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Pituitary–Testicular Function of Prostatic Cancer Patients During Treatment with a Gonadotropin-Releasing Hormone Agonist Analog

I. Circulating Hormone Levels

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Eight patients with advanced prostatic carcinoma (ages 59 to 78 years) were treated with a potent gonadotropin-releasing hormone (GnRH) agonist analog (buserelin, Hoechst; 600 μg intranasally, 3 times daily) and orchiectomized after 6 months of treatment. Endocrine responses were followed by serum hormone measurements during agonist treatment and for 3 months after orchiectomy. Six other patients (65 to 86 years) with advanced prostatic cancer had been orchiectomized as the first therapeutic measure and their blood samples were used as controls. In the GnRH agonist-treated patients, serum immunoreactive luteinizing hormone (LH) and follicle stimulating hormone (FSH) decreased after initial stimulation by 70 to 80%, within 1 to 3 weeks ($P < 0.01$). FSH partly recovered ($P < 0.05$) after the first month of treatment. Serum prolactin (PRL) displayed a slight tendency to decline during buserelin treatment ($P < 0.05$). Serum total and free testosterone (T) of the buserelin-treated patients decreased to the castrate range within 3 to 4 weeks after an initial 5-day increase ($P < 0.01$). Serum progesterone and 17-hydroxyprogesterone (17-OHP-4) decreased to the castrate range (by 50 to 70%) in 1 week. Only minor changes were observed in sex hormone binding globulin (SHBG). Significant, acute elevations of LH, FSH, T, and 17-OHP-4 were observed only on day 1 after an injection of buserelin (500 μg i.m.) and not when assessed between day 7 and month 6 of treatment. After 6 months of buserelin treatment, orchiectomy did not affect the serum steroids measured. After orchiectomy, immediate increases in serum LH, and somewhat later in FSH, were seen in the control patients. Initial treatment with buserelin did not affect the postcastration rise of FSH, whereas the rise of LH was delayed by about 2 weeks. In summary, these results indicate that pituitary–testicular function becomes refractory to stimulation of high-dose buserelin treatment within a week. Testicular steroids decrease to the castrate range within 3 to 4 weeks, probably through inhibition of steroidogenesis proximally to progesterone and 17-OHP-4 formation. After simultaneous cessation of treatment and surgical castration, the desensitization of the pituitary applies only to LH secretion, whereas the postcastration rise of FSH is essentially similar to that of orchiectomized control patients.

Key words: prostatic cancer, GnRH agonist, orchiectomy, gonadotropins, testosterone.

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The paradoxical inhibitory action of GnRH agonist analogs on gonadotropin secretion is now well established and the phenomenon has numerous clinical applications for the inhibition of pituitary–gonadal function, including prostate and breast cancer, endometriosis, polycystic ovarian disease, precocious puberty and contraception (see Labrie et al, 1984). We have recently reported some findings from our study

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on the endocrine effects of GnRH agonist treatment in prostatic carcinoma (Huhtaniemi et al, 1985). To understand better the mechanisms of action of this therapy, we have now performed detailed measurements of changes in circulating pituitary and testicular hormone levels in groups of buserelin-treated and surgically orchiectomized prostatic cancer patients. The accompanying paper (Huhtaniemi et al, 1987) deals with the endocrine and morphologic features of the testis tissue from the same patients.

Materials and Methods

Patients

Eight patients (aged 59 to 78 years) with advanced prostatic cancer, confirmed by biopsy, were examined in this nonrandomized study. The TNM classification (International Union Against Cancer, 1978) of the patients was T3-4 M1. All patients were recently diagnosed, and none had received any treatment for prostatic cancer. Consent was obtained after the available therapeutic options were explained. At the time of treatment, buserelin was available for 6 months, after which one of the generally accepted routine treatments was to be chosen (subcapsular orchiectomy or estrogen therapy). All eight patients chose orchiectomy. For control studies on postcastration hormone levels, we recruited six age-matched prostatic cancer patients (aged 65 to 86 years) with the same stage of disease. In these patients, orchiectomy was the first form of treatment. The study was approved by the ethics committee of the hospital. Some of the hormone levels during buserelin treatment (selected T and gonadotropin values) were presented in a recent report on this research (Huhtaniemi et al, 1985).

