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Inhibition of Peripheral Aromatization of Androstenedione to Estrone in Postmenopausal Women with Breast Cancer Using Δ^1-Testololactone*

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ABSTRACT. To determine if Δ^1-testololactone can inhibit the peripheral aromatization of androstenedione (Δ), nine postmenopausal women with metastatic breast cancer were studied before and after 2 weeks of therapy with 250 mg of the drug, given every 6 h by mouth. The conversion ratio of Δ to estrone (E_1) was significantly reduced ($P < 0.005$) from a mean (±SE) of 0.0098 ± 0.0025 before to 0.0009 ± 0.0005 after treatment. The drug's effect on the metabolism of Δ seemed to be specific since significant changes in the MCR of Δ and in the conversion ratio to testosterone were not observed. That this inhibition of peripheral aromatization had an effect on E_1 metabolism was shown by the significant decrease ($P < 0.01$) of mean serum E_1 levels from 22 ± 3 pg/ml before to 12 ± 1 pg/ml after treatment. Serum estradiol levels rose slightly from 8 ± 0.8 to 12 ± 4 pg/ml. Serum Δ and testosterone levels were unchanged by therapy.

These data are consistent with the concept that Δ^1-testololactone is a potent inhibitor of peripheral aromatization of Δ to E_1. This mechanism could explain the antitumor properties of this compound. (*J Clin Endocrinol Metab* **49:** 672, 1979)

IN POSTMENOPAUSAL women, the major source of estrogen is thought to be the peripheral conversion of androgenic precursors, particularly androstenedione (Δ) to estrone (E_1) (1, 2). Direct glandular secretion of estrogen by either the ovaries or the adrenal glands appears to be minimal (3–5). Based on this concept, it should be possible to lower endogenous estrogen production in postmenopausal women by inhibiting the peripheral aromatization of androgens. This possibility could have significant clinical implications in the treatment of women with metastatic or inoperable breast cancer. Both Siiteri (6, 7) and Schwarzel (8) evaluated the ability of numerous compounds to inhibit placental aromatization *in vitro*. One of these, Δ^1-testololactone (Teslac, E. R. Squibb and Sons, Inc., Princeton, NJ), has been used to treat patients with metastatic breast cancer, and objective remissions have been reported (9, 10). To date, the precise mechanism for this antineoplastic effect has not been understood.

The present study was performed to examine the ability of Δ^1-testololactone to inhibit the *in vivo* peripheral aromatization of Δ and to determine the effect of the drug on circulating estrogen and androgen levels in postmenopausal women with metastatic breast cancer.

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Materials and Methods

Patient studies

Nine postmenopausal women with metastatic carcinoma of the breast agreed to the study protocol and gave written informed consent. Seven patients had undergone spontaneous cessation of menses more than 1.5 yr before study. Three patients had undergone oophorectomy, two surgically and the other with radiation. Clinical information on each patient is summarized in Table 1.

All studies were performed in the Surgical Oncology Outpatient Care Facility at University Hospital, University of California, San Diego. At 0800 h, four 10-ml blood samples were drawn at 15-min intervals for the measurement of serum Δ, E_1, testosterone (T), and estradiol (E_2) levels. The measurement of the MCR of Δ (MCR^{Δ}) and its conversion ratios (CRs) to T and E_1, were then carried out using a constant infusion technique patterned on the method of Horton and Tait (11).

After completion of these studies, the patients were given Δ^1-testololactone (250 mg, by mouth) every 6 h for 14 days. The pretreatment studies were then repeated in the same manner as described above.

