HORMONAL THERAPY IN CANCER OF THE BREAST

XXIV. Effect of Corticosterone or Medroxyprogesterone Acetate on Clinical Course and Hormonal Excretion

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A total of 44 patients with advancing cancer of breast were treated in a double-blind study comparing corticosterone, NSC 9705, in a dose of 400 mg per day plus 3 Gm of potassium chloride, with medroxyprogesterone acetate, NSC 26386 (Provera), in a dose of 100 mg per day of the micronized preparation plus 3 Gm of potassium chloride. One of the 21 patients who received corticosterone sustained an objective regression of her advanced disease but none of the patients receiving medroxyprogesterone acetate were objectively improved. There were no apparent effects from medroxyprogesterone acetate on hormonal excretion patterns. Corticosterone produced increases in the excretion of formaldehydogenic corticoids and blue tetrazolium corticoids but not in Porter-Silber chromogens. Corticosterone also induced significant increases in pregnanediol excretions.

CORTICOSTERONE IS A MAJOR STEROIDAL product of the adrenal cortex in many animal species including man. Despite this, it has received scant attention as a potential steroid for the treatment of human adrenal insufficiency or as an anti-inflammatory agent. Early studies demonstrated its potency as a mineralocorticoid[1] and as a life-maintaining steroid in adrenalectomized patients.[5] Nevertheless, its inactivity as an anti-inflammatory agent in animals, and probably in man, and the difficulties involved in its synthesis served to stifle interest in corticosterone for human use.

Our interest in corticosterone as an antitumor agent was stimulated by the fact that in the early years of the Cancer Chemotherapy National Service Center of the National Cancer Institute it was found to be active in carcinoma 755, sarcoma 180 and leukemia 1210. Since the initial testing it has been found inactive in leukemia 1210 and is likewise inactive in KB-cell tissue culture and Walker 256 carcinosarcoma. There is, however, evidence of activity in hormone sensitive tumor systems, notably the 4941 mouse mammary adenocarcinoma, the R3396 rat prostate carcinoma and the D362 rat prostatic carcinoma. Neither significant inhibition of tumor growth nor increase in host survival time was obtained at the dosages tested in a number of other animal tumor systems.

Medroxyprogesterone acetate (NSC 26386, Provera) is an extremely interesting compound which, in man and animals, appears to be a purely progestational agent without estrogenic activities; however, there is evidence that the material is hydroxylated and indeed may show sufficient adrenal cortical activity to maintain adrenalectomized patients.[3] This compound also has been reported to induce a significant number of objective regressions in advanced mammary cancer.[2] Accordingly, it was deemed to be an ideal agent to join with corticosterone in a

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double blind study of therapy of advanced mammary cancer according to our protocol.

MATERIALS AND RESULTS

Although adequate phase I and phase II studies had been carried out on the proposed 100 mg per day of micronized medroxyprogesterone acetate, the available information on corticosterone (NSC 9705) in man was inadequate and a phase I study was undertaken with this material.

Seventeen patients with various malignancies were treated with corticosterone in doses starting initially at 25 mg per day and going as high as 600 mg per day. In these preliminary studies we had no objective tumor regressions although three patients had substantial subjective improvement. One of these had neurologic findings and convulsions due to metastases to brain as well as widespread osteolytic metastases. She obtained what we frequently see with corticoids—a marked subjective improvement with suppression of the seizures. The second woman also had osteolytic metastases from her mammary cancer and came in with a sixth nerve palsy which cleared rapidly on the corticosterone treatment, despite the fact that there was progression elsewhere in her disease. The third, a young woman with pulmonary metastasis from adenocarcinoma of the colon, had a marked subjective and functional improvement on corticosterone without unequivocal evidence of pulmonary lesion regression.

The effects of corticosterone in patients with hypercalcemia are not those we have ordinarily associated with potent corticoids. Indeed, in one patient 400 mg per day of corticosterone failed to control the hypercalcemia which was readily controlled by modest doses of dexamethasone. In other patients we have seen suggestions of control of hypercalcemia but we do not consider that corticosterone is capable of controlling the hypercalcemia of metastatic malignancy.