Treatments

The GnRH agonist analog [buserelin; D-Ser-(tBu)^{6}-des-Gly^{10}-GnRH *N*-ethylamide] was provided by Hoechst AG (Frankfurt am Main, West Germany). The agonist treatment was initiated with a 7-day period of s.c. injections (500 μg every 8 hours). Thereafter, the peptide was administered intranasally, 600 μg 3 times daily. The bioavailability of this peptide via the nasal route is 2.5% (Sandow and Petri, 1985). This therapy was given for 6 months, after which the patients underwent orchiectomy (approximately 12 hours after the last dose of buserelin). The antigonadal effects of the treatment were followed by frequent measurements of serum gonadotropin and T levels (see below). The clinical outcome of the patients was followed by frequent assessment of subjective symptoms and by objective measurements, such as serum prostate-specific acid phosphatase and alkaline phosphatase measurements, as well as by x-ray, ultrasound, and technetium bone-scanning studies.

Blood Sampling

Blood samples for measurements of LH, FSH, prolactin (PRL), T, progesterone, and 17-hydroxyprogesterone (17-OHP-4) were drawn between 0730 and 0830 hours, always before the morning dose of buserelin. The basal levels of these serum hormones were the means of two or three morning samples obtained before initiation of buserelin treatment or orchiectomy (controls). Samples were obtained thereafter every morning during the first week of treatment, once a week up to a month, and once a month thereafter. Following orchiectomy (also in control patients), blood samples were drawn on days 1, 2, 4, and 7, and after that at 2, 4, 8, and 12 weeks (controls also at 4, 5, and 6 months). The sera were separated by centrifugation and stored at −20 C until analyzed.

In addition, the serum levels of LH, FSH, T, progesterone, and 17-OHP-4 were followed at times 0, 0.5, 1, 2, 4, and 8 hours in relation to an i.m. injection of 500 μg buserelin given at 0800 hours on days 1 and 7, and months 1, 3, and 6 of treatment (at these times the injection replaced the morning intranasal application of the peptide).

Hormone Measurements

Serum T was measured by RIA as we have recently described (Huhtaniemi et al, 1985). Progesterone was measured using a kit purchased from Farmos Ltd. (Turku, Finland), and 17-OHP-4 by a kit from CIS (St. Quentin-Yvelines, France). The manufacturers' reference range in the male for serum progesterone was 1.4 to 7.0 nmol/1 (personal communication), and that for 17-OHP-4 1.64 to 7.58 nmol/1. Our serum T levels in old men (60 to 80 years) are 4.5 to 38.5 nmol/1 (mean ± 2 SD, n = 20). Serum SHBG was measured using a kit purchased from Farmos Ltd. (Turku, Finland). The manufacturer's reference range for SHBG in males is 10 to 50 nmol/1. Serum free T was calculated from the levels of SHBG and total T according to Anderson (1976).

Pituitary hormones were measured using RIA kits purchased from CIS (St. Quentin-Yvelines, France; for LH and FSH) and Pharmacia (Uppsala, Sweden; for PRL). LH levels were expressed in terms of the MRC 68/40 standard (international units per liter), those of FSH using the Second International Reference Preparation 78/549 (international units per liter), and those of PRL using the First International Reference Preparation 75/504 from WHO (international units per liter). The reference ranges given by the manufacturers for normal men were 1.6 to 12.5 IU/1 for LH, 0.9 to 9.8 IU/1 for FSH, and up to 600 IU/1 for PRL.

All samples from the same patient were analyzed in the same RIA run. The intraassay and interassay CVs of the individual RIA methods were below 8 and 13%, respectively.

Statistical analysis of the results was performed using paired and unpaired student's *t* tests (comparison of two means), Duncan's multiple range tests (multiple comparisons), and linear regression analysis. A *P*-value of 0.05 was chosen as the limit of statistical significance.

