosages were compared by Chi-squared analyses. *P*-values less than 0.05 were considered significant.

Results

Pharmacokinetics of MPA on day 1

The serum concentration profiles of MPA on day 1 obtained from 15 patients treated with MPA at 600 mg/day and from 12 patients treated with MPA at 1200 mg/day are shown in Fig. 1A, B, respectively. The drug serum concentration increased rapidly, achieving Cmax in a median of 2 hours (range 1–6 h for 600 mg/day; 1–12 h for 1200 mg/day). In eight patients Cmax was achieved at 1 hour on day 1. Because this was the earliest time sampled, it is possible that Cmax might actually have been achieved earlier. Marked interindividual variability was observed in both schedules. The Cmax was more than 100 ng/ml in two patients (no. 1 ∇ and no. 2 Δ in Figs. 1 and 2 and Table 2) treated at 600 mg/day, while in three patients (no. 3 ◇, no. 4 × and no. 5 ○) it was less than 10 ng/ml (Table 2). Patient no. 1, who had a high Cmax, had liver metastasis which produced an increase in the levels of transaminases (GOT/GPT 159/65 IU/l) and hyperbilirubinemia (total bilirubin 1.7 mg/dl), and another patient with a high Cmax (patient no. 2) had normal liver function. Patient no. 3, whose Cmax was less than 10 ng/ml, was receiving simultaneous daily dexamethasone (2 mg/day) for brain metastasis of breast cancer. Of the patients treated with MPA at 1200 mg/day, one (patient no. 6 ▲) showed a Cmax of more than 100 ng/ml and two (patient nos. 7 ◆ and 8 ⊞) showed Cmax values of less than 10 ng/ml. The patient with the highest Cmax had normal liver and renal function, and was receiving simultaneous prednisolone (10 mg/day). Patient no. 8, with the lowest Cmax, was receiving phenobarbital (120 mg/day) for prophylaxis of epilepsy, and patient no. 7 was receiving betamethasone (1.5 mg/day) concomitantly.

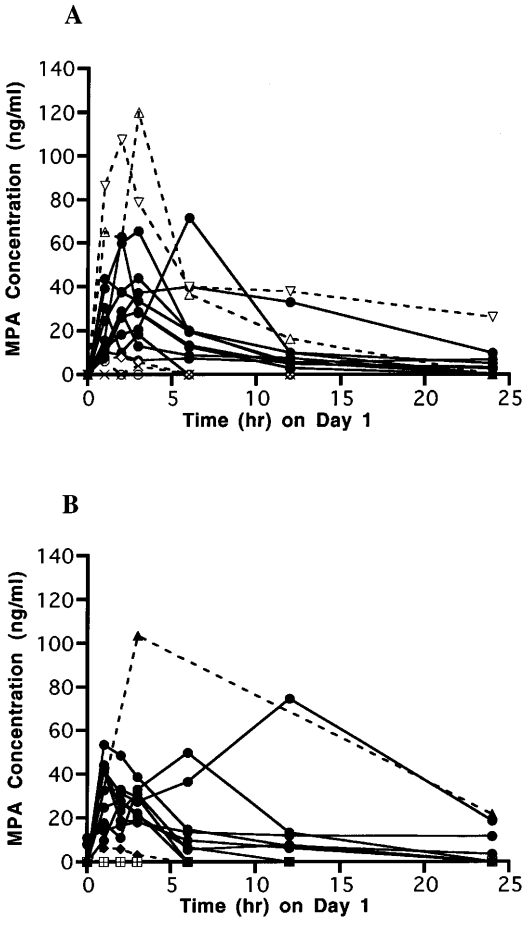

Fig. 1A,B Serum MPA concentration versus time curves on day 1 of oral MPA administration for the 600 mg/day group ($n = 15$, **A)** and for the 1200 mg/day group ($n = 12$, **B**)

Pharmacokinetics of MPA after more than 4 weeks of MPA administration

The serum PK profiles of 15 patients (8 at 600 mg/day and 7 at 1200 mg/day MPA) were examined after the steady-state concentration of MPA had been attained. Marked interindividual variability was also observed, but all patients showed a Cmax of more than 10 ng/ml (Fig. 2A,B). Patient no. 8, who had shown undetectable serum concentrations throughout day 1, was receiving concomitant phenobarbital (⊞ in Fig. 1B), and showed an average serum profile with a Cmax exceeding 50 ng/ml after the cessation of phenobarbital. The patient with the highest Cmax (Patient no. 9 ▼) had normal liver and renal function.