Even in the dose of 600 mg per day we saw neither euphoria nor mental abberations apparently induced by the corticosterone. There did not appear to be any hypertensive effect of the corticosterone except in the three patients who received our maximum dose of 600 mg per day. These three patients sustained elevations of blood pressure from 140/80 to 180/110; from 120/84 to 160/100; and from 120/70 to 154/108. The few patients treated in our phase I study who had hypertension at the onset were not changed by the corticosterone therapy.

There was no evidence of bone marrow, cardiac, renal, hepatic or central nervous system toxicity. No patient developed hyperglycemia and none developed a Cushingoid appearance.

Essentially the only toxic effect observed was the induction of hypokalemia. This appeared to be a dose-related response. All patients who received more than 200 mg of corticosterone daily for more than one month without potassium supplementation developed hypokalemia with levels varying from 1.8 mEq to 3.6 mEq per liter. The patients with the most marked hypokalemias had electrocardiographic changes consistent with such hypokalemia, which reverted to normal with the return of potassium levels to normal. Because even supplementation with potassium chloride at 12 Gm per day failed to maintain normal serum potassium in some patients on the 600 mg per day level of corticosterone, we carried out the present study at 400 mg per day of corticosterone with supplemental potassium chloride initially at 3 Gm per day.

So that the double blind nature of the trial could be preserved, all patients entered into the study received the supplemental potassium chloride in enteric coated potassium chloride tablets.

The distribution of the 44 patients between the two therapies and their responses are given in Table 1. There was a disappointing effect on the clinical course of the disease. The only objective regression seen was on corticosterone.

During the course of this double blind study we did not, of course, know which of the two medications any patient was getting. When the double blind was broken at the completion of the study, we found that five of the patients who received medroxyprogesterone acetate had initial potassium values of less than 4 mEq per liter, the lowest of these being 3.5 mEq per liter. All these patients subsequently had improvement in their serum potassium levels while on therapy.

The situation in the patients on corticosterone was strikingly different. Of these patients seven had initial potassium values of less than 4 mEq per liter and their response to therapy was variable. Only five of them sustained increase in their serum potassium on therapy. On the other hand, a few patients

who had normal potassiums at the onset of therapy did develop hypokalemia which, in all except one instance, responded to increasing the potassium chloride supplement.

None of the patients in whom such studies are available sustained increases in blood sugar, significant changes in sodium, or any other chemical changes ascribable to the medication. None of the patients on either medication developed edema or a Cushingoid appearance. Nitrogen and uric acid excretions were not measured.

Tables 2 and 3 show the effect of medroxyprogesterone acetate on urinary hormonal excretions. It is immediately apparent that there are no significant changes in any of the ex-

TABLE 1.

Dominant lesion	Objective regressions/no. of patients by years postmenopausal <1	1–5	5–10	10+	Total
Corticosterone					
Breast	0/0	0/1	0/1	0/3	0/5
Osseous	0/1	0/2[1]	0/1	0/3	0/7
Visceral	0/4[2]	0/0	0/2	1/3[1]	1/9
TOTAL	0/5	0/3	0/4	1/9	1/21
Medroxyprogesterone acetate					
Breast	0/1	0/2	0/2	0/2	0/7
Osseous	0/0	0/3	0/1	0/3[2]	0/7
Visceral	0/2	0/0	0/3	0/4	0/9
TOTAL	0/3	0/5	0/6	0/9	0/23

Superscript numbers denote number of patients in a category who had less than 15 days therapy.