The MCR^{Δ} and peripheral conversion of Δ to T and E_1 were

TABLE 1. Clinical data on nine postmenopausal women with metastatic breast cancer

Patient no.	Age (yr)	Wt (kg)	Ht (cm)	Menstrual status (yr)	Surgical procedure (date)	Metastatic site
1	55	59	170	Postmenopausal (5)	Left radical mastectomy (1975)	Bone, multiple
2	60	59	159	Postmenopausal (10), bilateral oophorectomy in 1967	Left modified mastectomy (1976)	Bone, soft tissue
3	58	66	165	Postmenopausal (5)	Right modified mastectomy (1976)	Bone, lung
4	56	66	160	Postmenopausal (1.5)	Right radical mastectomy (1971)	Bone, lung
5	57	65	157	Postmenopausal (7)	Left modified mastectomy (1975)	Soft tissue
6	50	60	163	Postmenopausal (4), x-ray oophorectomy in 1973	Left radical mastectomy (1971)	Bone, soft tisuse
7	47	70	174	Postmenopausal (10), bilateral oophorectomy in 1967	Segmental mastectomy and axillary biopsy (1977)	Bone
8	74	58	170	Postmenopausal (20)	Left modified mastectomy (1977)	Bone
9	67	53	165	Postmenopausal (11)	Left radical mastectomy (1963)	Soft tissue, chest wall

also measured in five premenopausal women for comparison with previously published results.

Hormone analysis:

The serum concentrations of Δ, T, E_1, and E_2 were measured by previously published RIA procedures (12, 13). The tube sensitivities of these assays were 10.4, 2.3, <2, and <2 pg for the respective hormones. The MCR^{Δ} and CRs were measured in the following manner. Patients were studied under basal conditions in the supine position. A priming dose of 10 μCi [^{3}H]7α-Δ was given iv and this was followed by an infusion of 30 μCi of the same steroid (in 10% ethanol saline solution) through Teflon tubing for 180 min at a rate of 5.8 cc/h. From the opposite arm, 40-ml blood samples were collected into heparinized tubes 120, 150, and 180 min after the priming dose. The plasma was separated immediately and frozen. At the end of the patient's study, samples were also obtained from the infusion tubing for measurement of the rate of infusion of radioactivity.

To assess the tritiated hormone in the plasma, a 20-ml aliquot of each plasma sample was added to a flask containing [^{14}C]4-T, 4[^{14}C]4-Δ, and 4[^{14}C]4-E_1 to account for recovery. The plasma was extracted twice with 30 ml ether for 1 min and washed with 20 ml distilled H_2O. The ether extract was transferred to a beaker, evaporated to dryness, and redissolved in 5 ml isooctane. An ethylene glycol-celite (1:2) column was prepared in a 5-ml disposable pipette, and the sample extract was applied to the column. The following elution pattern was used to separate the individual steroids:

Added solvents	Amount (ml)	Fraction
Sample (isooctane)	1	
Rinse (isooctane)	0.5	
Isooctane	5	Δ
Isooctane	5	
Cyclohexane/benzene (90:10)	5	T
Ethyl acetate/isooctane (15%)	4	E_1

The individual hormonal fractions were rechromatographed by thin layer chromatography on Chromac 7GF plates with cold steroid standards using benzene-ethyl acetate (3:2) for the solvent system. The spots were located with UV light and the steroids were eluted with ethyl acetate directly into scintillation vials, dried, and counted after the addition of scintillation fluid. Tritium and carbon-14 contents of the samples were assayed by simultaneous scintillation counting in a model LS 3150P Beckman liquid scintillation spectrometer system (Beckman Instruments, Palo Alto, CA) with efficiencies for ^{14}C and tritium of 62% and 29%, respectively. Less than 10% of the ^{14}C was counted in the tritium channel. Calculations of the MCR^{Δ} and the peripheral conversion of Δ to T and E_1 were accomplished by the methods of Horton and Tait (11).

Method proofs of the MCR technique were of three types. Firstly, proof that a steady state was reached for the radioactivity in the plasma during the infusion was accomplished. Initially, five premenopausal subjects were studied and the concentrations of radioactivity in the plasma, whether as precursor or product, were found to be in a steady state. The same steady state conditions were observed for the breast cancer patients. Secondly, radiochemical purities of the tritiated Δ, T, and E_1 after the above chromatography were verified by constancy of isotope ratios studies. Isotope ratios were unchanged during subsequent derivative formation, additional thin layer chromatography, and sequential recrystallization. Thirdly, values measured in five normal premenopausal women were compared to previously published results and were found to be similar (Table 2) (11, 14, 15). It should be noted that the conversion of Δ to E_2 was also measured but is not reported. The actual tritium in the E_2 spots was 2 or less cpm above background. This was considered to be too low to measure accurately.