Comparison of pharmacokinetic parameters between low-dose and high-dose MPA

Table 3 shows the mean PK parameters of the patients on both schedules. There were no significant differences between the two patient groups in terms of AUC, Cmax on either day 1 or at steady-state, or Css min; however,

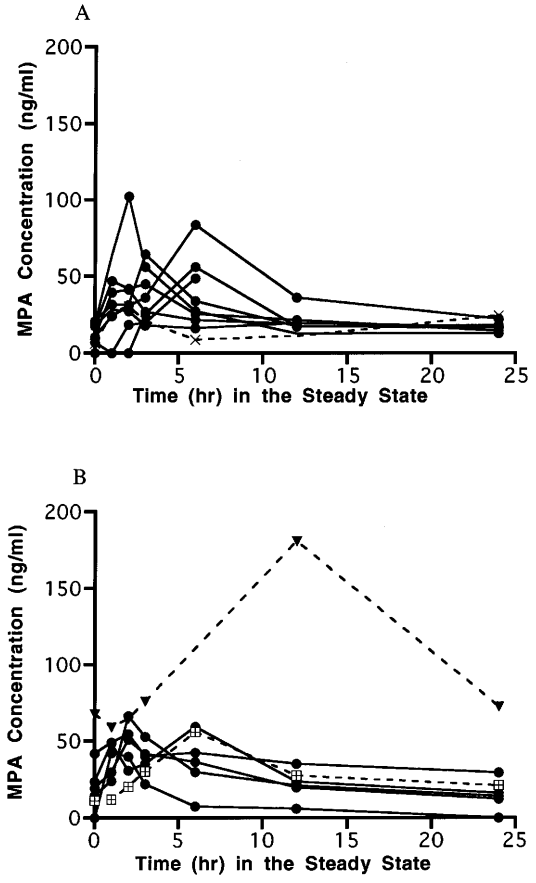

Fig. 2A,B Serum MPA concentration versus time curves after 4 weeks of oral MPA administration for the 600 mg/day group ($n = 8$, **A**) and for the 1200 mg/day group ($n = 7$, **B**)

there was large interpatient variability. There was particularly marked interpatient variability for Css min, ranging from near the detection limit to more than 70 ng/ml. The most frequent values of Css min were between 10 and 20 ng/ml. Figure 3 demonstrates the scattergram of Css min of MPA in the two dose groups. The mean Css min values in the 600 mg/day dose group ($n = 16$) and in the 1200 mg/day dose group ($n = 13$) were 16.9 ng/ml and 24.1 ng/ml, respectively, and they were not significantly different.

Comparison of pharmacokinetic parameters on day 1 and at steady state

The scattergrams of the AUC on day 1 versus the AUC at steady state or the Css min are shown in Fig. 4A, B. There was a significant correlation between the AUC on day 1 and the AUC at steady state ($n = 13$, $P < 0.01$, Fig. 4A).

Effects of TAM and of liver dysfunction on the pharmacokinetics of MPA

The mean Css min values of the patients treated with ($n = 20$) and without ($n = 10$) TAM were 16.80 and 28.99 ng/ml, respectively ($P > 0.05$). In five patients with liver dysfunction including abnormal levels of GOT, GPT and total bilirubin, the mean Css min did not differ from that of patients with normal liver function, although the number of patients with liver dysfunction was very small.