Results

Serum LH, FSH, and PRL

Circulating levels of LH, FSH, and PRL in the buserelin-treated and orchiectomized control patients are presented in Fig. 1. After initiation of buserelin

treatment, both gonadotropins show the expected acute stimulation, which was 2- to 3-fold in the morning of the second day of treatment (8 hours after the last buserelin injection) ($P<0.01$). The nadir of LH levels was reached in 3 to 4 weeks, but occurred in 1 to 2 weeks for FSH. LH levels remained about 70 to 80% suppressed for the rest of the treatment, whereas a secondary increase ($P < 0.05$) was seen in FSH when the mean levels of weeks 1 to 2 and months 1 to 3 of treatment were compared.

As expected, the postcastration levels of LH and FSH started rising immediately in the control patients, being significantly ($P < 0.05$) elevated on day 1 for LH. However, FSH was significantly increased only by week 2. In contrast, in the buserelin-treated patients, the first significant elevation of LH ($P < 0.01$) after orchiectomy was noticed as late as 4 weeks after surgery. The rise of FSH in these samples was evident at 2 weeks ($P < 0.05$), as in the controls.

PRL levels showed a slight tendency to decline in the buserelin-treated patients ($P<0.05$) although, on the whole, only minor changes occurred before and after surgery in both groups of patients.

Serum Progesterone, 17-OHP-4 and Testosterone

Serum progesterone decreased by about 50% in the orchiectomized patients (Fig. 2). A similar drop was attained gradually in the buserelin-treated patients during the first weeks of therapy; thereafter, the levels of the two groups did not differ significantly. Orchiectomy had no effect on progesterone levels in the buserelin-treated patients.

The pretreatment levels of 17-OHP-4 differed ($P< 0.05$) in the orchiectomy and buserelin treatment groups, probably due to the small number of subjects. A 75% drop of 17-OHP-4 occurred after orchiectomy (Fig. 2). The buserelin-treated patients showed a rapid 2-fold increase in 17-OHP-4 levels during the first treatment day ($P<0.01$), but did not differ from the castrates after day 6. Orchiectomy had no effect.

Serum T showed an initial peak of about 50% during the first week of buserelin treatment ($P < 0.05$ to 0.01), and thereafter the levels decreased sharply to the castrate range by week 3 (Fig. 2). When the last 3 months of treatment were compared with the post-castration period (Fig. 2, inset), the serum T concentrations did not differ, although they varied somewhat during peptide treatment.

