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Original Articles

Pharmacokinetic Approach to the Selection of Dose Schedules for Medroxyprogesterone Acetate in Clinical Oncology

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Summary. *The pharmacokinetic and bioavailability properties of medroxyprogesterone acetate (MPA) after single PO and IM doses in man were used as a basis to predict, on a theoretical pharmacokinetic basis, the blood level profile of the drug during repeated dose administration with various dosage schedules.*

Because of the unusually long-lasting depot effect of IM MPA, a different build-up process of blood levels is expected during repeated IM or PO administration, and this should be taken into account when dose schedules for use in clinical oncology are selected. As regards the IM route, dose schedules based on 4 weeks' treatment with daily injections of 500–1,000 mg followed by a maintenance therapy with 1,000 mg/week are suggested, since they permit rapid achievement and maintenance of relatively high plasma levels.

A similar plasma level profile can be obtained with oral MPA provided that daily doses twice as large as the IM doses are given during the first month of treatment and continued during the maintenance period. The serum levels observed in 25 patients with advanced breast cancer treated with MPA given IM or PO according to various dose schedules and recent literature data are very close to the serum level profiles predicted on a theoretical pharmacokinetic basis.

Introduction

Medroxyprogesterone acetate (MPA), a potent progestogen active by both IM and PO routes, has been widely used in clinical practice in the hormonal treatment of endometrial carcinoma [1] as well as, more recently, of advanced breast cancer [5]. At present widely different dose schedules are employed in clinical oncology, depending on the type of tumor and the route of administration.

Doses as low as 200–1,000 mg/week by IM injection or 100–200 mg/day PO are currently employed in endometrial cancer, whereas, in breast cancer, 500–1,500 mg/day IM and/or PO has been successfully used [4, 10, 12, 13].

The scant knowledge of the pharmacokinetic and bioavailability properties of MPA probably accounts, at least in part, for such wide differences in the dose schedules proposed for therapy.

The recent availability of very sensitive radioimmunoassay (RIA) methods [3, 16], the specificity of which has been improved by suitable extraction of serum samples before RIA [7, 8, 11, 14, 16], and of a specific but less sensitive GLC method [9] has stimulated the research on drug serum levels in patients after single and repeated MPA administration. However, no attempts have been made to evaluate the pharmacokinetic and bioavailability parameters of MPA and to draw general conclusions about the relationship between dose schedules and the drug blood level profile.

The aim of this paper is to discuss on a theoretical pharmacokinetic basis how the different bioavailability properties of IM and PO MPA are expected to influence the drug blood level profile during repeated administration. These theoretical predictions will be compared with the serum levels observed in patients with advanced breast cancer during treatment with high-dose MPA by the IM and PO routes and with literature data.

Theoretical Pharmacokinetics

The mean plasma levels reported by Salimtschik et al. [14] after single PO and IM administration to patients of various doses ranging from 100 to 1,200 mg were

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used to calculate some kinetic parameters of MPA. For both routes of administration, plasma levels increased with dose, suggesting linear pharmacokinetics in the dose range tested.

With the PO route, the absorption was rapid and plasma levels decreased with a terminal plasma $t^1/_2$ of about 48 h. The total area under the plasma level curve (AUC) increased linearly with increasing dose, being about 250 ng/ml × h for each 100 mg dose.

After IM injection, MPA plasma levels were practically steady during the 1-week observation period, reaching mean values of about 1 ng/ml for each 100 mg dose.

The plasma levels achieved were several times higher after oral MPA than after IM administration of the same dose.

Literature data [7, 11] indicate that MPA plasma levels after a single IM injection decrease very slowly, reflecting a slow, long-lasting absorption from the injection sites. The plasma $t^1/_2$ after IM injection appears to be about 6 weeks, which fully explains the duration of the contraceptive effect (3 months) of a single IM injection of MPA. The rate of absorption can be estimated as only a few milligrams per day even after doses of 500–1,000 mg/day, so that the true amount absorbed does not correspond to the large doses administered.

