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Androgens during different modes of endocrine treatment of prostatic cancer

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Summary. Serum levels of testosterone (T), 17α-hydroxyprogesterone (17OHP), 4-androstene-3,17-dione (A-4), dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS) and cortisol were measured before and after 6 months of treatment in prostatic cancer patients treated by orchidectomy (ORX) or with oral + parenteral estrogens (OE), single parenteral estrogens (PE; 160 or 320 mg polyestradiol phosphate i.m. every fourth week), estramustine phosphate (ECYT) or LHRH agonist without (LHRH) or with (LHRH-F) flutamide. Castration values of T and 17OHP were reached in all types of treatment (PE at the higher dose). A-4 levels were suppressed by all treatment regimens except ECYT; DHA by OE and LHRH-F and DHAS by ORX, OE and LHRH-F. The most pronounced suppression was found in the LHRH-F group. Cortisol levels were markedly increased by OE and ECYT. The observed effects on the adrenal androgens A4, DHA and DHAS and on cortisol probably reflect different degrees of liver interaction rather than interaction with adrenocortical steroid synthesis.

Key words: Prostatic cancer – Endocrine treatment – Androgens – Testis – Adrenals – Liver

Introduction

A possible role of adrenal "rest androgens" for tumor growth during endocrine treatment of prostatic cancer (CAP) has been widely discussed [11, 13, 14]. However, there are few comparative studies on adrenocortical steroids during different regimens of endocrine CAP treatment, especially when "alternative" or "novel" therapeutic principles are concerned [2, 12, 15]. The present paper describes adrenal and testicular steroid levels in CAP patients during seven different regimens of endocrine treatment.

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Materials and methods

Patients and treatment

The clinical material comprised 72 patients aged 54–85 years (mean age 71.4 ± 0.9 (SEM) years) with cytologically confirmed prostatic carcinoma. None of the patients had any clinical or laboratory signs of cardiovascular, hepatic, biliary or renal malfunction or of endocrine abnormality. Pretreatment serum levels of the steroids studied were normal in all patients. Apart from the specific CAP treatment, the patients received no medication that could interfere with the steroids studied.

The patients were consecutively allocated to following regimens of tretatment:

Group 1: Twentyfour patients were subjected to bilateral orchidectomy under general anesthesia.

Group 2: Thirteen patients were given single drug therapy with intramuscular polyestradiol phosphate (PEP; Estradurin®, Leo AB, Helsingborg, Sweden) at a dose of 160 mg every fourth week.

Group 3: Nine patients treated similarly as group 2, but with 320 mg doses.

Group 4: Seventeen patients received oral ethinyl estradiol (EE_2; Etivex®, Leo AB, Helsingborg, Sweden) in a dose of 0.5 mg twice daily during 2 weeks, thereafter in a dose of 0.15 mg daily. Intramuscular PEP was given in the 160 mg dose during the first 3 months of treatment, thereafter the dose was reduced to 80 mg every fourth week.

Group 5: Seven patients received oral estramustine phosphate (Estracyt®, Leo AB, Helsingborg, Sweden) at a dose of 840 mg daily.

Group 6: Six patients were treated with a long acting LH-RH agonist (Zoladex Depot®, ICI 118630, ICI Ltd Macclesfield, UK, was given as s.c. injections at a dose of 3.6 mg every month).

Group 7: Five patients treated similarly as group 6 but with addition of 750 mg of oral flutamide (Fugerel®, Schering Corp, Kenilworth, NJ, USA) daily.

