PERCUTANEOUS 17 β-ESTRADIOL IN TREATMENT OF CANCER OF PROSTATE

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ABSTRACT — A natural estrogen, 17 β-estradiol, was given percutaneously to 21 patients with untreated cancer of the prostate. The follow-up lasted three to six months, and the results of the survey were encouraging. The hormonal controls showed good plasma diffusion of estrogen, a significant drop in plasma testosterone, and decreased hypophyseal secretion as shown by lower follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Triglycerides and very low density lipoproteins (VLDL) which are considered to be good indicators of cardiovascular risk were unchanged.

The response of prostatic cancer to hormones has been well established by Huggins and Hodges'[1] original study. Estrogen therapy is aimed at acting on intracellular enzyme, 5-alpha reductase which changes testosterone into dihydrotestosterone.[2]

Estradiol is considered the most active of these hormones on 5-alpha reductase,[3] but estrogen therapy has been questioned since Veterans Administration studies[4] have shown that it can cause cardiovascular disease and ischemic and embolic complications.[5]

However, estrogens, particularly estradiol, protect genitally active women against cardiovascular disease while estroprogestative hormones promote it.[6] To prevent these risks, two points are of importance: (1) natural estrogens should be given; and (2) a direct route through the portal system and the liver should be avoided. This can be achieved by parenteral and percutaneous[7] administration. Percutaneous estrogen therapy has been shown to be well tolerated by women undergoing menopausal treatment.

We studied the effects on 21 patients of a percutaneous natural estrogen, 17 β-estradiol, the most active hormone on 5-alpha reductase.

Material and Methods

Twenty-one untreated patients with adenocarcinoma of the prostate were studied. Diagnosis was made either by discovery of class IV or V cells on Franzen transrectal aspiration–biopsy[8] or by pathologic findings after prostatic transurethral resection or adenomectomy done on patients with dysuria.

Treatment consisted of three periods: (1) a fifteen-day period without treatment (patient being his own witness); (2) a one-month period during which patient applied daily 5 Gm. of gel (or 3 mg. of estradiol per day) equal to 300 γ per day[7-9] because of percutaneous uptake of estradiol; and (3) a one-month period when the patient applied two doses of gel (10 Gm. per day) or 600 γ after absorption. All patients were followed by the same consulting physicians.

Clinically, four stages were considered according to size and infiltration of the prostate:[10] (1) nonpalpable lesions diagnosed on histology; (2) local lesions found on digital examination of the rectum, B_1 if only on one lobe, B_2 if on both; (3) lesions beyond the prostatic capsule, C_1 if only one lobe, C_2 if on both; and (4) lesions of the prostate with metastasis.

Improvement was defined as lesions becoming of a lesser stage, and worsening as becoming superior in stage. Follow-up of all patients included regular blood creatinine levels, and any change resulted in an intravenous pyelogram.

Each month at 8:00 A.M., after twelve hours of fast following the last application of estradiol gel, serum lipids were checked. This study will

TABLE I. *Estrone (E_1) and estradiol (E_2) levels with percutaneous 17 β-estradiol treatment*

Doses	Mean Results	Standard Deviation
ESTRONE (pg./ml.)*		
0	37.6	16.2
1	86.7	42.5
2	150.9	101.4
ESTRADIOL (pg./ml.)†		
0	23.2	10.8
1	84.2	54.3
2	184.7	98.46

*Significant differences between 0 and 1 dose, $P < 0.001$; 1 and 2 doses, $P < 0.05$; and 0 and 3 doses, $P < 0.01$.

†Significant differences between 0 and 1 dose, $P < 0.01$; 1 and 2 doses, $P < 0.01$; and 0 and 2 doses, $P < 0.0001$.

TABLE II. *Testosterone and dihydrotestosterone levels with percutaneous 17 β-estradiol treatment*

Doses	Mean Results	Standard Deviation
TESTOSTERONE (mg./ml.)*		
0	3.41	1.8
1	1.88	1.25
2	1.05	1.13
DIHYDROTESTOSTERONE (μg./ml.)†		
0	0.36	0.27
1	0.23	0.14
2	0.12	0.12

*Statistically significant differences between 0 and 1 dose, $P < 0.02$; 1 and 2 doses, $P < 0.01$; and 0 and 2 doses, $P < 0.001$.

