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Short Communication

Medroxyprogesterone Acetate (MAP) Plasma Levels After Simultaneous Oral and Intramuscular Administration in Cancer Patients

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Summary. *After simultaneous administration of medroxyprogesterone acetate (MAP) 1,000 mg PO and 1,000 mg IM to ten cancer patients, we observed mean plasma MAP profiles that could be exactly superimposed on the two absorption/decay curves obtained after administration of single doses IM or PO. Treatment with MAP given simultaneously by the IM and PO routes may be effective in overcoming the drawbacks of both routes, and can also more reliably guarantee plasma levels in the therapeutic range.*

Introduction

Medroxyprogesterone acetate (MAP) can be given to cancer patients either PO or IM [2]; administration PO is characterized by fast absorption but low global bioavailability of the drug; while after IM administration there is a slow but efficient absorption phase [3]. It therefore seems promising to explore the possibility of simultaneous IM and PO administration. During extensive studies on MAP pharmacokinetics, we determined the MAP plasma levels following simultaneous administration of 1,000 mg PO and 1,000 mg IM, which were then compared with levels following treatment with MAP 1,000 mg and 2,000 mg PO and IM (10 patients in each group).

Materials and Methods

The experimental procedure for the MAP analysis has been described elsewhere [3]. It consists of a modification of the gas-chromatographic method proposed by Kaiser and it is characterized by an average coefficient of variation of 8%; minimal detectable quantity is about 0.5 pg per chromatographic injection; however, the accuracy of the method is slightly decreased for plasma levels below 2 ng/ml, probably due to clean-up problems.

Patients entered in this study had histologically proven advanced cancer and a life expectancy of not less than 2 months; all were assessed as having normal liver and renal functions according to standard clinical tests. Oncological treatments were discontinued at least 1 month before this study, and any other treatment, at least 2 days before. Blood samples were collected in heparinized tubes before and at various times after the administration (1, 2, 4, 6, 8, 10, 26, 30, 50, 74, 98, and 146 h) up to the 7th day, and centrifuged.

Table 1. Mean plasma levels (ng/ml) of MAP after single administration by different routes[a]

Time (h)	PO and IM 1,000 mg + 1,000 mg	PO		IM	
		1,000 mg	2,000 mg	1,000 mg	2,000 mg
0	0.0	0.0	0.0	0.0	0.0
1	24.2 (7.4–41.0)	12.5 (5.0–19.9)	18.1 (6.3–29.8)	5.7 (2.7– 8.7)	8.6 (0.0–18.4)
2	23.4 (9.7–37.1)	12.4 (4.7–20.1)	29.9 (9.6–50.3)	11.0 (2.9–19.2)	8.9 (1.9–15.9)
4	27.6 (0.6–54.6)	8.1 (3.0–13.2)	24.6 (12.2–36.9)	11.9 (3.5–20.3)	9.3 (4.9–13.6)
6	24.8 (0.0–53.1)	4.7 (1.9– 7.4)	15.7 (7.1–24.3)	8.5 (4.2–12.7)	6.7 (3.0–10.3)
8	16.2 (2.1–30.2)	3.0 (0.6– 5.5)	10.9 (4.0–17.8)	6.2 (1.1–11.2)	7.7 (4.6–10.8)
10	13.5 (3.0–24.0)	2.5 (0.3– 4.8)	8.8 (3.5–14.2)	5.6 (2.4– 8.8)	9.3 (3.7–14.9)
26	9.7 (5.8–13.6)	1.5 (0.4– 2.7)	4.2 (1.4– 6.9)	6.9 (2.4–11.5)	9.3 (4.4–14.1)
30	14.2 (7.4–21.0)	1.6 (0.4–2 .9)	3.8 (1.1– 6.6)	7.3 (2.3–12.2)	10.8 (4.9–16.6)
50	8.0 (4.3–11.7)	1.2 (0.0– 2.4)	0.9 (0.0– 2.2)	8.7 (4.2–13.1)	10.0 (5.4–14.6)
74	7.5 (4.0–11.0)	1.4 (0.4– 2.5)	1.3 (0.2– 2.4)	6.7 (2.9–10.5)	9.9 (4.5–15.2)
90	4.6 (1.9– 7.3)	1.3 (0.3– 2.3)	1.0 (0.0– 2.2)	4.4 (2.3– 6.5)	11.5 (1.7–21.4)
146	4.4 (1.6– 7.2)	0.8 (0.0– 1.7)	1.0 (0.1– 2.0)	8.1 (1.4–14.6)	11.1 (6.2–16.2)
AUC (ng/ml · h)	1.230 (0.798–1.701)	0.277 (0.142–0.413)	0.570 (0.388–0.760)	0.972 (0.492–1.452)	1.494 (0.823–2.167)

[a] There were ten patients in each group
[b] AUC, area under absorption/decay curve

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Plasma samples were kept frozen at −20° C until analysis. Vials of Farmitalia MAP (Farlutal depot) were used for both IM and PO administration. Statistical analysis of the results was accomplished with the SPSS package of programs on a CDC 6600 computer [1].

Results and Discussion

Table 1 gives mean plasma levels following a single 1,000 mg PO+1,000 mg IM administration and, for comparison, plasma levels after single doses of 1,000 mg or 2,000 mg PO and IM [3]. The figures in parentheses give the 95% confidence intervals [95% C.I. $= \bar{x} \pm t.(s\sqrt{n})$, where t is Student's t for 0.025 probability and $n-1$ degrees of freedom]; each value is the mean of determinations in ten patients. Notwithstanding the large interindividual concentration ranges, the 1,000 mg PO + 1,000 mg IM mean curve can be exactly superimposed on the two absorption/decay profiles obtained after administration of the single doses IM or PO. The same conclusion can be drawn from an examination of the bioavailability of the drug in the first 146 h after administration, as indicated by the area under the concentration/time curve obtained by the trapezoidal rules (Table 1).

The simultaneous administration of MAP by the IM and PO routes may be effective in overcoming the drawbacks of both routes, i.e., the local intolerance sometimes observed in high-dose IM treatment and the low percentage of absorbed drug typical of PO administration. Administration IM can guarantee long-term MAP plasma levels with a low incidence of side-effects, while the simultaneous administration of higher daily doses PO will raise MAP plasma levels to the therapeutic range.

References

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