The wide differences in pharmacokinetic and bioavailability properties between PO and IM MPA discussed above have important consequences for the build-up process of plasma levels following repeated dose administration. The drug plasma level profile during multiple-dose treatment can be theoretically predicted by applying the pharmacokinetic techniques of dose regimen calculations [17]: assuming that the disposition of MPA after IM dosing can be described in terms of a one-compartment model with a plasma $t^1/_2$ of 6 weeks and Co = D/V = 1 ng/ml for each 100-mg dose, the plasma level profile expected during a repeated administration of a dose D at time interval τ is described by the following equation:

$$Cn(t') = Co \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} e^{-Kt'} \quad (1)$$

where $Cn\ (t')$ = plasma level after the nth dose; $K = 0.693/t^1/_2$ = rate constant of drug elimination; t' = time elapsed after the nth dose.

As regards the PO route, the data available do not allow reliable assessment of the whole time-course of plasma levels. However, knowledge of the AUC after a single dose and of the plasma $t^1/_2$ is sufficient to predict the average steady-state plasma levels $\bar{C}ss$ achieved during repeated administration of a dose D at time interval τ according to the equation:

$$\bar{C}ss = \frac{\text{AUC}\ (\tau)ss}{\tau} = \frac{\text{AUC}\ (\infty)sd}{\tau} \quad (2)$$

where AUC $(\tau)ss$ = area under curve at steady-state within a dosage interval τ; and AUC $(\infty)sd$ = total area under curve after the single dose D.

The steady-state plasma levels will be practically reached after 5 times the plasma $t^1/_2$ of the drug (for oral MPA after 5 × 48 h = 10 days). As a consequence of the very long plasma $t^1/_2$ of IM MPA an unusual profile of accumulation is expected during repeated administration, with a continuous increase of plasma levels up to a steady-state situation which will be reached after about 6–8 months of therapy, corresponding to 4–5 times the plasma $t^1/_2$ of 6 weeks. The steady-state levels will be many times those reached after the first dose, as a function of the dosage interval τ, according to the equation:

$$\frac{C\ (\text{steady state})}{C\ (\text{first dose})} = \frac{1}{1 - e^{-K\tau}}. \quad (3)$$

Figure 1 shows the plasma level profile expected theoretically during treatment with 1,000 mg/week by the IM route, the dosage schedule most frequently used in endometrial carcinoma. It is evident that the dose schedules based on weekly injections are not rational from a pharmacokinetic point of view, because on the assumption that relatively high steady-state levels are necessary for therapy, it takes too long to reach them. The time to reach steady-state levels of the same order of magnitude can be substantially shortened by adopting a dose schedule based on a loading phase with daily injections of 500 mg for 4 weeks, followed by a maintenance therapy with one weekly injection of 1,000 mg, as shown in Fig. 1.

As regards PO administration, the plasma level profile theoretically expected during repeated dosing is completely different. In fact, because of the relatively short apparent plasma $t^1/_2$ of about 2 days, the steady-state levels will be reached after 10 days of treatment. This means that with MPA administered PO the steady-state levels can be maintained as long as administration continues with the same dosage schedule, and that any reduction of the daily dose will produce a linearly related decrease in steady-state levels. The average steady-state plasma levels expected according to Eq. 2 with various dose schedules of oral MPA are shown in Table 1. It must be stressed that $\bar{C}ss$ is the average steady-state level [17], and not the minimum. In the same table the

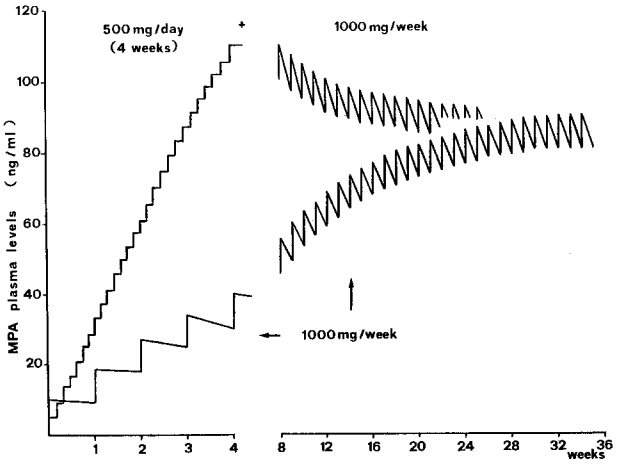

Fig. 1. MPA plasma level profile expected during repeated administration with two different dose schedules by IM route

Table 1. MPA plasma levels (ng/ml) predicted during treatment with various dose schedules

