Rat Prostatic Weight Regression in Reaction to Ketoconazole, Cyproterone Acetate, and RU 23908 as Adjuncts to a Depot Formulation of Gonadotropin-releasing Hormone Analogue

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ABSTRACT

The effects of the s.c. administration of a depot formulation of the luteinizing hormone-releasing hormone (LHRH) analogue Zoladex were studied in normal male rats, alone and in combination with three drugs with "antiandrogenic" action (ketoconazole, cyproterone acetate, and RU 23908) on prostatic weight and on circulating hormone levels in order to investigate whether these antiandrogens might prevent the LHRH-A-induced initial increase in these parameters. These effects were compared with those caused by surgical castration. In addition the effects of the antiandrogens on the activity of the hypothalamic-pituitary-adrenal axis were investigated.

The depot LHRH analogue caused an initial increase in ventral prostatic weight after 4 days but suppressed the prostatic and testicular weights, the pituitary luteinizing hormone (LH) content, and plasma LH and testosterone levels after 10 and 17 days. All three antiandrogenic drugs used prevented the initial LHRH analogue-induced rise in prostatic weight, while RU 23908 suppressed its weight after only 4 days. After 10 and 17 days cyproterone acetate and RU 23908 had a similar significantly greater suppressive effect on prostatic and testicular weights than the LHRH analogue alone, while the additive inhibitory effect of ketoconazole was smaller. Surgical castration suppressed prostatic weight significantly more after 4 days, while its effects after 10 and 17 days were similar to that exerted by the combination of LHRH-A and RU 23908.

The antigonadotropic effect of cyproterone acetate and the indirect gonadotropin-stimulating effects of ketoconazole and RU 23908 were not recognized in rats simultaneously treated with the LHRH analogue and did not interfere with the LHRH analogue-induced rapid depletion of the pituitary LH content and the decrease in circulating LH and testosterone levels.

The LHRH analogue stimulated circulating progesterone and suppressed 17-hydroxyprogesterone levels. Ketoconazole and cyproterone acetate caused disorders in the pituitary-adrenal axis via different mechanisms: ketoconazole caused adrenal hypertrophy with normal circulating corticosterone levels caused by a compensatory increase in ACTH secretion; while cyproterone acetate exerted glucocorticoid-like effects causing a depletion of the pituitary adrenocorticotrophic hormone content, adrenal atrophy, and lowered corticosterone levels. The addition of RU 23908 did not change the LHRH agonist-induced changes in adrenocortical activity. The adrenal effects probably were the cause of a significant delay in body growth in the ketoconazole- and cyproterone-treated rats, in comparison with those treated with the LHRH analogue alone or in combination with RU 23908.

This study shows that: (a) the Zoladex depot formulation causes a transient increase in gonadotropin secretion but results in a suppression of circulating LH and testosterone levels after 10–17 days; (b) addition of ketoconazole, cyproterone acetate, or RU 23908 prevents the initial LHRH analogue-induced stimulation of growth of the ventral prostate; (c) both ketoconazole and cyproterone acetate affect pituitary-adrenocortical function via different mechanisms; and (d) the peripherally acting antiandrogen RU 23908, together with the LHRH analogue, causes after 10 and 17 days the same "maximal" decrease of the prostatic weight as surgical castration without compromising the pituitary-adrenal axis.

INTRODUCTION

LHRH₂ agonists initially stimulate pituitary gonadotropin secretion resulting in an enhanced testosterone secretion, which is eventually followed by a depletion of pituitary LH stores and desensitization of LHRH receptors in the pituitary gland and of LH receptors in the gonads, and "medical" castration (1–4). For these reasons treatment with LHRH-A results in inhibition of the growth of gonadal steroid-dependent tumors in humans and animals (5–9). Several problems remain, however, with regard to LHRH analogue treatment of male prostatic cancer patients: (a) the initial LHRH-induced increase in testosterone secretion has been shown to cause a "flare-up" of the disease in some patients (10, 11); (b) despite adequate suppression of testicular testosterone production during long-term LHRH analogue treatment, the remaining androgen production from the adrenal cortex may play a role causing tumor progression in some of these patients (12, 13), while most "antiandrogenic" drugs used to suppress this androgen production cause other potential harmful effects on the hypothalamic-pituitary-adrenal axis in humans (14–17). All three problems cannot be investigated properly in the model of the rat because the adrenal gland of this species does not produce androgens. An initial LHRH-A-induced increase in prostatic weight and the effects of different antiandrogentic compounds on the activity of the hypothalamic-pituitary-adrenal axis in the rat might well be extrapolated to the human situation, however.