Pharmacodynamics

Since the present patients had heterogeneous diseases and various previous treatments, the antitumor effect of MPA per se was not evaluated in this study. There was no marked adverse effect of MPA except weight gain. A weight gain of more than 10% of the patient's baseline weight occurred in 12 of the 29 patients in whom the Css min was evaluated. A comparison of patients with versus those without weight gain did not show a significant difference in the mean Css min ($P = 0.39$, data not shown). Three of 16 patients who received 600 mg/day MPA and nine of 13 who received 1200 mg/day

Table 2 MPA Pharmacokinetics in specific patients (*NE* not examined, *ND* not detected)

Patient no.	Age (years)	Special condition	Time of examination	$AUC_{(0-24)}$ (ng h/ml)	Cmax (ng/ml)	Symbol in Figs.
MPA at 600 mg/day						
1	53	Liver dysfunction	Day 1	1026.7	107.6	▽
2	61		Day 1	579.5	120.0	△
3	40	With dexamethasone	Day 1	24.1	7.8	◇
4	55		Day 1	5.9	3.9	×
			Steady state	171.7	30.4	
5	50		Day 1	3.1	6.1	○
MPA at 1200 mg/day						
6	60	With predonisolone	Day 1	NE	103.5	▲
7	48	With betamethasone	Day 1	13.7	6.2	◆
8	56	With phenobarbital	Day 1	ND[a]	ND[a]	⊞
			Steady state	792.4	55.6	
9	44		Steady state	2519.2	180.7	▼

[a] The serum concentration could not be detected throughout day 1

Table 3 Comparison of mean pharmacokinetic parameters between groups treated with low-dose and high-dose MPA

	Low-dose (600 mg/day)				High-dose (1200 mg/day)				
	n	mean	SD	CV(%)	*n*	mean	SD	CV(%)	*P*-value[a]
Day 1									
$AUC_{(0-24)}$ (ng h/ml)	15	296.1	287.1	96.9	11	239.0	303.6	127	0.59
Cmax (ng/ml)	15	44.7	35.4	79.3	12	39.9	28.8	72.2	0.81
Steady state (>4 weeks)									
$AUC_{(0-24)}$ (ng h/ml)	8	531.7	236.1	44.4	7	903.8	749.1	82.9	0.13
Cmax (ng/ml)	8	56.5	25.9	45.8	7	72.7	48.2	66.3	0.49
Css min (ng/ml)	16	16.9	16.7	98.7	13	24.1	18.8	78.0	0.10

[a] Mann-Whitney *U*-test

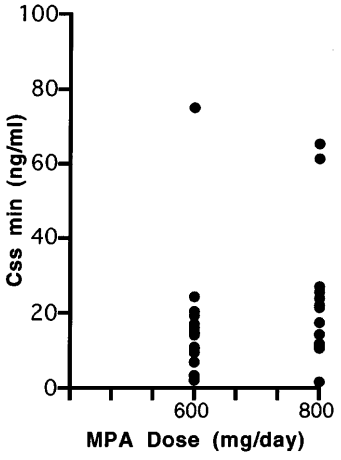

Fig. 3 Scattergram of Css min of MPA in the two dose groups. The mean Css min values in the 600 mg/day group ($n = 16$) and in the 1200 mg/day group ($n = 13$) were 16.86 ng/ml and 24.14 ng/ml, respectively. The difference was not significant ($P = 0.10$)

experienced weight gain. A chi-squared analysis revealed a significant increase in weight gain in the 1200 mg/day group compared with the 600 mg/day group ($P < 0.01$).

Discussion

The goal of treatment for patients with advanced breast cancer is almost always palliative, and hormonal therapy is the first systemic therapy for many patients with advanced breast cancer. Because the toxicities of hormone therapies are usually mild and are not clearly dose-related, it is difficult to determine the maximum tolerated dose (MTD) and the recommended dose for hormone therapies in phase I clinical trials unlike most cytotoxic drugs. Therefore, the dosages of classic hormonal therapy agents such as TAM and MPA used clinically have not been determined on the basis of scientific dose-escalation studies but rather selected empirically. MPA is commonly used as both first- and second-line hormonal therapy for advanced breast cancer. A wide range of doses of MPA for breast cancer have been tested, from 400 mg/day to 2000 mg/day, but the standard dose is considered to be somewhat lower (400–600 mg/day).