SHBG and Serum Free Testosterone

Relatively small variation was seen in SHBG levels

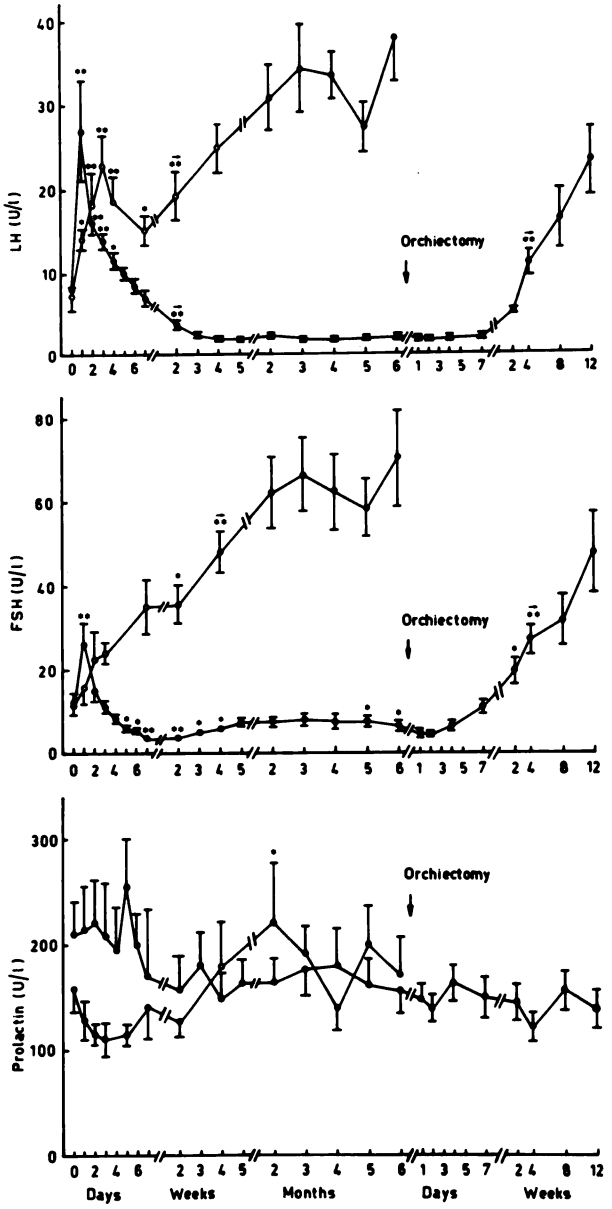

Fig. 1. Serum LH, FSH and PRL in eight prostatic cancer patients during buserelin treatment (●—●) and six patients orchiectomized as the first therapeutic measure (○—○). The 0-levels are calculated from means of 2 to 3 pretreatment measurements. The time of orchiectomy after the 6-month treatment with buserelin is indicated, and the serum hormone levels were followed up to 12 weeks thereafter. Each point is the mean ± SE. The asterisks above the data points of the buserelin-treated patients indicate significant differences from the 0-day levels, or after orchiectomy from the level measured on day 1 after surgery. The asterisks above data points of the control patients refer to differences from the 0-day level of this group. For the sake of clarity, some other statistical comparisons are only presented in the text (see Results). $^*P<0.05$; $^{**}P<0.01$ (Duncan's test); →, the same *P*-value beyond this point.