Route of administration	Dose schedule	Duration of treatment	Plasma levels (ng/ml)
PO	200 mg/day	> 10 days	~ 20[a]
	500 mg/day	> 10 days	~ 50[a]
	800 mg/day	> 10 days	~ 80[a]
	1,000 mg/day	> 10 days	~ 100[a]
IM	1,000 mg/week	> 6 months	~ 90
	1,000 mg/week	4 weeks	~ 40
	500 mg/day	4 weeks	~ 110
	1,000 mg/day	4 weeks	~ 220

[a] Average steady-state plasma levels

plasma levels that can be achieved with various dose schedules of IM MPA are also shown. From these data it appears that, on a long-term treatment basis, the bioavailability of MPA given by the PO route is substantially lower than that of MPA given IM. Moreover, to achieve similar plasma levels at the end of the 4-week loading period, daily PO doses twice as large as the IM doses are necessary.

Materials and Methods

Three pharmacokinetic studies were carried out in patients with advanced breast cancer who were being treated with various dose schedules of MPA. A group of nine patients admitted to a randomized clinical trial aiming at a comparison of the therapeutic efficacy of two different dose schedules of MPA by the IM route [2] entered the first kinetic study. Four patients were treated with 1,000 mg/day (5 days each week) for 4 weeks, followed by maintenance therapy with 500 mg/week up to progression, and five patients received 2 × 500 mg/week for 4 weeks and the same maintenance therapy. Blood samples were taken before and at various days during 4 months of therapy, in those patients whose treatments lasted for this period.

In the second study, a group of six patients with advanced breast cancer were given MPA by PO route at the following doses: 500 mg/day (4 patients) and 1,000 mg/day (2 patients). Blood samples were taken before and on various days during the first month of treatment.

The third study was carried out in 10 patients with advanced breast cancer. The aims of this study were to assess the MPA steady-state blood levels in patients treated with 500 mg PO b.i.d. and to compare the relative bioavailability of two dosage forms: tablets containing 200 mg MPA and a suspension obtained by diluting the content of one 500-mg vial for IM injection in a glass of water. A randomized cross-over design was followed: each patient was given one formulation for 15 days and the alternative formulation for a further 15 days. Blood samples were taken on the following days during treatment: 11, 12, 13, 14, 15, and 26, 27, 28, 29, and 30, i.e., the last 5 consecutive days of treatment with each dosage form.

Farlutal tablets (100, 200 mg of MPA) and Farlutal Depot suspension for injection, 200 mg MPA/ml (Farmitalia Carlo Erba, Milan, Italy) were used throughout all the studies.

In all studies, blood samples were taken in the morning before the scheduled daily administration. The serum separated was frozen at −20° C until analyzed. Serum MPA levels were assayed as described by Shrimanker et al. [16].

An antiserum raised in rabbits against MPA-3-(0 carboxy-methyl)-oxime BSA, obtained from Dr. K. Fotherby, Royal Postgraduate Medical School, London, Great Britain was used at a 1 : 5,000 dilution and 1,2 ^{3}H-MPA obtained from New England Nuclear, Boston, Mass. USA with a specific activity of 40 Ci/mmole, was used as a tracer.

All the reagents and methodology were exactly as described in the original method [16] except that samples of MPA used to construct the standard curve were extracted with diethyl ether in the same manner as the experimental samples. The MPA determinations were done in duplicate and the mean coefficient of variation was 11%. The coefficient of variation of inter-assay analysis, carried out on different days on plasma samples containing various concentrations of MPA (20, 10, 5 ng/ml) was 15%.

Results

The serum level profiles observed in nine patients treated with two different dose schedules of MPA by the IM route are shown in Fig. 2. During the loading period there was a progressive increase of MPA serum levels up to 140−170 ng/ml with the 1,000 mg/day (5 days per week) schedule and up to 35−70 ng/ml with the 1,000 mg/week (2 × 500 mg/week) schedule. During the 3-month maintenance treatment with 500 mg IM/week the serum levels were similar to or slightly higher than those reached at the end of the loading period. The MPA serum level profile in these patients is very close, from both quantitative and qualitative points of view, to that theoretically expected.