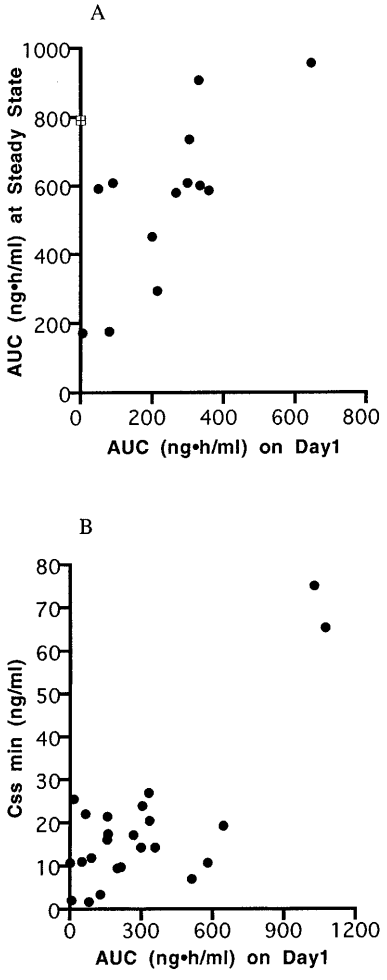

Fig. 4A,B The AUC of MPA on day 1 versus the AUC of MPA under steady-state conditions except for patient no. 8 (**A**) and versus Css min (**B**). There was a significant correlation between the AUC on day 1 and the AUC at steady state ($n = 13$, $P = 0.037$ in **A**)

Large-scale randomized trials comparing low-dose with high-dose hormonal therapy of TAM [16] and of toremifene (TOR) [17] for breast cancer have been reported recently. The former trial was accompanied by a PK study and confirmed that there is no advantage of the higher dose (40 mg/day) over the lower dose (20 mg/day) for TAM, nor any evidence of a correlation

between tumor response and the serum TAM level [16]. The latter study also disclosed no clear evidence of a dose-response effect or any survival benefit of the higher dose (200 mg/day) over the lower dose (60 mg/day) for TOR [17]. Likewise, the present study demonstrated no PK benefit of high-dose over low-dose MPA.

The present results revealed no significant differences related to the MPA dose in the PK parameters Cmax, AUC and Css min. This may have been a result of the small number of patients and the interpatient variability of PK. MPA is extensively metabolized in the intestinal mucosa and in the liver [18], and the bioavailability of MPA after oral administration is reported to be only approximately 5% [8, 19]. The present results confirm that absorption and clearance are variable enough between patients to introduce a high degree of heterogeneity.

Progesterone is known to be metabolized by the cytochrome P450 system including P450 CYP 3A [20–22]. It has also been suggested that MPA is metabolized in a similar way. Although a genetic polymorphism of progesterone metabolism has not been detected, there is reported to be marked interindividual variability in P450 of the small bowel and liver [23, 24]. Endogenous and exogenous factors (e.g. age, blood pH, concomitant diseases and drug therapy, meal preparation procedure, nutritional habits, and smoking) contribute to P450 system heterogeneity, which ranges over tenfold interindividually and over a few-fold intraindividually [23, 24]. The interpatient variabilities of PK demonstrated in the present study may be reasonable if MPA is metabolized by the cytochrome P450 system.

The therapeutic MPA concentration "threshold" remains unclear. Studies have variously suggested that the optimal therapeutic range for the MPA Css min is higher than 50 ng/ml [5], 80 ng/ml [9], or 100 ng/ml [10]. Because in all these studies different methods were employed for the MPA assay, including HPLC [5], GC [9] and RIA [10], the Css min values cannot be compared with each other. The present study using an HPLC method to evaluate approximately equal numbers of patients with MPA administered at 600 mg/day and at 1200 mg/day demonstrated that only 10% ($n = 3$) of the patients had Css min values more than 50 ng/ml and that the most frequent Css min range was 10–20 ng/ml. Etienne et al. have reported a most frequent Css min range similar to ours [5]. Fornasiero et al. have reported that the mean Css min is around 40 ng/ml, as determined using a GC method, when the oral MPA dose is 1000 mg/day [9]. The optimal therapeutic concentration was attained in fewer than 50% of the patients in the study by Etienne et al. [5] and in only a few percent of the patients in the study by Fornasiero et al. [9]. Another study using GC [8] has demonstrated a much lower plasma concentration of MPA than that observed in our study. These lower concentrations might be related to the dose schedule of once a day MPA administration, although a greater bioavailability of MPA when delivered in a fractionated administration has not been reported. Endocrine effects of MPA have been recognized at concentrations less than 5 ng/ml in patients receiving intermittent intramuscular MPA as a contraceptive [25]. The present study demonstrated a pharmacodynamic effect of MPA in the form of weight gain in patients with a Css min value of less than 10 ng/ml. Although the exact mechanisms by which MPA causes the regression of breast cancer and weight gain have not been fully elucidated, these results suggest that the therapeutic effect may be achieved by a concentration far below the above suggested optimal Css min.