In the present study we evaluated the effects of the use of a long-acting depot formulation of the LHRH agonist Zoladex alone and in combination with three differently acting "antiandrogenic" drugs (ketoconazole, cyproterone acetate, and RU 23908) in normal male rats on organ weights, circulating and pituitary LH levels, circulating and pituitary ACTH concentrations, and circulating progesterone and 17-hydroxyprogesterone, testosterone, and corticosterone levels. The effects of these different combinations of these drugs were compared with the effects of surgical castration.

MATERIALS AND METHODS

Animals. Young adult Wistar rats, weighing 200–220 g, were housed in a light (14 h/day, lights on at 6 a.m.) and temperature-controlled (22°C) environment. They received Purina rat chow and water ad libitum.

Treatments. A group of 18 animals received a single s.c. injection of 0.9 mg of the depot formulation of the LHRH analogue. Zoladex [D(-)-Ser(Bu⁴)AZGly⁵)LHRH, ICI, Rotterdam, The Netherlands], in which the LHRH analogue is dispersed throughout a matrix of DL-polymer lactide-glycolide copolymer (18). In addition 3 groups of 18 animals were given injections of 0.9 mg of this LHRH analogue and also received daily i.p. injections of 10 mg/rat ketoconazole (Janssen, 2 The abbreviations used are: LHRH, luteinizing hormone-releasing hormone; LHRH-A, LHRH analogue; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone.

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Beersse, Belgium), 20 mg/rat cyproterone acetate (Schering, Berlin, Federal Republic of Germany), or 5 mg/rat RU 23908 (Roussel, Paris, France). In addition a control group of 18 rats and a group of 24 rats which had been castrated on day 0 received daily placebo injections. The 3 latter drugs were injected in 0.5 ml 1% gelatin (0.9% NaCl). On the morning of the last day of treatment, all animals were sacrificed by decapitation 30–60 min after the last injection. The organs were rapidly removed, deposited on ice, and weighed. Trunk blood was collected for plasma hormone determination (see below). The pituitary glands were homogenized in 0.1 N HCl for determination of the LH and ACTH contents.

Groups of 36 rats (6 rats of each of the treatment groups) were decapitated after 4, 10, and 17 days of treatment. From the first group which was killed on day 4, additional tail blood was collected on day 2.

The dosages of the antiandrogenic compounds used in this study were chosen on the basis of data published in the literature. The dose of 10 mg/rat of ketoconazole i.p. (40 mg/kg/day) was chosen on the basis of studies by English et al. (19) and Trachtenberg et al. (20) who showed a maximal inhibitory effect on testosterone levels with 20 mg/kg twice daily s.c. and 10 mg/kg once daily i.p., respectively. The dose of 20 mg/rat cyproterone acetate (80 mg/kg/day) is maximal with regard to its antiandrogenic effect as shown in several studies reviewed by Neumann (16). The dose of 5 mg/rat RU 23908 (20 mg/kg/day) was chosen on the basis of studies by Moguliewsky et al. (21) who showed that this is the maximal antiandrogenic dose in normal male rats.

Hormone Determinations. Rat LH in the plasma and pituitary extracts was measured by a double antibody radioimmunoassay using National Institute of Arthritis and Metabolic Disease rat LH 1-1 for iodination and National Institute of Arthritis and Metabolic Disease rat LH RP-1 as standard. The antiserum was obtained by immunization of rabbits with NIH-LH S 17, as described previously (22). The intraassay variation was 16.3%, while the interassay variation mounted to 10.8%.

ACTH was measured by direct radioimmunoassay in unextracted plasma and in pituitary homogenates using a commercial kit supplied by Byk-Mallinckrodt (Dietzenbach, Federal Republic of Germany). The intraassay variability of plasma ACTH determinations was 12%, and of that of pituitary extracts was 6.8%. All samples were measured in duplicate within the same assay.

Plasma testosterone was estimated as described by Verjans et al. (23), and corticosterone was measured by radioimmunoassay in ethyl acetate extracts of the plasma, using the antiserum described by van Zon et al. (24). This antiserum was a gift from Dr. T. Benraad, Nijmegen, The Netherlands. The intraassay variations for the testosterone and corticosterone assays were 8.1 and 5.0% and the interassay variations were 11.8 and 9.3%, respectively. Plasma progesterone and 17-hydroxyprogesterone concentrations were also measured by radioimmunoassay, using the procedures described earlier (25). The antisera used were raised in the department of Biochemistry, Division of Chemical Endocrinology, Erasmus University (Rotterdam, The Netherlands), and their specificity was described earlier (25, 26). Intraassay variations for the progesterone and 17-hydroxyprogesterone assays were 11.2 and 12.7%, respectively, while the interassay variations were 13.7 and 11.8%, respectively.

Statistics. All results have been expressed as means ± SEM. Statistical evaluation was performed by analysis of variance.