TABLE 2. Urinary Excretions before and during Therapy with Medroxyprogesterone Acetate in Patients with Metastatic Cancer of Breast

Pt. case no.	Category*	Creatinine Gm/24 hr		Creatin Gm/24 hr		17-Ketosteroids mg/24 hr		Formaldehydogenic corticoids mg/DOC/24 hr†		Pregnanediol chromogen mg/24 hr	
		Before	During	Before	During	Before	During	Before	During	Before	During
J.R. 1001	1–5 breast	0.62(3)	0.32(3)	0.07(3)	0.06(3)	5.0(2)	7.5(2)	0.38(1)	0.44(1)	0.29(1)	0.11(1)
L.G. 1018	1–5 osseous	0.97(3)	0.91(9)	0.52(3)	0.31(9)	9.0(2)	5.8(7)	0.16(1)	0.80(4)	0.27(1)	0.19(4)
C.J. 993	10+ visceral	0.61(3)	0.70(8)	0.09(3)	0.11(8)	6.1(2)	6.7(6)	0.26(1)	1.21(3)	0.20(1)	0.11(3)
A.R. 1042	5–10 visceral	0.78(1)	0.72(1)	0.06(1)	0.04(1)	4.4(1)	6.7(1)	0.28(1)	0.71(1)	0.35(1)	0.36(1)
E.U. 1049	10+ breast	0.56(3)	0.84(3)	0.06(3)	0.14(3)	3.0(2)	4.8(2)	0.18(1)	0.62(1)	0.09(1)	0.15(1)
C.A. 1059	10+ breast	0.57(3)	0.77(3)	0.04(3)	0.18(3)	4.1(2)	6.9(2)	0.16(1)	0.46(1)	0.24(1)	0.00(1)
R.M. 553	<1 visceral	0.59(6)	0.66(6)	0.04(6)	0.09(6)	7.3(3)	5.3(5)	0.71(2)	0.70(2)	0.13(2)	0.08(2)
A.J. 1037	10+ visceral	0.85(3)	0.85(3)	0.18(3)	0.06(3)	8.0(2)	6.0(2)	0.59(1)	0.54(1)	0.20(1)	0.11(1)
B.B. 1062	10+ visceral	0.45(3)	0.66(7)	0.04(3)	0.19(7)	3.2(2)	5.9(5)	0.22(1)	0.36(3)	0.11(1)	0.14(3)
N.D. 1055	5–10 breast	0.82(6)	0.83(5)	0.03(6)	0.26(5)	5.8(4)	5.8(4)	3.51(2)	0.67(2)	0.12(2)	0.14(2)
L.G. 1065	1–5 osseous	1.28(3)	1.21(7)	0.13(3)	0.16(7)	7.2(2)	6.8(4)	0.89(1)	1.79(2)	0.13(1)	0.13(2)
B.G. 876	10+ osseous	0.72(3)	0.82(4)	0.04(3)	0.08(4)	3.5(2)	5.1(2)	0.33(1)	0.65(1)	0.13(1)	0.25(1)
D.F. 1031	<1 osseous	0.82(3)	0.90(6)	0.08(3)	0.05(6)	6.8(2)	5.6(4)	0.48(1)	0.30(2)	0.05(1)	0.20(2)
A.D. 1094	10+ visceral	0.60(4)	0.70(4)	0.06(4)	0.10(4)	5.1(2)	7.1(2)	0.54(1)	0.26(1)	0.15(1)	0.23(1)
J.D. 1064	<1 visceral	1.29(1)	1.67(3)	0.28(1)	0.51(3)	8.1(1)	8.6(1)	0.90(1)	1.14(1)	0.09(1)	0.03(1)
E.C. 1086	5–10 osseous	0.65(3)	0.74(3)	0.09(3)	0.37(3)	7.3(2)	11.2(2)	0.00(1)	0.62(1)	0.14(1)	0.48(1)
C.M. 1095	1–5 osseous	0.47(3)	0.70(15)	0.49(3)	0.61(15)	5.2(2)	7.7(7)	2.10(1)	0.49(3)	0.19(1)	0.20(3)
M.M. 1066	10+ breast	1.07(4)	1.33(8)	0.19(4)	0.25(8)	10.5(2)	1.1(4)	0.76(1)	0.69(2)	0.12(1)	0.17(2)
W.P. 1043	10+ visceral	0.22(4)	0.36(4)	0.02(4)	0.02(4)	3.1(2)	3.6(2)	0.60(1)	2.77(1)	0.09(1)	0.21(1)
AVERAGE		0.72(19)	0.83(19)	0.13(19)	0.19(19)	5.9(19)	6.7(19)	0.69(19)	0.80(19)	0.16(19)	0.17(19)

Numbers in parentheses indicate number of determinations. Numbers in parentheses following average values indicate number of patients for whom determinations were made.

