Am J Clin Oncol (CCT) 11(Suppl. 2): S101–S103, 1988.

Single Drug Polyestradiol Phosphate Therapy in Prostatic Cancer

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Serum concentrations of testosterone (T) and estradiol-17β (E_2) were analyzed in prostatic cancer patients treated with 160, 240, or 320 mg polyestradiol phosphate (PEP) i.m. every fourth week as single drug therapy during a 6 month period. Estrogen effects on the liver were studied by analyzing serum levels of sex hormone binding globulin (SHBG) in the 320 mg group and compared with values obtained in patients treated with 80 mg PEP i.m. every fourth week + oral ethinylestradiol (EE_2) 150 μg daily, or by orchidectomy. Orchidectomy levels of T were reached within 3 weeks in the 320 and 3 months in the 240 mg group. In the 160 mg group, mean T levels reached the upper limit of orchidectomy values after 6 months. Accumulation of E_2 occurred to mean levels 1,300–2,500 pmol/L at 6 months. At 6 months, SHBG levels had increased to 617% of pretreatment values in the oral EE_2 group, to 166% in the 320 mg group, and were unaffected by orchidectomy. No cardiovascular side effects occurred during single-drug PEP treatment.

Key Words: Prostatic cancer—Parenteral estrogen therapy—Testosterone suppression—Cardiovascular side effects.

Insufficient suppression of testosterone (T) levels has been reported for polyestradiol phosphate (PEP) as a single drug at previously used dosages (≤160 mg i.m. every fourth week) (1,2). Higher doses of PEP have been avoided due to the well-known cardiovascular side effects of high-dose estrogen (3). These results refer to oral administration exclusively. Recent investigations on liver protein patterns during different regimens of estrogen therapy have clearly shown that liver side effects are strongly decreased or even nonexistent when the drug is given parenterally (4,5). The aim of the present study was to investigate T suppression during different dosages of i.m. PEP treatment and to study possible side effects.

Synthetic estrogens with nonsteroid (e.g., diethylstilbestrol) or modified steroid (e.g., ethinylestradiol) structures are usually difficult to assay, which makes monitoring of treatment difficult. However, the primary and active metabolite of PEP is estradiol-17β (E_2), which is analyzed by routine procedures. Assays of serum E_2 were therefore included in the present study as a complementary analysis in the treatment supervision.

MATERIALS AND METHODS

Twenty-seven consecutive patients with untreated histologically and/or cytologically proven cancer of the prostate (CAP) (T_{2-4}; G_{2-3}; M_{0-1}; N_x), with a mean age of 70 ± 1.2 (SEM) years, were randomly allocated to three treatment groups (N = 9 each), receiving 160, 240, or 320 mg PEP i.m. (Estradurin, Leo AB, Helsingborg, Sweden) every fourth week. There were no significant differences between the three subgroups with respect to age, tumor classification, and pretreatment laboratory

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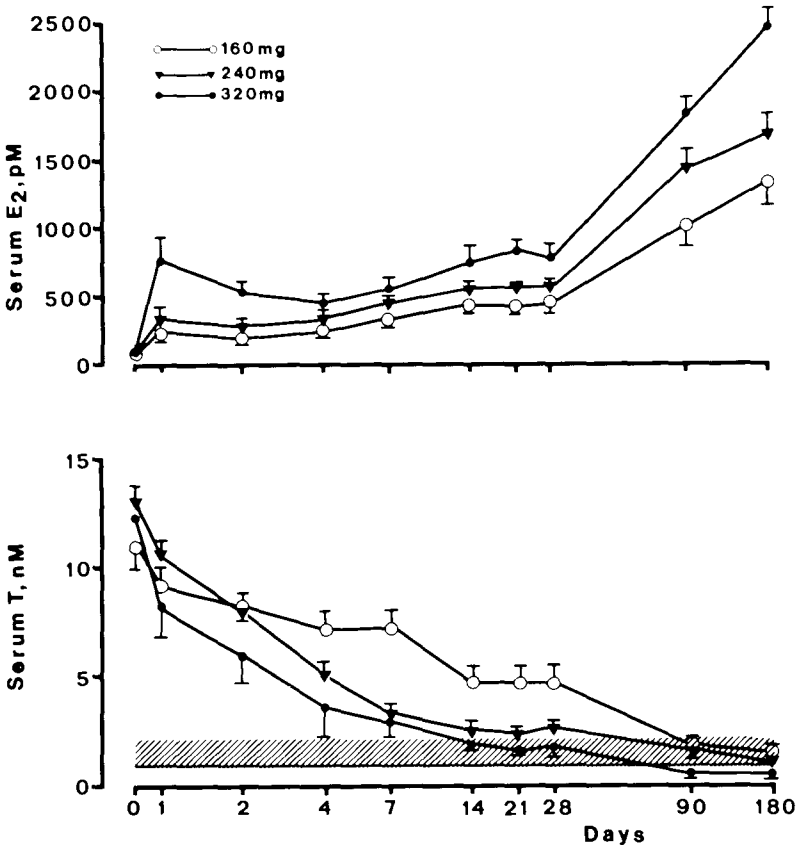

FIG. 1. Serum concentrations of estradiol-17β (E_2) and testosterone (T) in CAP patients treated with 160, 240, or 320 mg PEP i.m. every fourth week. Values are given as mean and SEM. Mean ± 2 SD of T values after orchidectomy are indicated by the horizontal dotted line and hatched area (6).

values. None of the patients had any signs of endocrine, cardiovascular, intestinal, or renal malfunction. Apart from the described estrogen treatment, no medication was given that could interfere with the analyses performed.