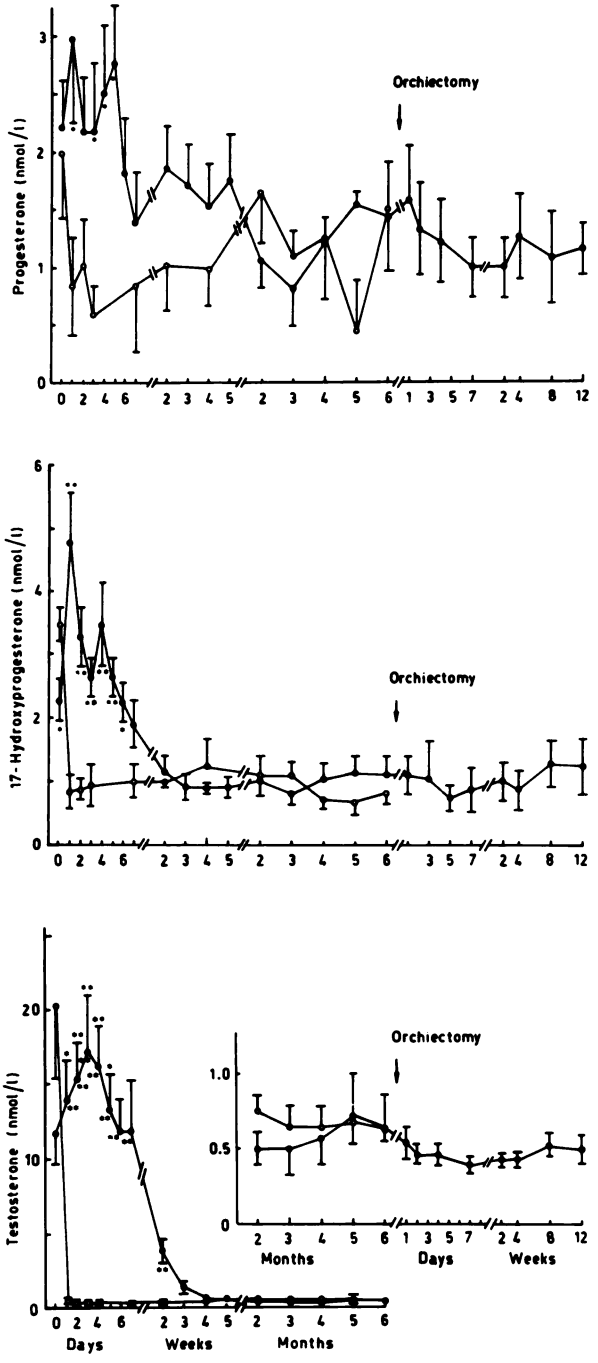

Fig. 2. Serum progesterone, 17-OHP-4 and T in the buserelin-treated (●—●) and orchiectomized control (○—○) patients. The insert in the testosterone panel represents magnification of the y-axis between month 2 of treatment and week 12 after castration of the buserelin patients. The asterisks *above* the data points indicate significantly increased levels compared with the 0-day level, those *below* the points indicate significant differences between this level and that measured in the castrated controls on the same day. For further details, see the legend of Fig. 1.

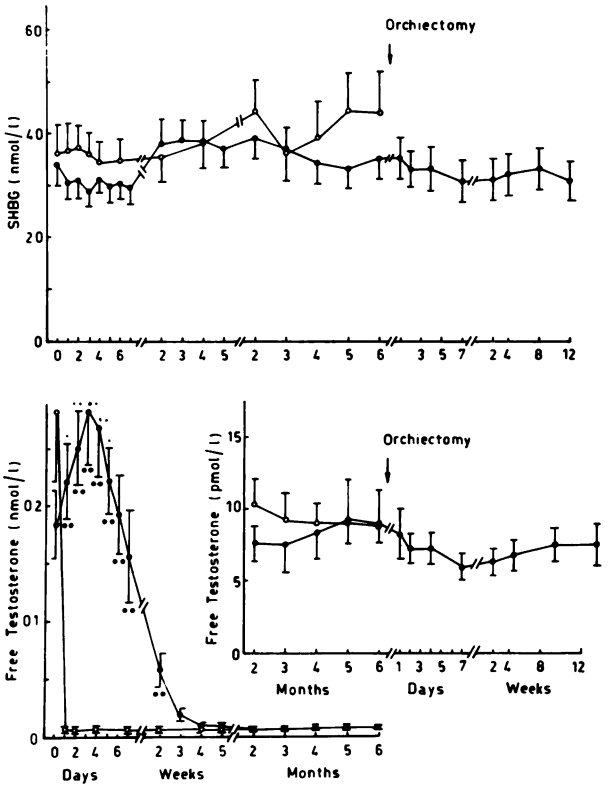

Fig. 3. SHBG and free T levels of the buserelin-treated (●—●) and orchiectomized (○—○) control patients. The y-axis of the free T levels is magnified in the inset. The meaning of the asterisks is the same as in Fig. 2. For further details, see the legend of Fig. 1.

during the agonist therapy or after orchiectomy (Fig. 3). However, the mean day 1 to 6 level of the buserelin-treated patients was significantly ($P < 0.01$) lower than baseline. Similarly, a significant increase in SHBG levels ($P < 0.01$) occurred from day 1 to 6 when compared with the mean during weeks 2 to 5 of treatment. The levels decreased somewhat with advancing time of treatment, but orchiectomy, either in the control or buserelin-treated patients, had no obvious effect on serum SHBG.

The response of serum free T to the treatments was essentially identical to that of total T levels (Fig. 3). The buserelin-treated patients displayed castrate levels of free T from week 3 of treatment onwards, and orchiectomy after 6-month buserelin treatment had no effect.