* Category includes menopausal age and dominant lesion.

† DOC indicates deoxycorticosterone.

TABLE 3. Urinary Excretions before and during Therapy with Medroxyprogesterone Acetate in Patients with Metastatic Cancer of Breast

Pt. case no.	Gonad-stim. hormone MU/24 hr		Prolactin IU/24 hr		Luteinizing hormone prostate wt.[x]		P and S[†] chromogens mg/24 hr		Calcium mg/24 hr		Blue tetrazolium mg/24 hr	
	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During
J.R. 1001	13(1)	26(1)	0(1)	35(1)	0(1)	0(1)	0.18(1)	0.11(1)	242(2)	239(2)	1.08(1)	3.69(1)
L.G. 1018	192(1)	20(4)	0(1)	34(3)	200(1)	32(2)	0.44(1)	0.76(4)	189(2)	141(7)	2.21(1)	4.14(4)
C.J. 993	26(1)	9(3)	85(1)	41(2)	—	0(1)	0.36(1)	0.46(3)	114(2)	101(6)	2.72(1)	2.54(3)
A.R. 1042	96(1)	26(1)	—	—	158(1)	65(1)	0.35(1)	0.86(1)	180(1)	146(1)	2.36(1)	3.94(1)
E.U. 1049	53(1)	13(1)	80(1)	10(1)	—	20(1)	0.14(1)	0.92(1)	54(2)	86(2)	0.69(1)	3.52(1)
C.A. 1059	26(1)	13(1)	38(1)	0(1)	—	13(2)	0.10(1)	0.25(1)	52(2)	53(2)	1.14(1)	1.86(1)
R.M. 553	288(2)	26(2)	120(2)	35(2)	49(2)	222(2)	0.31(2)	0.58(2)	128(4)	69(4)	1.53(2)	2.90(2)
A.J. 1037	26(1)	26(1)	0(1)	0(1)	233(1)	48(1)	0.37(1)	0.65(1)	528(2)	487(2)	1.35(1)	2.58(1)
B.B. 1062	26(1)	11(3)	83(1)	155(1)	25(1)	34(1)	0.12(1)	0.54(3)	183(2)	333(6)	0.88(1)	2.65(3)
N.D. 1055	—	4(2)	28(2)	0(1)	145(1)	—	0.77(2)	0.35(2)	40(4)	36(4)	4.01(2)	1.95(2)
L.G. 1065	96(1)	20(2)	4(1)	13(2)	145(1)	31(2)	0.12(1)	0.31(2)	75(2)	88(4)	1.30(1)	2.89(2)
B.G. 876	192(1)	53(1)	0(1)	16(1)	52(1)	131(1)	0.17(1)	0.72(1)	179(2)	92(2)	0.73(1)	2.47(1)
D.F. 1031	13(1)	26(1)	39(1)	25(1)	—	—	0.26(1)	0.23(2)	233(2)	83(4)	1.54(1)	1.53(2)
A.D. 1094	53(1)	26(1)	15(1)	0(1)	76(1)	0(1)	0.18(1)	0.36(1)	132(2)	120(2)	1.17(1)	1.36(1)
J.D. 1064	13(1)	—	—	—	0(1)	235(1)	0.33(1)	0.94(1)	289(1)	566(1)	2.50(1)	4.81(1)
E.C. 1086	53(1)	7(1)	—	—	—	—	0.39(1)	0.43(1)	135(2)	42(2)	3.02(1)	3.24(1)
C.M. 1095	53(1)	86(3)	62(1)	55(2)	131(1)	49(2)	0.09(1)	0.53(3)	342(2)	167(6)	2.50(1)	3.10(3)
M.M. 1066	192(1)	61(2)	0(1)	0(1)	124(1)	83(2)	0.07(1)	0.48(2)	42(2)	42(4)	3.83(1)	3.09(2)
W.P. 1043	13(1)	96(1)	39(1)	23(1)	35(1)	0(1)	0.28(1)	3.58(1)	74(2)	29(2)	1.42(1)	5.88(1)
AVERAGE	79(19)	31(18)	37(16)	28(16)	98(14)	60(16)	0.27(19)	0.73(19)	169(19)	154(19)	1.89(19)	3.06(19)