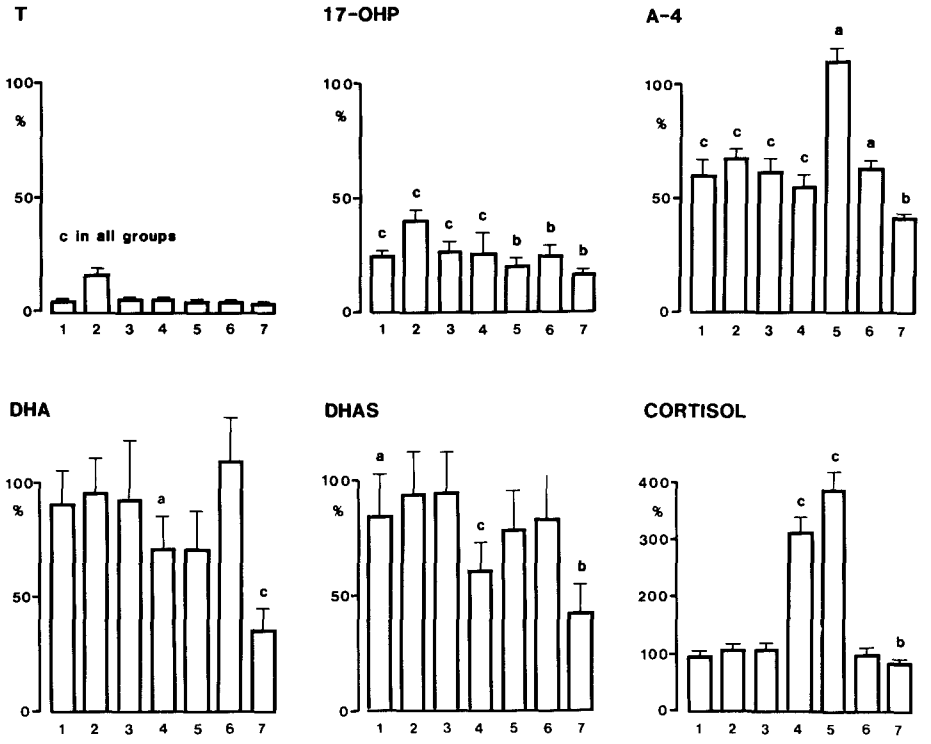

Fig. 1. Peripheral serum concentrations of testosterone (T), 17α-hydroxyprogesterone (17-OHP), 4-androstene-3,17-dione (A-4), dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS) and cortisol in prostatic cancer patients treated by orchidectomy (1), with intramuscular polyestradiol phosphate in 160 mg dose (2) and in 320 mg dose (3), with oral ethinyl estradiol + i.m. polystradiol phosphate (4), with estramustine phosphate (5), with LH-RH agonist (6) and with LH-RH agonist + flutamide (7). Values after 6 months of treatment are given as per cent of pretreatment values (Mean and SEM). Values during treatment significantly different from pretreatment values are denoted by a) = $P<0.05$; b) = $P<0.01$ and c) = $P<0.001$

Venous blood samples were taken between 09.00 h and 12.00 h at 1–4 weeks before and at 6 months after initation of treatment. Serum was separated and stored at −20°C until analyzed.

Analytical methods

Serum concentrations of testosterone (T), 17α-hydroxyprogesterone (17OHP), 4-androstene-3,17-dione (A-4), dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS) and cortisol were determined by radioimmunological methods as previously described [3, 4, 15].

Statistical methods

The significance of differences between treatment and pretreatment values was tested using *t*-test for paired observations.

Results

There were no significant differences between the treatment groups with respect to mean age and mean pretreatment steroid levels (data not shown). Serum steroid levels after 6 months of treatment, expressed as per cent of pretreatment values, are shown in Fig. 1. Castration values of T and 17OHP were reached in all treatment groups except in the 160 mg PEP group (group 2). The levels of A-4 were significantly decreased in all groups except in the estramustin phosphate group (group 5), in which a slight but significant increase was observed. Mean DHA values below 75% of pretreatment values were found in the oral + parenteral estrogen group (group 4), the estramustine phosphate group (group 5, not statistically significant) and in the LH-RH against + flutamide group (group 7). For DHAS, mean values below 85% of pretreatment values were found after orchidectomy (group 1) and during treatment with oral + parental estrogens (group 4), with estramustine phosphate and with LH-RH agonist (groups 5 and 6, not statistically significant) and with LH-RH agonist + flutamide (group 7). Serum cortisol levels were significantly increased in the groups treated with oral + parenteral estrogens (group 4) and with estramustine phosphate (group 5) and slightly but significantly decreased in the LH-RH agonist + flutamide group. For all steroids, the most pronounced decrease was found in the patients treated with LH-RH agonist + flutamide. The second lowest levels of adrenal androgens (A-4, DHA, DHAS) were found in the oral + parenteral estrogen group (group 4).

