Cancer Chemother Pharmacol (1985) 14 : 232–234

Cancer Chemotherapy and Pharmacology

Medroxyprogesterone acetate bioavailability after high-dose intraperitoneal administration in advanced cancer

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Summary. *Administration of medroxyprogesterone acetate IP in advanced cancer with peritoneal metastases and ascitic effusion generates considerably higher drug plasma levels than those observed after PO or IM treatment. Comparison of areas under the time-concentration curves (AUC) with reference to the three administration routes indicates that after oral administration only 0.2%–17.4% (mean 5.7%; SD 3.77; 40 patients) of the administered dose is absorbed; after IM treatment a daily absorption of 0.7%–7.7% (mean 2.5%; SD 1.66; 30 patients) of the administered dose per injection site was computed.*

Introduction

High-dose medroxyprogesterone acetate (MAP) is widely used in metastatic breast cancer therapy. Objective tumor response is induced in 25%–45% of the patients even after failure of other hormonal treatments and combination chemotherapy [10, 12, 14]. Both IM and PO treatments are currently used; the two administration routes are not equipotent [2, 12]. MAP plasma levels were first measured after low-dose administrations for contraceptive purposes [7, 15]. Only recently, however, have extensive studies on the pharmacokinetics of MAP given in moderate to high doses as treatment for cancer been published [1, 2, 5, 8, 9, 11, 13].

We report here results concerning the extent of MAP absorption, obtained by comparison of drug bioavailability after PO, IM, and IP treatment.

Materials and methods

The subjects of this study were 11 hospital inpatients with histologically documented advanced cancer, peritoneal metastases, and ascitic effusion, all of whom were elegible for MAP therapy. All were assessed as having normal liver and renal functions by standard clinical tests, and to avoid any pharmacological interference no other treatment was carried out during the study.

A single administration of MAP (2,000 mg, 150 mg/ml vials) was performed IP after paracentesis in 10 of these patients. No attempts were made to estimate the volume of ascites fluid left in the peritoneal cavity. MAP is almost insoluble in water and dilution effects are negligible.

Blood samples for MAP assay were drawn into heparinized tubes (before treatment and 1, 2, 4, 8, 26, 50, 98, 146, 194, and 243 after) and centrifuged.

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In an additional patient, MAP was administered IP in 2,000-mg daily doses for 30 days. Blood samples were collected before treatment and on days 4, 8, 12, 15, 21, 28, 30, 31, 33, 35, 37, and 40.

Plasma samples were analyzed following a gas-chromatographic procedure described in detail elsewhere [2, 6, 13]. Unlike the currently available RIA assays [1], our analytical method is not subject to interference from MAP metabolites.

Calibration curves were obtained over the 2–1,000 ng/ml interval, using blood bank plasma spiked with known amounts of MAP and internal standard (17-α-hydroxyprogesterone caproate).

Typical accuracy was 5%–8% for MAP plasma levels > 2 ng/ml. Analysis of blank samples gave MAP concentration values of 0–1.3 ng/ml (mean value on 20 samples = 0.3 ng/ml).

Calculations

The MAP plasma concentration-time course was fitted with a polyexponential equation

$$C = \Sigma\, Ai \cdot \exp\left[-\alpha^{i} \cdot t\right]$$

using the Gauss-Newton algorithm of the PAR program of the BMDP package [3].

Areas under the time-concentration curve (AUC) from $t = 0$ to infinity were obtained by analytical integration of the exponential equation. Mean residence time (*MRT*, i.e., the time interval for 63.2% of the drug to be cleared from the body) was obtained as

$$MRT = \int tCdt / \int Cdt\,.$$

Plasma clearance (*PlCl*) and volume of distribution at steady state (*Vss*) can be computed – assuming complete peritoneal absorption – from the following equations:

$$PlCl = \text{Dose} / \int Cdt\,,$$

$$Vss = MRT \cdot PlCl.$$

Results

After IP treatment, MAP plasma levels increased rapidly, reaching a peak 8–12 h after drug administration (Fig. 1).

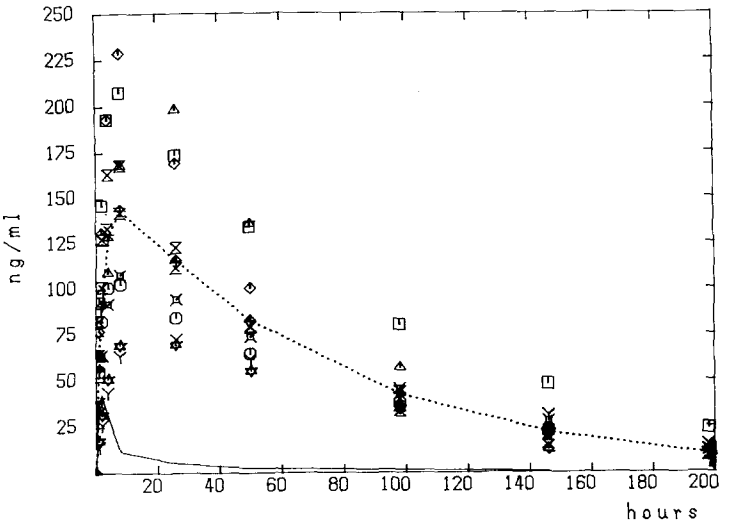

Fig. 1. MAP plasma levels after single IP administration (2,000 mg) in 10 patients with advanced cancer. *Continuous line,* mean MAP plasma levels after single 2,000 mg oral treatment (10 pts)