Hormone Responses to Acute Buserelin Stimulation

The 8-hour responses of LH and FSH to the i.m. injection of buserelin are shown in Fig. 4. Only the

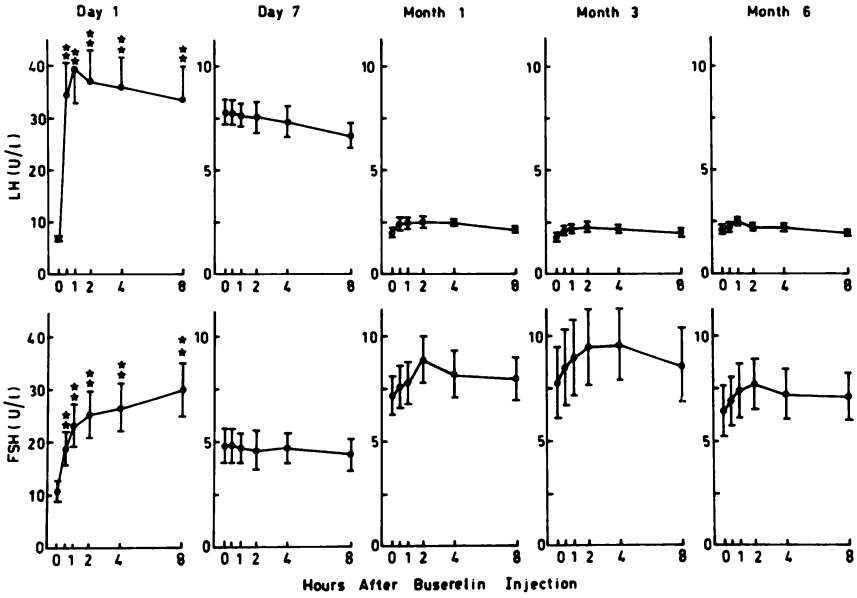

Fig. 4. Acute (0 to 8 hours) responses of LH and FSH to an i.m. injection of 500 μg buserelin on days 1 (first dose of buserelin) and 7, and months 1, 3 and 6 of therapy. The injection was given in each case at 0800 hours. Each point is the mean ± SE of measurements from eight patients. The asterisks indicate significant elevations of the concentrations in relation to the 0-hour level (*$P < 0.05$; **$P < 0.01$). Note that scales of the y-axis change between the different times of treatment.

first injection of the peptide resulted in significant increases of either hormone ($P < 0.01$). No response was seen on day 7 of treatment or thereafter. The slight increase in FSH and LH levels, especially in stimulation tests performed during months 1 and 3, did not reach statistical significance.

A similar result was observed with the steroid levels (Fig. 5): T and 17-OHP-4 showed a clear response after the first dose of buserelin ($P < 0.05$), but no response thereafter. Progesterone showed no response even after the first injection.

Discussion

The therapeutic value of GnRH agonist treatment as an alternative to surgical orchiectomy or estrogen in hormone-dependent forms of prostatic carcinoma is now well established (The Leuprolide Study Group, 1984; Labrie et al, 1984; Huhtaniemi et al, 1985; Parmer et al, 1985). The present study was designed to examine in more detail the endocrine effects of this treatment. Circulating hormone levels after agonist treatment were first related to those obtained after surgical castration, and second to those in the same patients subsequent to surgical castration, immediately following a 6-month period of buserelin treatment.

The decreases in immunoreactive LH and FSH during buserelin treatment and the loss of the acute positive response to GnRH agonist within a week agree well with previous observations (Faure et al, 1982; Ahmed et al, 1983; Walker et al, 1983; Warner et al, 1983; Wenderoth and Jacobi, 1983). Slight acute responses of the gonadotropins were observed later, but did not reach statistical significance. The bioactive fraction of LH has been shown by others to decrease even more dramatically (Warner et al, 1983; Evans et al, 1984), in agreement with the pronounced drop of T. We observed a transient secondary increase in FSH immunoreactivity during the treatment. This has also been demonstrated by others (Santen et al, 1984), and could be due to changes in the proportion of the FSH release inhibiting and stimulating dimers of inhibin (Ling et al, 1986; Vale et al, 1986) during the peptide treatment. It could also be due to the persistence of effects of a putative FSH releasing factor, the existence of which has recently been supported by the discovery of a hypothalamic GnRH-associated peptide (GAP) (Nikolics et al, 1985; Millar et al, 1986). Describing the biologic activity of circulating FSH during GnRH agonist treatment would be of great interest for further understanding the regulation of this hormone.