Discussion

Castration values of the mainly testicular steroids T and 17OHP can be achieved with all types of endocrine treatment, even with single parenteral estrogens, provided adequate doses are use. A testicular contribution

of about 30% has been reported for circulating levels of A-4 [15]. Castration values or even lower levels of A-4 were found in all groups except in the estramustine phosphate treated patients, in which a slight but significant increase was observed. One may speculate that the effects of testicular suppression and a possible induction of hepatic steroid-metabolizing enzymes may be outweighed by an inhibition of hepatic enzyme activity by the enormous amonts of estrogens or estrogen-like compounds (up to 400,000 pmol/l estrone equivalents) during this type of treatment [10].

The elevated cortisol levels in patients treated with oral estrogens or estrogen derivatives (groups 4 and 5) probably reflect induction of hepatic transcortin synthesis. The absence of this effect in patients treated with parenteral estrogens further illustrates the difference in hepatic side effects between orally and parenterally administered estrogens [16].

DHA and DHAS are usually considered a "purely adrenal" androgens, although the present and previous studies on orchidectomized subjects indicate a testicular contribution of 10–15% [15 and references cited therein]. The decrease in DHA and DHAS was most pronounced in patients receiving oral estrogens or estrogen derivatives or LH-RH-agonist + flutamide. DHAS is strongly bound to albumin and we have shown a concomitant decrease in albumin and DHAS values during oral estrogen treatment, probably resulting in an increased metabolic clearance rate of DHAS [15]. Furthermore, we have recently demonstrated that this treatment is without effect on the adrenal androgen response to ACTH stimulation [5]. Oral estrogens are also reported to induce hepatic 16α-hydroxylase, which is a key enzyme in the metabolism of DHA and DHAS [7]. The more pronounced decrease in DHA and DHAS during oral estrogen treatment may therefore simply be another reflexion of the liver side effects of this treatment.

Treatment with LH-RH-agonist + flutamide induced the most pronounced decrease in adrenal androgen levels. Similare results have previously been reported by Labries's group [1, 12]. They did also report a diminished adrenal androgen response on ACTH stimulation, and suggested that the decreased adrenal androgen levels reflected specific inhibition of adrenal C_{17-20}-lyase activity by flutamide [1]. However, in an ongoing study, using a similar ACTH test protocol, we have hitherto failed to observe any effects of LH-RH-agonist + flutamide treatment in this respect (Stege and Carlström, to be published).

Three studies on flutamide and steroid metabolism in CAP patients, published by the same group about 10 years ago, have been "forgotten" in the present discussion. Their results concerning the metabolism of T [9], cortisol [7] and estradiol-17β [17] strongly resembled those seen in liver cirrhosis. Elevated transaminase and/or bilirubin values were also frequently observed, and the authors concluded that the observed changes in steroid metabolism reflected intrahepatic cholestasis and/or hepatocellular damage. Their findings concerning cortisol metabolism [7] has special relevance to the present discussion. The metabolic pattern was changed, the biological half-life was increased and the secretion rate of cortisol was decreased by 47% but the serum cortisol levels were uneffected by flutamide treatment.

The decreased cortisol secretion in flutamide treated patients is probably mediated via a decreased ACTH stimulation. This will lead to decreased serum levels of other adrenocortical steroids, including adrenal androgens, provided the metabolic clearance rate of these compounds is not decreased. In the study of Hellman et al. [9] plasma DHA was decreased by 10–40%. One may also speculate over an increased hepatic metabolism of adrenal androgens during flutamide treatment. Irrespective of the exact mechanism, we consider it as highly likely that the strongly decreased adrenal androgen levels during LHRH-agonist + flutamide treatment reflect hepatotoxicity of flutamide rather than a selective action on adrenal androgen biosynthesis.

To conclude, profound suppression of adrenal androgen levels seems only to be aquired in treatment regimens associated with heavy liver side effects, i.e. oral estrogens or estrogen derivatives and LHRH-agonist + flutamide. If this decrease in adrenal androgens is worth the prize of liver related side effects may be discussed. We have recently finished a controlled study on possible associations between therapy response and adrenal and testicular steroid levels in CAP patients [6]. The study included 78 patients randomly allocated to orchidectomy or oral + parenteral estrogen treatment and the observation time was 3 years. There was no association, whatsoever, between therapy response and steroid levels before and during treatment.

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