Student's paired *t* test was used to determine differences between pre- and posttreatment hormone values.

Results

Figure 1 shows the mean (±SE) MCR^{Δ} and the CRs of Δ to T ($CR^{\Delta T}$) and E_1 ($CR^{\Delta E_1}$) in the patients before and after 2 weeks of Δ¹-testololactone therapy. Before treatment, the mean MCR^{Δ} was 1588 ± 104 liters/24 h (range,

TABLE 2. Comparison of MCRs and CRs measured with celite system with previously published results

	MCR^{Δ} (liters/24 h)			$CR^{\Delta T}$			$CR^{\Delta E_1}$		
	Celite	Olivo	Horton	Celite	Olivo	Horton	Celite	Olivo	Longcope
Mean	1616	1830	1951	0.162	0.136	0.142	0.019	0.01	0.013
SD	106	340	320	0.032	0.021	0.023	0.032	0.021	0.023
SE	53	155	143	0.016	0.009	0.019	0.006	0.0005	0.002

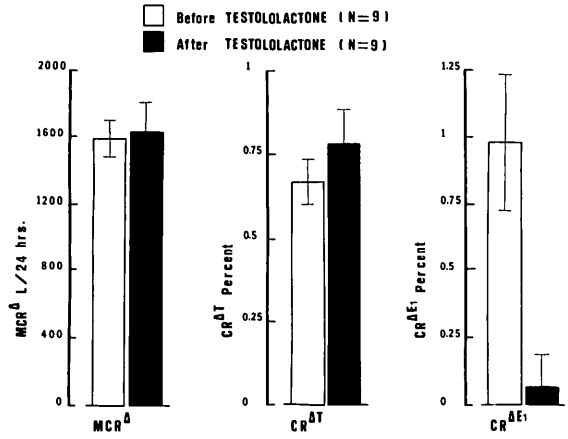

FIG. 1. The MCR^{Δ} and its $CR^{\Delta T}$ and $CR^{\Delta E_1}$ before and after 2-week administration of Δ^1-testololactone.

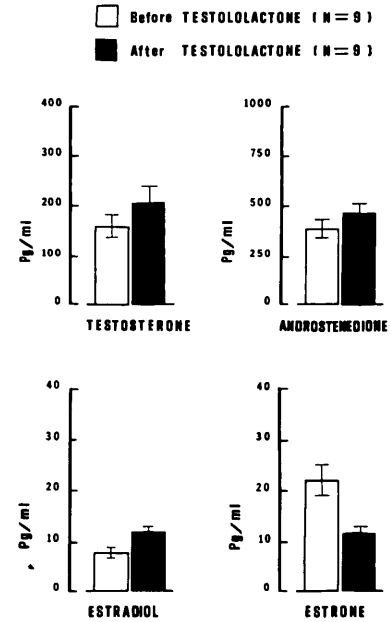

FIG. 2. The serum concentrations of Δ, T, E_1, and E_2 before and after Δ^1-testololactone administration.

546–1907). After 2 weeks of treatment, it was similar at 1626 ± 176 liters/24 h (range, 883–2443). The $CR^{\Delta T}$ were also similar at 0.067 ± 0.007 (range, 0.046–0.107) and 0.07 ± 0.012 (range, 0.033–0.109) before and after treatment, respectively. The baseline $CR^{\Delta E_1}$ was 0.0098 ± 0.0025 (range, 0.001–0.022). After Δ^1-testololactone administration, it was significantly lower ($P < 0.005$) at 0.0009 ± 0.0005 (range, 0–0.003). In six of the nine subjects, no radioactivity above background could be detected in the E_1 fraction of the plasma samples.