Two points in the comparison of the postcastration increases of gonadotropins in the primarily orchiectomized and buserelin-treated patients are of

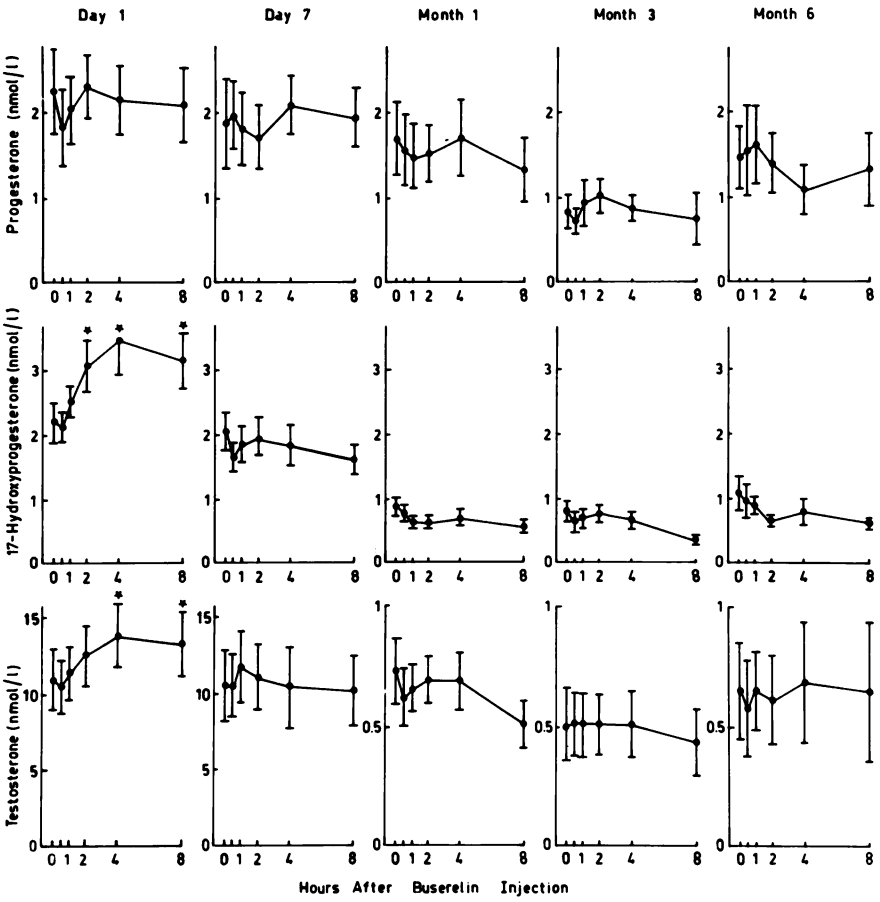

Fig. 5. Acute (0 to 8 hours) responses of progesterone, 17-OHP-4 and T to a 500-μg i.m. injection of buserelin. For further details, see the legend of Fig. 4. Note that the scales of the y-axis change between the different times of treatment.

special interest: 1) the LH response was clearly slower in the buserelin group, and 2) the FSH responses in the two groups were remarkably similar. Continuous GnRH agonist treatment reduces pituitary LH synthesis and storage and results in a state of pituitary desensitization (Sandow, 1982). In humans, the state of desensitization seems to persist for 2 weeks after the present treatment mode. This finding has a clinical implication: once pituitary desensitization is reached, it persists and is not subject to immediate recovery, such as after occasionally missed doses of buserelin.

No clear evidence was obtained for desensitization of FSH by the GnRH agonist treatment. Although the doubling times of the FSH levels after orchiectomy were 6 versus 3 days in the buserelin and control groups, the first significant elevation was reached at the same time (2 weeks) in both groups. This may indicate that FSH synthesis and/or release are less closely dependent on GnRH than that of LH.

