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Medroxyprogesterone Acetate (MAP) Plasma Levels After Multiple High-Dose Administration in Advanced Cancer Patients

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Summary. *Medroxyprogesterone acetate plasma levels were measured in advanced cancer patients after multiple PO or IM administration (500, 1000, 2000, 3000, 4000, and 5000 mg/day PO and 500, 1000, 2000 mg/day IM for 30 days). After PO administration, the plasma concentration rises quickly and plateau level is reached in 4–10 days. Discontinuation of the treatment produces a fast decay ($t_{1/2} = 62.4$ h) of the drug levels. When medroxyprogesterone acetate is given IM plasma levels steadily increase and after drug discontinuation no noticeable decay is observed for at least 6 months; plateau plasma levels are about three times higher than after the corresponding PO treatment. Extremely high interpatient variation in bioavailability is present with both administration routes. These data may well rationalize the results of previous clinical trials and will help in planning treatment schedules.*

Introduction

High-dose medroxyprogesterone acetate (MPA) induces objective tumor response in 25%–45% of patients with metastatic breast cancer. Even after the vast majority of conventional treatments for advanced disease have failed, MPA can still produce a useful objective, as well as subjective, response and improved survival [3, 5, 10, 12–15, 21].

MPA treatment schedules – although sometimes supported by the results of extensive clinical studies – are currently still proposed on something of an empirical basis, and some relevant pharmacologic factors, i.e., drug plasma concentration over time, MPA metabolism, and maximum tolerated oral dose, are still unknown or not well documented. Following our work on the pharmacokinetics of single-dose administration [6, 16, 17], we present here results on the drug plasma concentrations after multiple administration of high and massive doses of MPA.

No clear-cut dose-response correlation has been reported up to now for MPA therapy, and a therapeutic MPA plasma concentration has still not been defined. Our results will hopefully create the basis for subsequent determination of these parameters.

Materials and Methods

A total of 45 hospital inpatients with histologically proved far advanced cancer have been entered on the study.

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Patients were not excluded if they had had prior treatment with chemotherapy or hormone therapy other than MPA, and all were assessed as having normal liver and renal functions.

Oncological treatments were discontinued at least 1 month before the start of this study.

All patients underwent physical examination and extensive clinical tests before the treatment. These measurements were repeated after drug discontinuation, and the results were recorded together with other relevant clinical data in our computer system in a format compatible with the BMDP package of biomedical programs [6].

Extensive uni- and multivariate statistical analysis of the factors connected with MPA therapy have been carried out, and will soon be published [16].

Thirty patients received MPA treatment PO over 30 days using commercially available MPA vials (Farlutal depot, Farmitalia, Milan, Italy) whose contents we suspended in fruit juice, in the following modalities: doses of 500 mg/day (5 patients) and 1000 mg/day (5 patients) were each given in a single daily administration (8 a.m.); 2000 mg/day (5 patients) was given as 1000 mg twice daily (8 a.m. and 8 p.m.); 3000 mg/day (5 patients), as 1000 mg three times daily (8 a.m., 12 noon, 8 p.m.); 4000 mg/day (5 patients), as 2000 mg twice daily (8 a.m. and 8 p.m.); and 5000 mg/day (5 patients), as 2000 mg twice (8 a.m. and 8 p.m.) and 1000 mg once (12 noon) daily.

IM treatment was given over 30 days with a single daily injection (Farlutal depot, Farmitalia, Milan, Italy) for the 500 and 1000 mg/day levels (8 a.m., 5 + 5 patients) and with two 1000 mg injections (8 a.m. and 8 p.m.) for the 2000 mg/day level (5 patients).

Every treatment was discontinued after 30 days and was resumed 1 week later for patients who responded to the treatment.

Assignment to the treatment schedule was random.

Samples for MPA assay were drawn in heparinized tubes and centrifuged; plasma samples were analysed on the same day. Blood sampling in all patients was performed before the beginning and on days 4, 8, 12, 24, 28, 30 of the study 2 h after the first daily administration, and 1, 3, 5, and 7 days after discontinuation of the treatment.

The assay procedure has been described in detail elsewhere [17]. It consists of a modification of Kaiser's gas-chromatographic procedure [8], and it is not influenced by the presence of MPA metabolites as checked by periodic GC/mass spectrometric control (Jeol JMS D-100 mass spectrometer).