†Significant differences between 1 and 2 doses, $P < 0.01$; and 0 and 2 doses, $P < 0.01$.

only show triglycerides and VLDL levels since we consider these to be the best indicators of adverse cardiovascular effects of estrogen therapy.[6,11,12] Triglycerides were measured by an enzymatic method adapted to autoanalyzer II.[13]

Low-density lipoproteins (chylomicrons, VLDL, LDL) were assessed by two turbidimetric tests: calcium-heparin test to dose LDL + VLDL + chylomicron and sodium-laurylsulfate test to dose VLDL + chylomicron. Readings were done on a "Pasteur turbidimeter." In the present study, all serum samples were taken from patients who had fasted for twelve hours, and these samples contained no chylomicrons. This was confirmed by the aspect of the serums and by lipoprotein electrophoresis. Therefore the sodium-laurylsulfate test was considered to dose only VLDL.

Testosterone, dihydrotestosterone, estrone (E_1), estradiol (E_2), FSH, and LH were assessed after centrifugation and freezing of plasma samples. Plasma testosterone and dihydrotestosterone were dosed by radioimmunoassay. Nonconjugated plasma levels of E_1 and E_2 were measured by radioimmunoassay. FSH and LH level determinations were done by double antibody radioimmunoassay.

Results

Of the 21 patients, 11 were Stage B, 9 were Stage C, and 1 was Stage D (bone metastasis on scan studies). Two patients became clinically worse, 9 were stable, and 10 improved. Blood creatinine levels and intravenous pyelograms were unchanged.

As shown in Table I, the blood levels of estrone and estradiol are significantly raised by percutaneous administration of estradiol. Table II demonstrates the lowering of both testosterone and dihydrotestosterone. Table III shows no rising of triglyceride levels nor VLD levels. Table IV shows that percutaneous 17 β-estradiol lowers both FSH levels and LH levels although for LH levels the difference is not significant.

Comments

Percutaneous 17 β-estradiol is known to be well tolerated by women who show no change in lipid levels.[14] A number of studies have shown that triglycerides and VLDL are the best indicators of the metabolic risk involved with the use of estrogens and estroprogestative hormones.[15,16] Their increase can be linked with cardiovascular disease.

The purpose of this preliminary study was to determine if there is good absorption of percutaneous 17 β-estradiol in men, and if it is possible by this way to bring about a significant drop in testosterone and thus in hypophyseal

TABLE III. *Triglyceride and VLDL levels with percutaneous 17 β-estradiol treatment*

Doses	Mean Results	Standard Deviation
TRIGLYCERIDES (Gm./L.)*		
0	1.20	0.74
1	1.18	0.48
2	1.19	0.50
VLDL (Shank Hoagnand U.)*		
0	7.6	5.6
1	8.1	4.6
2	7.1	4.3

*Differences were not found to be significant.

TABLE IV. *FSH and LH levels with percutaneous 17 β-estradiol treatment*

Doses	Mean Results	Standard Deviation
FSH (mI.U./ml.)*		
0	7.56	4.9
1	6.44	5.0
2	4.13	5.0
LH (mI.U./ml.)†		
0	6.21	6.2
1	4.15	3.3
2	3.41	3.2

*Significant differences between 1 and 2 doses, $P < 0.05$; and 2 doses, $P < 0.01$.

†No significant differences.

secretion. Also we wished to determine if that type of estrogen does not increase triglyceride and VLDL levels. Increase is otherwise rapid in one or two months, temporary and proportional to estrogen dose.[17]

This study clearly shows that an efficient dose (600 γ/day) of estradiol is absorbed well, as shown by rising blood levels of estrone and estradiol, with improvement in 1 of 2 patients. It lowers testosterone and dihydrotestosterone. The levels reached here are similar to those found when 3 mg./day diethylstilbestrol is given.

As seen in Table III, there is no elevation of triglycerides and VLDL in this study under the influence of estrogen therapy.

To date studies on men with cancer of the prostate had been conducted with estrogen given parenterally[18] but not percutaneously. This method appears to avoid hepatic filtering of hormones, which is responsible for an increase in lipoproteins. This increase is due either to a rise in apoproteins or to enzyme induction[19] as shown by higher gamma glutamyl transferase or lower lipase levels.[20]

Conclusion

17 β-estradiol administered percutaneously is well absorbed by men. It lowers plasma testosterone levels as with 3 mg. diethylstilbestrol. It does not appear to affect lipids and lipoproteins.

These encouraging results prompt us to follow this preliminary study with long-term random studies of the effects of percutaneous natural estrogens versus oral synthetic estrogens in patients with cancer of the prostate.

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