The influence of drugs on the PK of MPA has not been reported, except that aminoglutethimide (AG) reduces the blood concentration of MPA [26]. We consider the greatest obstacle to MPA treatment to be the existence of a subgroup of patients with an extremely low blood MPA concentration who will not benefit from the treatment. Five patients demonstrated markedly low Cmax values of less than 10 ng/ml and a low AUC on day 1. Three of them were taking phenobarbital, dexamethasone or betamethasone at the same time that they were taking MPA. The MPA concentration in patient no. 8 remained under the detection limit but showed a marked increase after the discontinuation of phenobarbital. In patient no. 3, who was under treatment with betamethasone on day 1, the Css min reached 25.5 ng/ml 2 months after the betamethasone was discontinued.

Phenobarbital and dexamethasone, but not prednisolone, are known to increase the levels of various cytochrome P-450-related enzymes [20, 27], especially P450 CYP 2B [28] by phenobarbital and P450 CYP 3A by dexamethasone [27]. Since MPA is also considered to be a substrate for P450 [20–22], drug-to-drug interactions related to CYP 450 between MPA and phenobarbital or dexamethasone may reduce the concentration of MPA. Other drugs that are considered to induce or inhibit P450 enzymes [20] were not given to any of our patients during the study. The concomitant phenobarbital might have completely suppressed the serum MPA in patient 8 partly because this drug is one of the strongest P450 inducers; alternatively, CYP 450 2B might play a major role in the metabolism of MPA.

When MPA is used in patients with brain metastasis, care should be taken to avoid the concomitant use of P450 inducers and MPA. The same principle may apply to TAM, which is known to be metabolized by CYP P450 3A [29] and whose serum concentration is also decreased by AG [30]. In our present series, simultaneous TAM treatment did not seem to influence the PK of MPA, as reported previously [31], and the PK of TAM was not evaluated in the present study. Likewise, liver dysfunction did not seem to affect the PK of MPA, as also observed previously [5]. As the most informative PK parameter of MPA, previous reports consistently cite the Css min for PK/pharmacodynamic analysis [5, 9, 11–14]. We found that the AUC on day 1 was correlated with the AUC at steady-state, suggesting that we can predict the patients who are extensive metabolizers using the PK values obtained on day 1.

There was a significantly increased frequency of weight gain in the 1200 mg/day group compared with the 600 mg/day group ($P < 0.01$). Our observation that this drug adverse effect was more frequent in the higher dose treatment group is similar to previous reports that have failed to demonstrate any relationship between dose and antitumor effect [3–5]. Some authors have reported that the risk of toxicity is correlated with the MPA concentration as well as the dose administered [5, 10], but our study failed to demonstrate any difference in Css min between the patients with and without a weight gain of more than 10%. Hedley et al. also found no relationship between the MPA plasma concentration and hormonal function, tumor response or side effects [11]. The mechanism of MPA dose-related side effects has not been elucidated. At present, we recommend the low dose of 600 mg/day as the standard treatment from the PK and pharmacodynamic points of view. A recent study has indicated that another progestin, megestrol acetate, has no dose-response relationship in endometrial carcinoma [32]. We hope that the ongoing ABCSG-JCOG study will clarify whether high-dose MPA is clinically superior to low-dose MPA.

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