Calibration curves were obtained in the 2–1000 ng/ml interval. Throughout the study, the accuracy of the analytical procedure was checked by randomly submitting samples of blood bank plasma or blanks spiked with a known amount of MPA. Mean accuracy was typically 5%–8%.

Results

After multiple IM MPA administration drug plasma levels steadily increased, reaching a dose-dependent plateau only after the last administration (Fig. 1). No decay of plasma concentration was evident 1 week after discontinuation of the treatment; in five patients, who did not receive subsequent maintenance treatment, high plasma levels were observed after 3 months (20%–60% of the initial plateau level). The interindividual variance in MPA plasma concentration is high, and the 95% confidence interval [$= \bar{X} + t(S\sqrt{N})$; t = Student's t-test for 0.025 probability and N-1 degrees of freedom, S = standard deviation] is 50%–100% of the mean values reported in Fig. 1. Nonetheless, Multiway Analysis of Variance (BMDP 7D program) indicates a significant correlation between MPA plasma levels and the administered dose ($P < 0.03$).

PO treatment results in a faster increase of drug level in plasma (Fig. 2) and a steady state is reached in about 4–10 days.

With respect to the IM treatment, a plateau level is reached more quickly but is considerably lower. Here again, the interpatient variability is rather high (95% confidence interval is 50%–100% of the mean value) and Multiway ANOVA indicates, a significant linear trend between the administered dose and MPA plasma levels. In addition, after the last PO administration it can be observed that a fast decay begins, with a half-life of 62.4 h (SD = 4.6 h), which is in accordance with the results obtained by us in the single-dose pharmacokinetics investigations [17–19].

Table 1 shows the AUC (= area under the time-concentration curve) data of individual patients for better documentation of the interindividual variability observed.

The absence of decay after the last IM administration and the necessity of giving the patients maintenance treatment do not allow us to determine the total AUC values; therefore, this data relates only to the 0–37 day interval.

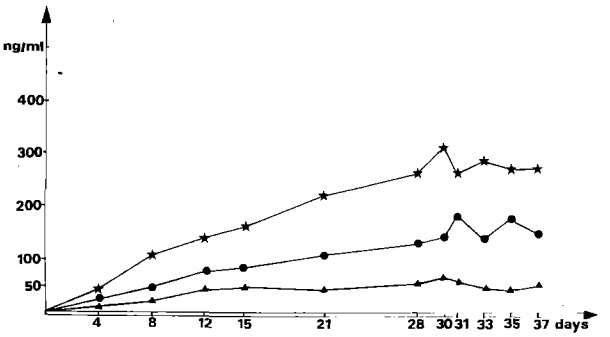

Fig. 1. Medroxyprogesterone acetate plasma levels after multiple high IM doses (mean values). The treatment was discontinued on day 30. (▲——▲) 500 mg; (●——●) 1000 mg; (★——★) 2000 mg

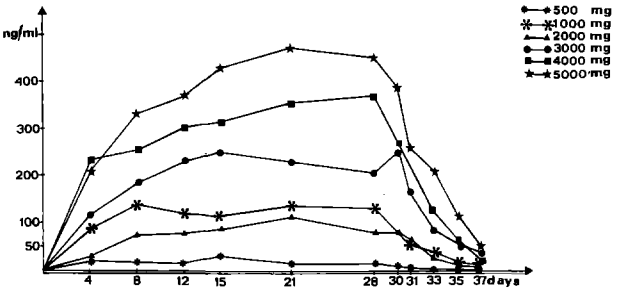

Fig. 2. Medroxyprogesterone acetate plasma levels after multiple high PO doses (Mean values). The treatment was discontinued on day 30

Discussion

In a recently published paper [1], it was reported that MPA is well absorbed after PO administration, and that plasma levels of 1–12 μg/ml are typical for 1.5 g/day treatments. Analyses were carried out with an RIA procedure.

Table 1. Medroxyprogesterone acetate (MAP): area under the time: concentration curves (ng/ml · h · 10^{-3}) following multiple-dose administration