T dropped immediately in the surgically castrated patients to less than 5% of the pretreatment level, while progesterone and 17-OHP-4 decreased by 50 to 70%. The levels of the latter two steroids were statistically indistinguishable from the postcastration levels in the buserelin-treated patients after the first week of treatment. However, it took 3 weeks for T levels to reach the castrate range. Previous animal studies (Belanger et al, 1980; Sandow et al, 1985) and also some observations in prostatic cancer patients (Labrie et al, 1980; Linde et al, 1981; Faure et al, 1982) have suggested that blockade of 17-hydroxylase and C_{17-20} desmolase are the main mechanisms of decreased androgen production during GnRH agonist treatment. In such a case, T levels drop rapidly in the face of persistent or elevated levels of progesterone and 17-OHP-4. Our present data are at variance with these findings, since the levels of T were maintained longer than those of the two C_{21} steroids. This means that the blockade with possible build-up of proximal precursors must be prior to formation of progesterone and 17-OHP-4. A difference from the steroidogenic lesion induced by high LH/hCG levels or acute GnRH agonist stimulation (Cigorraga et al, 1978; Catt et al, 1980; Labrie et al, 1980; Hsueh and Jones, 1981) is also evident since the decrease of T is

paralleled by decreased, and not by increased, gonadotropin levels. Moreover, direct actions of GnRH agonists in the human testis are unlikely (Clayton and Huhtaniemi, 1982). The drop of T production is therefore similar to changes observed in the testis in the hypogonadotropic state, ie, after hypophysectomy (Woods and Simpson, 1961; Menon et al, 1965; Steinberger, 1976), where decreased cholesterol side chain cleavage activity is the most conspicuous steroidogenic change.

It was important to note that the levels of the three steroids were indistinguishable from postcastration levels after 1 to 3 weeks of treatment, and that orchiectomy of the peptide-treated patients did not affect these levels. This indicates complete cessation of testicular formation of these steroids during the treatment. However, when measurements were made directly from testis tissue, and with a larger number of precursor steroids (Huhtaniemi et al, 1987), the blockade of steroidogenesis did not appear as complete.

SHBG levels were slightly decreased in the beginning of buserelin treatment, which is in keeping with the simultaneous increase in T levels. Accordingly, when the T levels decreased after the second week of treatment, a slight but significant increase was seen in SHBG. Orchiectomy, either primary or secondary to buserelin treatment, had no effect on these levels. Free serum T, calculated from the total T and SHBG levels, behaved very similarly to total T, in keeping with the minor changes of SHBG during the treatments.

From the clinical point of view, the present data bring further information about the timing and extent of blockade of pituitary gonadotropin and testicular steroid release during chronic treatment with GnRH agonist. In particular, comparative data are provided on circulating hormone levels in the peptide-treated and surgically orchiectomized control patients, as well as on the effects of surgical orchiectomy on hormone levels in patients originally treated with the peptide. The data indicate that no T of testicular origin can be detected in the circulation during buserelin treatment. Orchiectomy of the peptide-treated patients indicates that the desensitization of the pituitary lasts 2 to 3 weeks before the castration-associated increase in gonadotropin secretion ensues, and clear differences seem to prevail in the regulation of LH and FSH secretion by this releasing hormone.

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The Second International Symposium on Reproductive Medicine

The Second International Symposium on Reproductive Medicine will be held in Fiuggi, Italy, October 6–8, 1988. The theme of the Symposium will be nonsurgical therapy of reproductive system disorders including infertility. A group of international authorities in the field will participate in the various sessions and round tables. Brief communications will also be considered for presentation. For further information contact in Europe: Prof. G. Frajese, member of the Steering Committee, Via Di Porta Pinciana 4, 001387 Rome, Italy. In the United States contact: Dr. E. Steinberger, Texas Institute for Reproductive Medicine and Endocrinology, 7800 Fannin, Suite 500, Houston, Texas 77054.

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