[x] Measured in microgram equivalents of Armour luteinizing hormone standard S1-227-80.
[†] Determined by the method of Porter and Silber.

cretions measured in the patients given medroxyprogesterone acetate. There is a modest decrease in the gonad-stimulating hormone measured as mouse uterine weight or as luteinizing hormone but these figures are not considered significant. No other changes were observed in excretion values.

Tables 4 and 5 give the excretion values in the patients getting corticosterone. In sharp contrast to the patients getting medroxyprogesterone acetate, there is a significant increase in formaldehydogenic corticoids and in pregnanediol. The blue tetrazolium excretion also showed an increase in the patients treated with corticosterone. As expected, the Porter-Silber chromogen did not increase, since corticosterone lacks the side chain necessary for this reaction. The gonad-stimulating hormone excretion, whether measured by mouse uterine weight, by the hypophysectomized rat ventral prostate or as prolactin, did not show an increase such as that previously observed for the administration of other corticoids.

DISCUSSION

In the dosages employed in this study neither corticosterone nor medroxyprogesterone acetate produced favorable clinical change in the course of advanced cancer of the breast; however, corticosterone did have profound effect on serum potassium levels. This was correctable by the use of supplemental po-

TABLE 4. Urinary Excretions before and during Therapy with Corticosterone in Patients with Metastatic Cancer of Breast

Pt. Case no.	Category*	Creatinine Gm/24 hr		Creatin Gm/24 hr		17-Ketosteroids mg/24 hr		Formaldehydogenic corticoids mg/DOC/24 hr†		Pregnanediol chromogen mg/24 hr	
		Before	During	Before	During	Before	During	Before	During	Before	During
L.T. 1012	<1 osseous	0.68(3)	0.67(3)	0.29(3)	0.36(3)	6.9(2)	7.2(2)	0.33(1)	1.04(1)	0.29(1)	7.50(1)
E.M. 1024	10+ visceral	0.60(3)	0.65(6)	0.03(3)	0.07(6)	7.0(2)	8.5(4)	0.70(1)	3.89(2)	0.23(1)	32.10(2)
W.H. 1025	10+ visceral	0.94(2)	0.89(1)	0.16(2)	0.12(1)	9.2(2)	11.0(1)	0.55(1)	2.47(1)	0.18(1)	—
L.S. 1034	10+ breast	0.63(3)	0.64(3)	0.08(3)	0.07(3)	7.8(2)	7.0(2)	0.78(1)	0.59(1)	0.23(1)	0.04(1)
M.M. 1035	10+ osseous	1.03(6)	1.13(9)	0.14(6)	0.09(9)	14.1(4)	12.0(6)	3.25(2)	2.62(3)	0.17(2)	10.22(3)
B.B. 1003	5–10 visceral	0.59(6)	0.84(2)	0.18(6)	0.15(2)	7.3(4)	6.9(2)	0.65(2)	2.60(1)	0.10(2)	4.50(1)
E.G. 1082	5–10 osseous	0.90(4)	1.04(4)	0.23(4)	0.15(4)	5.9(2)	4.6(2)	0.20(1)	3.60(1)	0.10(1)	4.50(1)
O.B. 1091	5–10 breast	1.10(4)	1.00(8)	0.10(4)	0.03(8)	6.0(2)	6.1(4)	0.26(1)	1.37(2)	0.18(1)	0.50(1)
A.P.‡ 961	10+ visceral	0.94(4)	0.68(4)	0.10(4)	0.09(4)	4.9(2)	6.7(2)	0.19(1)	0.82(1)	0.09(1)	0.05(1)
AVERAGE		0.82(9)	0.84(9)	0.15(9)	0.13(9)	7.7(9)	7.8(9)	0.77(9)	2.11(9)	0.17(9)	7.43(8)

Numbers in parentheses indicate number of determinations. Numbers in parentheses following average values indicate number of patients for whom determinations were made.

