Cancer Chemother. Pharmacol. 4, 267–269 (1980)

Cancer Chemotherapy and Pharmacology

Comparative Pharmacokinetics of Medroxyprogesterone Acetate Administered by Oral and Intramuscular Routes

M. Salimtschik[1], H. T. Mouridsen[1], J. Loeber[1], and E. Johansson[2]

[1] Department R A, Finsen Institute,
49 Strandboulevarden, 2100 Copenhagen Ø, Denmark
[2] Department of Obstetrics and Gynaecology, University Hospital,
Uppsala, Sweden

Summary. *The present study was undertaken to elucidate (1) the relationship between plasma concentration of medroxyprogesterone acetate (MPA; Clinovir) administered by the PO and the IM routes; and (2) the relationship between dose and plasma concentration of MPA.*

Nineteen patients entered the study. In each patient the plasma concentration was monitored after a single PO and IM administration of MPA at the following dose levels: 100 mg (5 patients), 400 mg (5 patients), 800 mg (5 patients) and 1,200 mg (4 patients). The time interval between PO and the IM administration was 1 week.

The results show (1) a very large interindividual variation in plasma concentration; (2) increasing plasma concentration with both PO and IM dose; (3) after the IM administration plasma levels are steady or increase slightly within the test period; (4) after the oral administration the concentration increases rapidly to reach a peak before 2–7 h and subsequently decreases again, peak concentrations being 2–10 times higher than after IM administration; and (5) within the test periods the plasma concentration × time (0–168 h) is comparable with the two methods of administration.

Introduction

For the last 30 years medroxyprogesterone acetate (MPA) has been used in the treatment of advanced breast cancer. Until recently the doses most frequently used have been 100–300 mg daily, leading to response in up to 20% of patients [4, 5, 7, 10, 11]. In recent years, however, more studies have been published which seem to indicate a higher response rate with higher doses (0.5–1.5 g daily) of MPA [2, 6, 8, 9].

MPA is administered PO and IM. In most of the latter studies with high doses, MPA has been administered IM. However, the efficacy of IM and PO administered dosage has not been compared in randomized trials.

The present study was undertaken to elucidate (1) the relationship between plasma concentration of MPA administered by PO and IM route, and (2) the relationship between dose and plasma concentration of MPA.

Patients and Methods

Patients

Nineteen patients aged 45–77 years (median 65 years) entered the study. All patients were clinically resistant to previous cytotoxic and/or endocrine therapy and according to our present treatment strategy were candidates for treatment with MPA. Informed consent was obtained from all patients.

Method

Each patient received a single PO dose of MPA (Clinovir, Upjohn) followed 7–8 days later by a single IM dose of MPA (Clinovir, Upjohn) at one of the following dose levels: 100 mg (5 patients), 400 mg (5 patients), 800 mg (5 patients) and 1,200 mg (4 patients). Venous blood samples for MPA analysis were withdrawn in heparinized tubes immediately before the administration and after 2, 7, 24, 48, 72, and 168 h. The samples were centrifuged immediately and the plasma withdrawn and stored at −20° C until analysed for MPA.

MPA Assay

In the radioimmunoassay of MPA an antiserum raised in goats against MPA-3-(O-carboxy methyl)oxime-BSA (1) provided by

Reprint requests should be addressed to: H. T. Mouridsen

0344-5704/80/0004/0267/$ 01.00

the Upjohn Company, Kalamazoo, Michigan, USA, was used. The antiserum was diluted 1 : 10,000 in 0.1% gelatin PBS. To each sample to be assayed 0.1 ml antiserum was added.

1,2-^{3}H-MPA obtained from the New England Nuclear Company with a specific activity of 58 Ci/mmole was used as tracer. The amount of tracer used in each assay sample was 85 pg.

All steps in the assay system and all reagents used were the same as those described for the radioimmunoassay of estrone and estradiol [3], except that the column separation step was omitted and petroleum ether was used for extraction instead of diethyl ether.

The sensitivity, accuracy, specificity, and precision of the MPA assay has been described in detail elsewhere [12]. All MPA analyses were done in duplicate and the coefficient of variation was 14.5%.

There is no cross reaction with naturally occurring steroids. The antiserum has a 40% cross reaction with megestrol acetate and also substantial cross reaction with metabolites of medroxyprogesterone acetate. However, these metabolites appear to influence the measurements in only a very minor way.

Results

The results of this study are presented in Tables 1 and 2, which show the plasma concentrations in relation to time of sampling after administration of MPA PO (Table 1) and IM (Table 2). Each mean value is the mean of determinations in five patients except for the 1,200-mg dose level, where only four patients were studied. As can be seen from Tables 1 and 2 the interindividual ranges are very wide with both PO and IM administration.