Figure 3 shows the serum level profile observed in six patients during a 1-month treatment with MPA PO. In all patients the serum levels increased during 1−2 weeks of treatment, then fluctuated around a

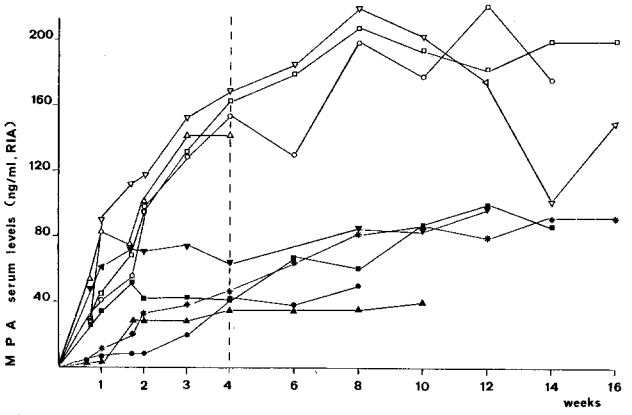

Fig. 2. MPA serum levels observed in two groups of patients with advanced breast cancer, treated by IM route with two different dose schedules. *Open symbols,* 1,000 mg/day (5 days/week) for 4 weeks, followed by 500 mg/week; *solid symbols,* 2 × 500 mg/week for 4 weeks, followed by 500 mg/week

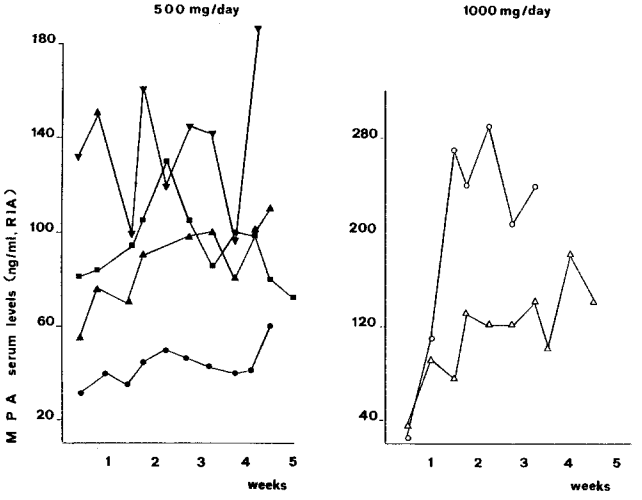

Fig. 3. MPA serum levels observed in six patients with advanced breast cancer, treated by oral route with 500 mg/day and 1,000 mg/day

steady state. Wide variations among subjects were observed in steady-state levels.

The results of the last study are collected in Table 2, expressed as mean serum levels observed in each patient during the last 5 days of each treatment period. The relative bioavailability of the two dosage forms has been calculated from the ratio between the mean serum levels observed in the same patient during the administration of MPA in tablets and suspension. The values represent a good estimate of MPA steady-state serum levels in a group of patients treated with 500 mg b.i.d. PO. On average, mean MPA serum levels were respectively 98.5 and 122.1 ng/ml in the two treatment periods, confirming that 10 days are usually sufficient to reach steady-state serum levels after PO dosing. The mean value of steady-state serum levels is quite close to that theoretically expected, but large variations between patients were found.

The two dosage forms investigated can be considered bioequivalent because the mean percentage of drug absorbed (suspension vs tablet) was close to 100%; however, wide differences were observed among patients in favour of one formulation or the other.

Discussion

The unusually long-lasting depot effect of IM MPA has been well known for the past 10 years, and it is fully exploited when the drug is used for contraceptive purposes. The potential consequences of this particular bioavailability profile on the blood level pattern over time following repeated IM administration have not been completely recognized , however,

Table 2. MPA serum levels observed in 10 patients during a 1-month treatment with 500 mg b.i.d. PO with tablets and suspension, and relative bioavailability of the two dosage forms

Subject	Sequence	Mean serum levels (ng/ml)[a] during the periods		Bioavailability (%, suspension vs tablets)
		11–15 days	26–30 days	
CR	Suspension – tablets	183.8 (12.5)	182.2 (26.5)	100.8
RG	Tablets – suspension	57.1 (18.4)	126.4 (19.5)	221.0
CP	Tablets – suspension	59.9 (11.2)	63.3 (7.8)	105,6
PG	Suspension – tablets	37.3 (34.2)	56.0 (12.9)	66.6
GR	Tablets – suspension	224.8 (26.0)	19.2 (17.5)	8.5
CN	Suspension – tablets	72.0 (5.1)	81.5 (9.9)	88.3
PG	Tablets – suspension	98.0 (15.6)	119.2 (6.1)	121.6
NC	Suspension – tablets	57.5 (6.1)	102.8 (9.1)	55.9
PT	Tablets – suspension	92.8 (11.2)	180.8 (20.3)	194.8
SG	Suspension – tablets	102.2 (18.3)	289.0 (29.6)	35.3
	Mean	98.54 (61.0)	122.04 (64.2)	99.84 (66.6)

[a] Figures in parentheses give coefficient of variation in each case

and this in part explains the widely different dose schedules used for MPA in clinical oncology.