RESULTS

Administration of the depot formulation of the LHRH agonist Zoladex s.c. resulted in a statistically significant increase of the weight of the ventral phosphate after 4 days (+27%; P < 0.01 versus control), which reversed to a decrease of 44% after both 10 and 17 days (P < 0.01 versus control in both instances; Fig. 1). Simultaneous administration of the agonist and ketoconazole, cyproterone acetate, or RU 23908 in all instances prevented the initial LHRH agonist-induced increase in the ventral prostatic weight after 4 days. Combined administration of the LHRH agonist with RU 23908 significantly reduced prostate weight after 4 days (P < 0.01 versus control and versus LHRH-A alone). The combined administration of the LHRH agonist and ketoconazole resulted after 17 days in a further decrease of the prostatic weight than after LHRH-A alone (P < 0.01), while both cyproterone acetate and RU 23908 had already caused a larger decrease of the weight of the prostate in comparison with that caused by the LHRH agonist alone (P < 0.01 in both instances). After 17 days the combination of cyproterone acetate or RU 23908 with the LHRH agonist caused no further reduction of the prostatic weight. At 10 and 17 days the prostatic weight was significantly lower in the LHRH-A plus cyproterone acetate and RU 23908-treated rats than in the animals treated with the combination of LHRH-A and ketoconazole (P < 0.05 in both instances). Actual weights of the anterior prostate at the end of the 17-day experiment are shown in Fig. 2. Four days after surgical castration the weight of the ventral prostate had already decreased by 49% (P < 0.01 versus control), which was a greater decrease than that observed by treatment with LHRH-A plus RU 23908 (P < 0.01). At days 10 and 17, however, the effects of surgical castration and the treatment with LHRH-A plus RU 23908 were similar but in all instances more inhibitory than that exerted by LHRH-A with or without ketoconazole and/or cyproterone acetate (P < 0.01 in all instances).

Changes of testicular weight differed from those of the prostatic weight in that no initial increase was noticed after a 4-day exposure to the LHRH agonist (Fig. 3). A significant decrease of the testicular weight (P < 0.01) was observed 10 days after the administration of the depot formulation of the LHRH analogue, while there was a further decrease after 17 days of the analogue (P < 0.05). Combined administration of the analogue with ketoconazole initially did not further decrease testicular weight, but it enhanced the effect of the LHRH analogue after 17 days significantly (P < 0.05). Combined administration of the analogue with both cyproterone acetate and RU 23908 suppressed testicular weight after 4 days (P < 0.05 versus control in both instances), while both combinations similarly further suppressed testicular weights after both 10 and 17 days in comparison with those measured after the LHRH analogue alone or after the combination of LHRH-A and ketoconazole (in all cases P < 0.01 versus LHRH-A alone or in combination with ketoconazole). The actual weight of the testes at the end of the 17-day experiment are shown in Fig. 2.

LHRH agonist administration resulted after 17 days in a
significant decrease of the anterior pituitary weight of the animals (P < 0.01), which was prevented by the simultaneous administration of ketoconazole, cyproterone acetate, and RU 23908 (Fig. 2). LHRH agonist administration did not affect the adrenal weight. The combination of the analogue with ketoconazole significantly increased and the combination with cyproterone acetate significantly decreased adrenal weights, however (Fig. 2).

During the 17-day experiment control rats gained 59 ± 5 g while the weights of the LHRH agonist-treated animals increased by 48 ± 9 g (P not significant), and that of the surgically castrated rats increased by 42 ± 8 g (P not significant). The LHRH agonist plus ketoconazole- and the LHRH agonist plus cyproterone acetate-treated rats gained only 15 ± 9 and 8 ± 7 g, respectively (in both instances P < 0.01 versus LHRH-A alone). After the combination of the agonist and RU 23908 the weight gain was 37 ± 6 g, which is not significantly different from the results in control and LHRH agonist-treated rats.

Plasma LH concentrations were highly stimulated on day 2 after the injection of the depot preparation of the LHRH agonist (P < 0.01 versus control). This increase was not significantly affected by the simultaneous administration of the three antiandrogenic drugs and was similar to that observed after surgical castration (Table 1). After 4 and 10 days the stimulatory effect of the agonist on LH secretion was no longer evident, while after 17 days circulating LH levels were significantly suppressed to a similar extent in the LHRH analogue and the three LHRH analogue plus ketoconazole-, cyproterone acetate-, and RU 23908-treated groups of rats (P < 0.05 versus control). After the combination of the agonist and RU 23908 the weight gain was 37 ± 6 g, which is not significantly different from the results in control and LHRH agonist-treated rats.
control in all instances). In contrast LH levels remained elevated after surgical castration. The pituitary content of LH was already significantly depleted on day 4 after LHRH agonist administration but was not affected by simultaneous administration of any of the three antiandrogenic drugs (Table 1). During further exposure to the LHRH analogue a further nonsignificant decrease of the LH content of the pituitary gland was noted on day 17, which again was not affected by the simultaneous administration of ketoconazole, cyproterone acetate, or RU 23908. The LH content of the pituitary gland of surgically castrated rats remained unchanged (days 4 and 10) or increased (after 17 days) in the presence of greatly increased circulating LH levels (Table 1).