Response to therapy was evaluated according to the guidelines of the Scandinavian Prostatic Cancer Group. Blood samples were taken as indicated in Fig. 1 and analyzed for serum T and E_2. The effect of estrogen upon the liver was studied by analyzing serum levels of sex hormone binding globulin (SHBG) in the 320-mg group and comparing with the values obtained in four patients treated with 150 μg ethinylestradiol (Etivex^R, LEO AB, Helsingborg, Sweden) daily + 80 mg PEP i.m. every fourth week and obtained in 33 patients treated by bilateral orchidectomy (6).

RESULTS

The time of treatment needed to reach castration levels of T was clearly dose-dependent and varied considerably between individual patients within the different dosage groups. In the 160 mg group, the mean T value was just below the upper limit of castration values 6 months after the start of treatment. The levels of E_2 increased in a dose-dependent manner, and, surprisingly, an accumulation was observed in all treatment groups (Fig. 1).

A first clinical evaluation of the patients after 6 months of treatment revealed the following distribution between response (R), stable disease (SD), and no response (NR) within the three dosage groups: 160 mg, R: 0, SD: 8, NR: 1; 240 mg, R: 4, SD: 3, NR: 2; and 320 mg, R: 5, SD: 3, NR: 1.

In 12 patients with intact potency prior to therapy, eight registered dysfunction during treatment. Gynecomastia and/or breast tenderness appeared in 21 of the 27 patients. No cardiovascular side effects were observed and the therapy could be continued in all patients. Liver effects as illustrated by SHBG values are depicted in Fig. 2. While oral estrogens induced a tremendous increase in SHBG levels, only minor changes occurred during parenteral administration, notwithstanding the dramatic changes in estrogen/androgen balance.

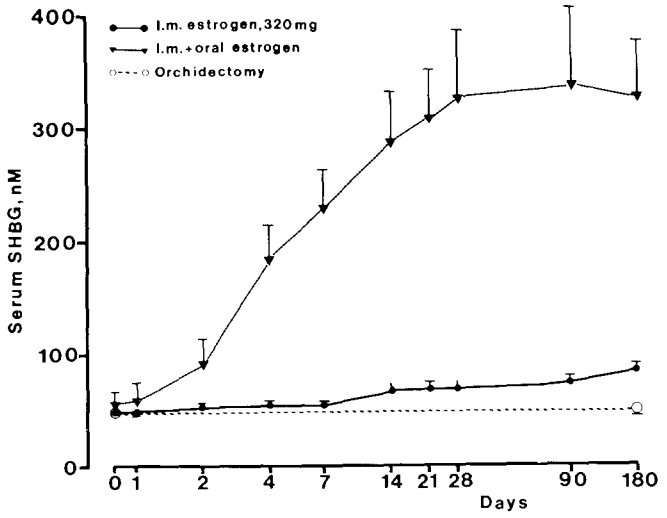

FIG. 2. Serum concentrations of sex hormone binding globulin (SHBG) in patients treated with 320 mg PEP i.m. every fourth week and in patients treated with 150 μg oral ethinylestradiol daily + 80 mg PEP i.m. every fourth week and in orchidectomized patients (6). Mean and SEM.

DISCUSSION

Cardiovascular side effects of oral estrogens are usually seen within 6 months of treatment (7). However, despite the dramatically increased E_2 levels, especially in the 320-mg group, no cardiovascular side effects at all were noted in the present study. We interpret this as another indication of the importance of the route of administration, and probably the first liver pass, for the liver-mediated side effects of estrogens (4,5). This is further illustrated by the different patterns in serum SHBG during parenteral and oral treatment. SHBG is considered as a most sensitive indicator of estrogenic effects upon the liver (for references, see ref. 5). In contrast to the tremendous increase in SHBG during oral estrogen treatment, the corresponding changes induced by sole parenteral estrogen, even at high doses, were only marginal. From the present results, no standard dosage of PEP can be recommended. However, it may be suggested to start with 320 mg and to monitor the treatment with monthly assays of circulating T and possibly also of E_2. When T values are well within the castration levels, the PEP dose may be modified.

To conclude, intramuscular polyestradiol phosphate may be an attractive alternative endocrine treatment of prostatic cancer providing sufficient T suppression at appropriate dosages and probably presenting no major cardiovascular side effects. Endocrine monitoring of the therapy can be easily done with conventional assays of circulating T and E_2.

Acknowledgment: This work was supported by grants from Riksföreningen mot cancer (2482) and from Maud & Birger Gustafssons Stiftelse.

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