After PO administration the plasma concentration increases rapidly to reach a peak 2–7 h after administration and then decline steadily. With 100 mg, MPA is undetectable in the serum after 72 h but with higher doses MPA is still detectable 168 h after administration.

After MPA by the IM route the plasma concentration increases to reach a plateau after 2–7 h, with fairly steady values at that level throughout the rest of the test period. It should be emphasized that in several of the patients MPA has not been totally eliminated after the previous PO administration and therefore the initial plasma concentrations are higher than zero.

The peak plasma levels achieved with PO administration are several times higher than with IM administration, and even after 168 h plasma levels after PO administration are comparable to those after IM administration, except in the 100-mg study.

Figure 1 shows the 12-h levels of MPA in plasma related to PO and IM administration. As is seen, MPA levels increase linearly with dose administered both PO and IM.

Table 1. Plasma concentrations (nmol/liter) of MPA in relation to time after single PO doses of 100–1200 mg MPA

Sampling time	Dose of MPA			
	100 mg	400 mg	800 mg	1200 mg
− 5 min	0 (0 − 0)	0.8 (0 − 4.4)	0 (0 − 8.0)	1.2 (0 − 5.0)
2 h	10.8 (2.1–25.0)	171.3 (25.6–267.0)	133.4 (37.6–248.6)	91.4 (65.0–175.2)
7 h	11.1 (2.9–36.0)	76.4 (47.9–111.0)	117.2 (24.1–393.3)	147.4 (44.5–210.3)
24 h	4.3 (1.7– 6.7)	19.6 (16.8– 80.1)	48.8 (10.4–181.3)	80.8 (18.0–205.5)
48 h	2.8 (1.3– 4.1)	12.6 (6.7– 16.3)	34.7 (6.2–116.6)	58.5 (15.6–125.3)
72 h	2.1 (1.0– 4.7)	9.9 (6.7– 13.0)	20.8 (3.1– 72.5)	42.3 (8.1–104.9)
168 h	1.6 (0 − 6.3)	3.7 (1.6– 7.0)	15.4 (2.6– 54.4)	26.8 (1.9– 80.8)

Table 2. Plasma concentrations (nmol/liter) of MPA in relation to time after single IM doses of 100–1200 mg MPA

Sampling time	Dose of MPA			
	100 mg	400 mg	800 mg	1200 mg
− 5 min	1.6 (0 − 6.3)	3.7 (1.6– 7.0)	15.4 (2.6–54.4)	7.2 (0 −20.5)
2 h	5.3 (1.2–16.3)	8.9 (6.5–13.5)	17.3 (3.6–45.3)	16.8 (1.3–43.4)
7 h	4.1 (1.4– 8.3)	11.3 (8.6–11.4)	18.0 (5.2–35.0)	20.2 (1.3–49.5)
24 h	5.1 (2.1– 8.8)	11.8 (18.6–14.3)	18.9 (6.5–47.0)	20.1 (6.3–27.0)
48 h	3.4 (2.2– 4.9)	13.5 (8.3–18.1)	24.9 (7.0–72.5)	17.0 (7.0–23.6)
72 h	4.1 (1.9– 7.5)	11.5 (6.5–23.0)	26.1 (5.7–68.9)	15.2 (5.1–24.5)
168 h	2.4 (0.6– 5.5)	6.7 (5.2–10.0)	25.8 (10.4–66.5)	17.9 (5.3–25.5)

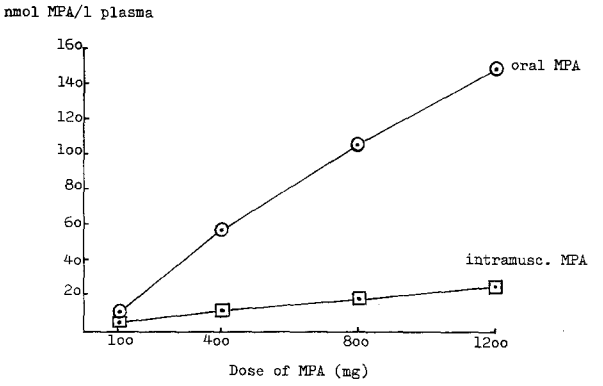

Fig. 1. Plasma concentrations of MPA 12 h after PO and IM administration of single doses of MPA at dose levels of 100–1,200 mg