* Category includes menopausal age and dominant lesion.

† DOC indicates deoxycorticosterone.

‡ Objective regression.

tassium except in those patients who had initial hypokalemia before therapy with corticosterone.

Neither medroxyprogesterone acetate nor corticosterone had any significant effect on urinary hormonal excretion patterns except for the increase in formaldehydogenic corticoids, pregnanediol chromogen and blue tetrazolium corticoid in the patients treated with corticosterone. These increases were interpreted as representing the excretion of the expected metabolites of corticosterone.

TABLE 5. Urinary Excretions before and during Therapy with Corticosterone in Patients with Metastatic Cancer of Breast

Pt. case no.	Gonad-stim. hormone MU/24 hr		Prolactin IU/24 hr		Luteinizing hormone prostate wt.ˣ		P and S† chromogens mg/24 hr		Calcium mg/24 hr		Blue tetrazolium mg/24 hr	
	Before	During	Before	During	Before	During	Before	During	Before	During	Before	During
L.T. 1012	26(1)	53(1)	29(1)	45(1)	41(1)	248(1)	0.27(1)	0.58(1)	281(2)	353(2)	1.99(1)	3.56(1)
E.M. 1024	53(1)	61(2)	10(1)	0(2)	—	66(1)	0.38(1)	0.90(2)	46(2)	242(4)	1.85(1)	7.65(1)
W.H. 1025	192(1)	—	—	—	214(1)	—	0.25(1)	0.78(1)	250(2)	—	1.51(1)	2.70(1)
L.S. 1034	53(1)	26(1)	76(1)	0(1)	—	235(1)	0.67(1)	0.19(1)	141(2)	119(2)	3.04(1)	1.50(1)
M.M. 1035	96(1)	35(3)	0(1)	30(1)	—	24(1)	0.33(2)	0.36(3)	46(4)	112(6)	2.92(2)	5.57(3)
B.B. 1003	40(2)	192(1)	17(2)	—	50(2)	—	0.30(2)	0.19(1)	186(4)	280(2)	1.74(2)	6.81(1)
E.G. 1082	53(1)	192(1)	41(1)	30(1)	107(1)	166(1)	0.13(1)	0.14(1)	197(2)	184(2)	1.71(1)	6.77(1)
O.B. 1091	384(1)	196(2)	0(1)	0(1)	52(1)	223(1)	0.13(1)	0.13(1)	312(2)	319(4)	1.39(1)	4.13(2)
A.P.‡ 961	53(1)	13(1)	0(1)	1(1)	62(1)	38(1)	0.19(1)	0.24(1)	25(2)	36(2)	1.54(1)	2.72(1)
AVERAGE	106(9)	96(8)	22(8)	15(7)	88(6)	143(7)	0.29(9)	0.39(9)	165(9)	206(8)	1.97(9)	4.60(9)

ˣ Measured in microgram equivalents of Armour luteinizing hormone standard S1-227-80.

† Determined by the method of Porter and Silber.

‡ Objective regression.

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Oncology Fellowships Available

Clinical research fellowships in oncology and cancer chemotherapy are now available at the University of Southern California School of Medicine, under sponsorship of the National Cancer Institute. The fellowships are of one or two years duration and are available immediately, January 1, 1968 and July 1, 1968. Fellows will have broad patient responsibility and will supervise three residents. The Oncology Service comprises of 60 beds plus an active outpatient clinic. Both standard and investigational chemotherapy is carried out under supervision of Jesse L. Steinfeld, MD, Chairman of the Western Cooperative Cancer Chemotherapy Group and Professor of Medicine. If desired, the fellowships can include a three-month rotation on the Hematology Service of Los Angeles County General Hospital. A year of fellowship can substitute for a year of residency for board eligibility. The stipend for the first year is $6000, of which $3600 is tax-free, and additional allowance is made for dependents.

Applicants should have completed one year of approved medical residency and be eligible for a California license. They should send a brief resume to:

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