500 mg	1,000 mg	2,000 mg	3,000 mg	4,000 mg	5,000 mg
Oral route					
SR 5.11	DF 126.33	PS 56.59	LI 258.73	SA 248.34	LL 217.77
GA 6.30	ZE 75.23	MF 42.52	ME 143.75	AE 186.18	FD 403.84
BM 24.87	MT 58.16	GA 69.16	MM 153.86	BE 277.02	LI 256.64
ME 17.16	LW 43.33	CD 91.14	GA 142.09	GN 160.61	SC 220.98
SM 11.31	CA 135.77	GG 42.23	CW 83.80	RA 273.90	AI 366.61
$\bar{X}$ 12.95	87.74	60.33	156.45	229.21	293.17
SD 8.19	41.23	20.53	63.47	52.93	86.42
Intramuscular route					
RA 25.96	RM 131.08	RE 153.38			
CC 67.88	FA 54.18	FE 229.25			
BE 19.56	LA 60.52	FL 144.22			
SI 22.23	BR 57.10	LG 95.73			
GB 36.28	CA 90.95	RC 139.74			
$\bar{X}$ 34.38	78.75	152.46			
SD 19.77	32.73	48.34			

$\bar{X}$, mean values; SD, standard deviation

In contrast, our recent comparison of PO and IP administration [19] seems to indicate that a rather low percentage of drug is absorbed (0.6%–10%) after PO administration, and the peak MPA plasma levels observed by us in this work after multiple PO treatment generally do not exceed 1 μg/ml even with the massive dose of 5 g/day.

In our opinion these discrepancies reflect the inadequacy of the currently available RIA methods for MPA analysis. In these procedures, the antibody for the steroid molecule is particularly sensitive to changes in configuration made at the D-ring and side chains of MPA, and this prevents cross reactivity with C17- and C21-modified metabolites [4, 22]. Conversely, it is less sensitive to the structure of the more biologically relevant α-side of the A and B ring of the MPA molecule and to the presence of bulky substituents at C3. Progesterone receptors actually interact with this part of the steroidal molecule [11]. Preliminary results in our laboratory on in vivo MAP metabolism indicate that conjugates, probably derived from the 3-enol form of MPA, are present in the plasma in appreciable concentrations.

These glucuronides or sulfates show no affinity for Pg receptors and very probably have no antitumor activity, but are liable to interfere drastically with the currently available RIA assay.

Automated gas-chromatographic analysis with internal standard calibration does not suffer from any of these problems, is less expensive, and allows a trained operator to process up to 40 samples per day.

From the clinical point of view, several relevant conclusions can be drawn from our results.

IM and PO MPA administration are definitely not equipotent. The plasma MPA profiles and long-term bioavailability are completely different. MPA plasma levels after IM administration rise slowly, but after 30 days the plateau level is at least three times higher than the level reached after an equidose PO treatment, and in addition the depot-effect guarantees high MPA plasma levels for many weeks after discontinuation of the treatment.

This depot-effect can well explain the results of our earlier trials [14]. With a single 30-day cycle of IM treatment (1500 mg/day) and no maintenance therapy we obtained a 40% objective remission, with a mean duration of 6 months. This rather prolonged remission time is very probably due to the persistence of high MPA plasma levels even after the IM treatment has been discontinued.

This particular feature must be kept well in mind when IM treatment schedules are planned. Maintenance therapy can be very light in this case (typically 500–1000 mg twice weekly) and this definitely overcomes the cost problems sometimes held against MPA treatment. On the other hand, IM administration cannot be used in 'true sequential' therapies, like MPA + tamoxifen (TMX) [7]; both IM MPA an PO TMX have a clear-cut depot-effect, and if MPA is given IM the therapy is no longer sequential, but rather simultaneous.

In addition, if or when a patient does not respond to MPA therapy, IM administration does not really allow an immediate stop to be put to the treatment; the depot maintains high MPA bioavailability for some months. In such cases high MPA plasma levels may actually interfere with subsequent therapy from both clinical and metabolic points of view.

Oral administration, in contrast, requires very high daily doses and continuous treatment to give the typical MPA plasma levels routinely obtained with 500–1000 mg/day IM. The advantages of oral administration lie in the very steep increase of MPA concentration and in the possibility of reducing MPA plasma levels quickly by discontinuing administration. No relevant side-effects were observed by us in a pilot study in patients treated PO with massive doses of MPA (3000–5000 mg/day until intolerance or progressive disease), and the objective response rate was similar to that observed in the kinetically equipotent IM treatment [20].

The high interpatient spread in MPA bioavailability can well explain the lack of a clear-cut dose-response correlation in MPA treatment. The percentage of drug that is absorved after oral administration and the rate of absorption in IM treatments – as well as the rate of metabolism of absorbed drug [19] – are highly variable parameters, and introduce additional discriminant functions in dose-response correlation. More promising, in our opinion, is the direct bioavailability-response correlation; we have recently reorted preliminary results of a short-term study [20].

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