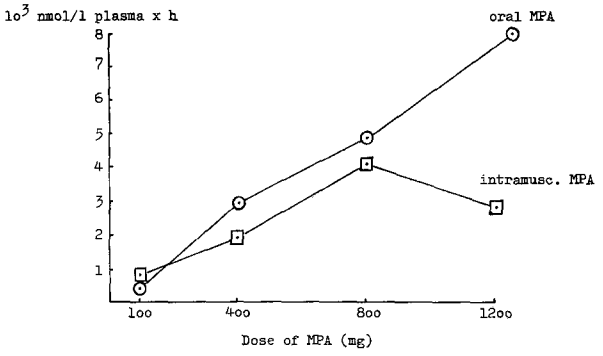

Fig. 2. Plasma concentrations of MPA × time (t = 0 to t = 168 h) after PO and IM administration of single doses MPA at dose levels of 100–1,200 mg

The area under the curves, constructed from the values in Tables 1 and 2, was calculated according to Simpson's rule from t = 0 to t = 168 h. As can be seen from Fig. 2, the areas under the curves obtained were comparable with the different routes of administration, except with the 1,200-mg dose level. However, this discrepancy might well be ascribed to the very large individual variations in connection with the small number of patients in each group.

Discussion

The most impressive results in the present study are the relationships between plasma concentrations achieved after PO and after IM administration.

In the treatment of advanced breast cancer MPA is administered both PO and IM, but as yet no randomized studies comparing the two routes of administration have been published, and therefore the relevance of the results of this study to the treatment of breast cancer still remains in doubt.

One may argue that the plasma sampling for MPA analyses should have been continued for longer periods to obtain exact knowledge about the elimination kinetics of PO and IM administered MPA. However, this was not the actual objective of the study and would have caused postponement of regular treatment with MPA for longer time.

Another impressive result is the very wide interindividual ranges in plasma concentrations after both PO and IM administration. The efficacy of MPA may depend upon an accumulation of MPA during long-term treatment, but at present it is not known whether the response rate is related to the individual plasma concentrations achieved. The results of the present study suggest that this relationship should be analysed in future trials.

References

1. Cornette JC, Kirton KT, Duncan GW (1971) Measurement of medroxyprogesteroneacetate (Provera) by radioimmunoassay. J Clin Endocrinol 33: 459
2. De Lena M, Brambilla C, Valagussa P, Bonadonna G (1979) High-dose medroxyprogesterone acetate in breast cancer resistant to endocrine and cytotoxic therapy. Cancer Chemother Pharmacol 2: 175
3. Edquist LE, Johansson EDP (1972) Radioimmunoassay of estrone and estradiol in human and bovine peripheral plasma. Acta Endocrinol (Kbh) 71: 716
4. Goldenberg IS (1969) Clinical trials of testolactone, medroxyprogesterone-acetate and oxylone acetate in advanced female mammary cancer. A report of the Cooperative Breast Cancer Group. Cancer 23: 109
5. Klaasen DJ, Rapp EF, Hirte WE (1976) Response to medroxyprogesterone acetate (NSC-26386) as secondary hormone therapy for metastatic breast cancer in postmenopausal women. Cancer Treat Rep 60: 251
6. Mattsson W (1978) High dose medroxyprogesterone acetate treatment in advanced mammary carcinoma. A phase-II investigation. Acta Radiol Oncol 17: 387
7. Muggia FM, Cassileth PA, Ochoa M Jr, Flatow FA, Gellhorn A, Hyman GA (1968) Treatment of breast cancer with medroxyprogesterne-acetate. Ann Intern Med 68: 328
8. Pannuti F, Martoni A, Lenaz GR, Piana E, Nanni P (1978) A possible new approach to the treatment of metastatic breast cancer: massive doses on medroxyprogesterone acetate. Cancer Treat Rep 62: 499
9. Robustelli Della Cuna G, Calciata A, Strada MRB. Bumma C, Campio L (1978) High dose medroxyprogesterone-acetate (MPA) treatment in metastatic carcinoma of the breast: a dose-response evaluation. Tumori 64: 143
10. Segaloff A, Cunningham M, Rice BF, Weeth JB (1967) Hormonal therapy in cancer of the breast. XXIV. Effect of corticosterone or medroxyprogesterone acetate on clinical course and hormonal excretion. Cancer 20: 1673
11. Stoll A (1967) Progestin therapy of breast cancer: comparison of agents. Br Med J 3: 338
12. Victor A, Johansson DB (1976) Pharmacokinetic observations on medroxyprogesteroneacetate administered orally and intravaginally. Contraception 14: 319

Received February 18/Accepted April 21, 1980