Figure 2 shows the levels of Δ, T, E_1, and E_2 before and after treatment. Pretreatment serum Δ (391 ± 44 pg/ml) and T (160 ± 22 pg/ml) levels were similar to posttreatment concentrations at 465 ± 44 and 207 ± 29 pg/ml for the same respective hormones. Δ^1-Testololactone administration was associated with a significant fall ($P < 0.01$) of E_1 from 22 ± 3 to 12 ± 1 pg/ml. For E_2, there was a small but statistically significant rise ($P < 0.02$) after treatment from 8 ± 0.8 to 12 ± 4 pg/ml.

The question was raised if this apparent rise of serum E_2 could be the result of cross-reactivity of the E_2 RIA with Δ^1-testololactone. To examine this question, five samples of a Δ^1-testololactone-saline solution (50 μg/ml) were assayed for E_2. The samples were extracted, chromatographed, and assayed in the usual manner. A 0.000002% cross-reactivity was observed. With this cross-reactivity, there would have to be more than 200 μg/ml Δ^1-testololactone in the plasma to account for an apparent elevation of 4 pg/ml in the circulating E_2 concentration. In women, the blood volume is approximately 66 ml/kg. If it is assumed that complete absorption of the orally administered drug with compartmentalization only in the plasma occurs, then the 250-mg oral dose of Δ^1-testololactone would result in a plasma concentration of approximately 105 μg/ml in a 60-kg woman with a hematocrit of 40. Thus, it is possible that the minute cross-reactivity of the drug with the E_2 immunoassay could account for the slight but statistically significant increase of circulating E_2 during Δ^1-testololactone administration. It should be noted that similar cross-reactivity experiments were done for the T, Δ, and E_1 assays and no cross-reactivity was found.

Discussion

This preliminary study showed that Δ^1-testololactone may function as a potent *in vivo* inhibitor of peripheral aromatization of Δ. Administration of Δ (250 mg every 6 h) for 14 days resulted in a significant reduction of $CR^{\Delta E_1}$ in nine patients with metastatic breast cancer. Previously, Siiteri and Thompson (7) had observed marked reduction of the $CR^{\Delta E_1}$ in two males with gynecomastia. This effect of Δ^1-testololactone on Δ metabolism seemed to be specific, since changes in either the MCR^{Δ} or $CR^{\Delta T}$ were not observed.

That this alteration of $CR^{\Delta E_1}$ had a significant effect on E_1 metabolism was demonstrated by the marked reduction of circulating E_1 levels with treatment to concentrations similar to those seen in oophorectomized and adrenalectomized patients (16). While this finding is consistent with inhibition of peripheral aromatization by Δ^1-testololactone, the mechanism responsible for the fall in E_1 levels could be the result of any one of several other possibilities. Firstly, the drug could be inhibiting direct glandular secretion of E_1. This is doubtful, since direct secretion of E_1 by the postmenopausal ovary has been found to be insignificant (4, 5). To date, no study has critically evaluated direct estrogen secretion by the adrenals, but currently available evidence suggests that this is also minimal (3, 5). Secondly, the drug could be reducing the production rate of Δ, resulting in a concomitant fall of E_1. This possibility can be discounted, since there was no change in either the MCR or serum concentration of Δ with treatment. Thirdly, the reduction of E_1 could occur because of increased clearance rather than decreased production of the estrogen. Although doubtful, this possibility has not been ruled out and is the subject of current research.

Based on the circulating level of Δ and the $CR^{\Delta E_1}$, approximately 4 pg/ml circulating E_1 could be derived from this conversion. The $CR^{\Delta E_1}$ has been calculated by both blood-urine and blood-blood techniques, with the former measuring higher CRs than the latter method (12, 14, 15). Recently, questions have been raised about the adequacy of both techniques in regard to steady state conditions and, to date, these questions have not been resolved (17, 18). For present purposes, the adequacy of either method to measure the absolute amount of conversion of Δ to E_1 is not critical, since the results quantitated by one of the techniques are compared before and after a treatment program.