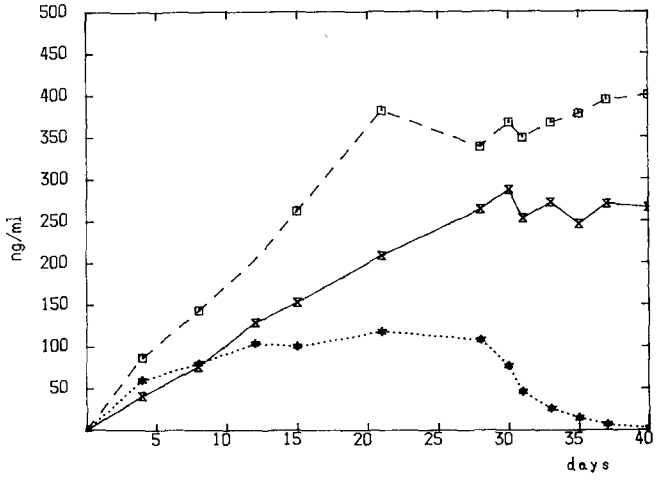

Fig. 2. Plasma levels of MAP after multiple PO (8 pts), IM (8 pts) and IP (1 pt) administration (2,000 mg/day for 30 days). ✱·····✱ PO; ⧖———⧖ IM; ⊡– – –⊡ IP

Table 1. Main pharmacokinetic parameters following single IP administration of MAP (2,000 mg) in advanced cancer with ascitic effusion

Patients	$t/2\ \alpha$ (h)	$t/2\ \gamma$ (h)	*MRT* (h)	AUC (ng/ml · h)
B. M.	1.79	68.3	101.2	11,820
M. M.	1.62	49.9	69.8	12,375
B. M.	2.10	32.1	49.3	12,486
Z. L.	0.99	62.6	91.7	10,018
C. T.	2.90	71.1	106.8	8,881
B. M.	3.73	97.5	146.0	11,908
C. S.	1.43	50.7	75.2	17,523
P. I.	5.09	37.5	61.4	16,150
S. C.	1.20	38.5	57.3	10,573
R. A.	1.31	48.6	72.1	11,069
$\bar{X}$	2.21	55.7	83.0	12,280
SD	1.25	18.7	27.5	2,528

MRT, mean residence time
AUC, area under time/concentration curve

Single patient curves can be equally well approximated by a nonlinear least-squares procedure using a bi- or a triexponential equation [16].

Fit of the experiment with the computed data is satisfactory in the time interval observed, but high correlation coefficients among parameters of the triexponential equation were obtained. In our opinion, this behavior suggests that physiological significance should not be assigned to model-dependent parameters.

Model-independent parameters were computed according to the statistical moment theory [4]. Computation of the AUC values gave similar results with integration of both bi- and triexponential equations; these values are consistent with those computed by the simple trapezoidal rule for the time interval observed.

Table 1 displays the main pharmacokinetic parameters. In addition, apparent plasma clearances (computed assuming complete peritoneal absorption) were in the range 114–225 l/h (mean 168.7 l/h; SD 31.51). Volumes of distribution at steady state, computed under the same assumption, were in the range 7,601–24,513 l (mean 14,300; SD 6,062.8).

Figure 2 shows the MAP plasma levels determined in the patient subjected to multiple IP administration, and for comparison, the mean MAP plasma levels observed by us in patients following equivalent treatments with 2,000 mg/day PO (8 patients) and 2,000 mg/day IM (8 patients) [12].

Discussion

MAP bioavailability after IP administration, as expressed by the AUC values in Table 1, was remarkably similar in eight of

the 10 patients observed; in contrast, there is a rather broad interpatient spread of MAP plasma levels (Fig. 1). Low MAP plasma levels and a prolonged apparent decay phase correspond to a slow absorption phase; conversely, higher MAP plasma levels correspond to a faster absorption, but also to a faster decay. A 2,000-mg dose of MAP is far in excess of the amount that can be held in solution by ascitic fluids, and a prolonged absorption phase is therefore not surprising.

The relative stability of AUC values after IP treatment allows estimation of the extent of MAP absorption, following other administration routes, without the necessity for a cross-over study.

The first-pass effect due to hepatic clearance is similar for both the PO and the IP routes (IP-administered drugs are mainly absorbed through the portal system). Assuming complete peritoneal absorption, the AUC ratio PO/IP-corrected for the administered dose-represents the fraction of the dose that is absorbed after oral treatment.

With the AUC values previously determined by ourselves [13] in a total of 40 advanced cancer patients treated with 500–3,000 mg MAP PO, a mean absorption of 5.7% of the administered dose (range 0.2%–17.4%; SD 3.77) was computed. These values, determined assuming complete peritoneal absorption, must be considered as upper limits.

Administration of MAP by the IM route results in a pronounced depot effect. Comparison of AUC values for the first 144 h determined by ourselves after IM administration in a total of 30 patients with advanced cancer [13] can give an estimate of the rate of drug absorption from the injection site. In the first 6 days following the administration, a 500-mg injection releases 13.7 mg MAP per day (range 7.0–38.5; SD 8.94), and a 1,000-mg injection, 26,9 mg/day (range 8.1–54.6; SD 17.1). Two 1,000-mg injections release a total of 40.8 mg MAP per day (range 14.7–107.4; SD 27.29).

Finally, IP administration of MAP was well tolerated in the subjects of this study; local or systemic toxicity was not observed even in the patient submitted to chronic treatment.

No other administration route can presently guarantee a similar absorption efficiency; IP MAP treatments are therefore in our opinion good candidates for clinical trials in patients with ascitic effusion and hormonosensitive tumors.

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Received March 7, 1984/Accepted September 11, 1984