We have shown on a theoretical basis that a continuous increase of serum levels can be expected during 6–8 months of therapy with weekly IM injections.

These theoretical predictions have been experimentally confirmed from both qualitative and quantitative points of view in a recent study carried out by Hesselius and Johansson [6] in women with endometrial cancer. On the reasonable assumption that relatively high steady-state serum levels are required for an effective treatment of endometrial carcinoma, the long time (months) required to reach them could have an adverse influence on the efficacy of the therapy.

This time lag in the attainment of high serum levels could be even more important in the treatment of advanced breast cancer. From the above-mentioned considerations it appears that the dose schedules recently used in the treatment of advanced breast cancer, which are based on 1-month loading phase with the daily IM injection of 500–1,000 mg, followed by a maintenance therapy with weekly injections, are fully rational from a pharmacokinetic point of view. In fact they permit MPA serum levels of about 100–200 ng/ml to be achieved relatively rapidly and maintained over a long period. Moreover, it must be taken into account that the serum levels reached after 1 month's treatment with 500 mg/day IM are expected to be simliar to those reached after 6–8 months of therapy with 1,000 mg/week. The usefulness of the loading phase with daily injections and of the consequent high MPA serum levels seems to be confirmed by the preliminary results obtained in the randomized study carried out by the SAKK cooperative group, where a significantly higher response rate was observed in the group of patients treated for 4 weeks with 1,000 mg/day (5 days/week) than in the patients treated with 2×500 mg/week [2].

As regards the PO route of administration, the theoretical and experimental data previously shown clearly indicate that, on a chronic treatment basis, the bioavailability of MPA given PO is substantially lower than that of MPA given IM in terms of efficiency of absorption. This appears to be in contrast with some literature data [1, 8, 15], which suggest an equivalent or a better bioavailability of MPA after administration PO. The discrepancy can be explained by the poor specificity of the RIA method used [1, 15] and by the short duration of IM treatment [8].

The lower bioavailability of oral MPA has been recently confirmed by Hesselius and Johansson [6] and Maskens et al. [9]. The data available do not permit us to ascertain whether this lower bioavailability depends on a presystemic metabolism (first-pass effect) or on incomplete absorption from the gastrointestinal tract.

As far as the question of equipotent doses of IM and PO MPA is concerned, the different bioavailability and accumulation profiles following the two routes of administration require different dose schedules. Taking into account the data shown in Table 1, it follows that steady-state plasma levels of the same order of magnitude can be reached with the two routes of administration, provided that when MPA is given PO daily doses twice as large as the IM doses are given during the loading period and continued during the maintenance period. It is during the maintenance period that the different bioavailability of PO and IM MPA becomes fully apparent.

Another pharmacokinetic aspect that could be of some importance in therapy is the wide inter-patient variation in steady-state serum levels after repeated PO administration, whereas with IM injections the serum levels achieved appear to be more reproducible. Similar results were also found by Hesselius and Johansson and Maskens et al. [6, 9].

In conclusion, the information so far available on pharmacokinetic and bioavailability properties of MPA allows reasonably accurate prediction of the time-course of mean drug serum levels in patients treated with various dose schedules by both the IM and the PO route. No conclusive data are available on the correlation between MPA serum levels and therapeutic efficacy in clinical oncology however, although from the combined evaluation of pharmacokinetic and therapeutic efficacy in advanced breast cancer it appears that, at least in this indication, serum MPA levels in the range of 100–200 ng/ml are necessary for a safe and effective treatment.

Accurately designed clinical trials are needed for further confirmation of the correlation between dose schedules, drug serum levels, and therapeutic efficacy of MPA in endometrial carcinoma and in advanced breast cancer.

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