The exact mechanism responsible for the inhibition of peripheral aromatization of Δ^1-testololactone has not been established. Siiteri (6, 7) and Schwarzel (8) have examined the ability of numerous compounds, including Δ^1-testololactone, to inhibit placental aromatization. These compounds appear to inhibit the process by binding to placental microsomal cytochrome P-450, the enzyme system that is essential for placental aromatization of Δ. A similar mechanism may be involved with the inhibition of peripheral aromatization.

Of the compounds found that would inhibit placental aromatization, most were androgens. For years, androgens have been used in the treatment of metastatic or inoperable breast cancer (19, 20). The finding that many of these compounds inhibited placental aromatization suggested that the underlying mechanism of androgen therapy of human breast cancer may be the reduction of endogenous estrogen production by the inhibition of peripheral aromatization as well as a direct androgenic effect of the compounds on the tumor cells. Δ^1-Testololactone is a compound which has no demonstrable androgenic activity but still retains antitumor properties (9, 10). Clearly, its antitumor activity cannot depend on a direct androgen effect on the tumor cells. The current study suggests that its antitumor properties are secondary to its ability to reduce endogenous estrone production.

The lack of a concomitant fall of E_2 during Δ^1-testololactone therapy was surprising. Currently, it is believed that in postmenopausal women, the major source of E_2 is the peripheral conversion of E_1 and T to E_2 and not direct secretion by either the ovaries or adrenals (3–5, 14, 15, 21). If this is true, then both E_2 and E_1 levels should decrease with Δ^1-testololactone therapy. As mentioned previously, the lack of a decrease of E_2 could be the result of minute cross-reactivity of the E_2 immunoassay with the compound or some metabolite; however, other possibilities exist. These include increased direct glandular secretion of E_2, enhanced peripheral conversion of E_1 to E_2 or T to E_2, and decreased clearance of E_2. Further investigations are necessary to determine the exact mechanism responsible for the apparent small rise rather than fall of E_2 during Δ^1-testololactone therapy.

Recently, it has been observed that the presence of estrogen receptors in breast cancer tissue is predictive of tumor responsitivity to hormonal manipulation (22, 23). This has renewed interest in the endocrine treatment of metastatic or inoperable breast cancer. One of the hallmarks of this type of treatment is the reduction of endogenous estrogen production. In the past, this has been accomplished surgically with oophorectomy, followed by either adrenalectomy or hypophysectomy. Since these latter two operations are associated with some serious complications (24, 25), investigators have been attempting to reduce endogenous estrogen production with chemical methods. Currently, there is considerable interest in the use of aminoglutethimide to accomplish a so-called medical adrenalectomy. This compound reduces steroid biosynthesis by competitive inhibition of the enzymatic conversion of cholesterol to pregnenolone (26–28) and blockade of aromatization (6, 28, 29). Initially, it was found that aminoglutethimide administration was associated with reduced endogenous corticosteroid production, but this action was not sustained (30, 31). The inhibition of cholesterol to pregnenolone conversion resulted in reduced adrenal cortisol production, and a reflex increase of ACTH occurred which overcame the drug's inhibition of adrenal secretion. Dexamethasone administration was combined with aminoglutethimide to prevent the reflex rise of ACTH (32), but this therapy was complicated by accelerated metabolism of dexamethasone secondary to the aminoglutethimide (33). This prob-

lem was avoided with the use of hydrocortisone rather than dexamethasone (34). Using this latter regimen, investigators have accomplished effective long term reduction of endogenous E_1 and E_2 levels to an extent similar to surgical adrenalectomy (16, 29).

The present results indicate that Δ^1-testololactone is also capable of reducing endogenous estrogen production, particularly E_1, in postmenopausal women. Since it does not block corticosteroid synthesis, it should not be necessary to prevent the reflex rise of ACTH which occurs with aminoglutethimide. Studies of a longer duration are needed to determine if the inhibition of peripheral aromatization with Δ^1-testololactone maintains the suppression of endogenous E_1 production in postmenopausal women with breast cancer.

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