Plasma testosterone concentrations had become undetectable in surgically castrated animals from 2 days onward. They were not affected yet by medical treatment on days 2 and 4 but were significantly suppressed on day 10 (*P < 0.01 versus control) and even further on day 17 (*P < 0.01 versus levels on day 10). Again the combination of the LHRH analogue with any of the three drugs mentioned above did not cause further suppressed testosterone levels, in comparison with the results after administration of the LHRH analogue alone (Table 1). Finally, the effect of the LHRH analogue alone or in combination with ketoconazole, cyproterone acetate, or RU 23908 was measured on the plasma concentrations and the pituitary content of ACTH and on the circulating corticosterone, progesterone, and 17-hydroxyprogesterone levels (Table 2). The combination of the LHRH analogue with ketoconazole resulted in higher circulating ACTH levels (*P < 0.05 versus control), without affecting the pituitary ACTH content and the corticosterone levels. Cyproterone acetate, however, significantly suppressed the ACTH content of the pituitary gland (*P < 0.05 versus control) and the corticosterone levels (*P < 0.01 versus control), without affecting plasma ACTH concentrations.

The administration of the LHRH analogue resulted after 17 days in a significant increase in progesterone (*P < 0.05 versus control) and a significant decrease in 17-hydroxyprogesterone levels (*P < 0.05 versus control; Table 2). The combined administration of the LHRH agonist with RU 23908 did not change these LHRH agonist-induced changes. Ketoconazole and cyproterone acetate, however, prevented both the LHRH agonist-induced increase in progesterone (*P < 0.05 versus LHRH-A alone in both instances), while cyproterone acetate prevented the LHRH agonist-induced decrease in 17-hydroxyprogesterone (*P < 0.05 versus LHRH agonist). The cyproterone acetate-mediated changes in the circulating progesterone and 17-hydroxyprogesterone levels, however, are probably influenced by the fact that cyproterone acetate cross-reacted in the radioimmunoassay of these two hormones, especially 17-hydroxyprogesterone. Cyproterone acetate and the other drugs used did not cause cross-reactivity in any of the other radioimmunoassays used in this study.

**DISCUSSION**

In the present study we evaluated whether a potential drawback of the treatment of men with metastatic prostatic cancer with LHRH analogues (an initial flare-up of the disease) might be prevented by the use of a depot formulation of a LHRH analogue (Zoladex) alone or in combination with a drug which either may suppress androgen production further (ketoconazole) or has antiandrogenic properties at the androgen receptor level (cyproterone acetate, RU 23908). These effects were compared with that of surgical castration. In addition we evaluated the effect of these three antiandrogenic compounds on the pituitary-adrenal axis.

The depot formulation in which the LHRH analogue Zoladex is dispersed slowly degrades after s.c. injection and the analogue is continuously released into the systemic circulation for 21–28 days. Previous studies involving twice daily administration of LHRH agonists in rats for several weeks showed incomplete inhibition of testicular androgen production in most studies (27, 28), resulting in regression of the ventral prostate to a lesser degree as reached after castration (28). Most injections of LHRH analogues even after 15–28 days of administration stimulated circulating LH and follicle-stimulating hormone levels (7, 27–29), in some instances by an ensuing pulse of testosterone (19). The hypothalamic-pituitary-testicular axis of rats seems less sensitive to the inhibitory effects of LHRH analogues than that of humans. Most reports regarding a lack of LH and testosterone suppression in men seem to reflect different doses and routes of administration of the analogues which resulted in insufficient absorption or circulating levels too low to achieve a therapeutic effect (30, 31). After implantation of the depot formulation of Zoladex in normal male rats, we observed only a transient stimulation of LH secretion on day 2. No stimulation was observed after 4 and 10 days, while plasma LH concentrations were significantly suppressed after 17 days. Testosterone levels remained unchanged on days 2 and 4 and were suppressed on days 10 and 17 after the injection of the depot LHRH analogue. In other studies it was shown that the effect of the Zoladex depot preparation in rat lingers after 21–28 days (32). Our data in the rat point to a considerable advantage of the use of such a long-acting depot formulation over chronic twice daily s.c. administration of the LHRH analogue. However, the early effects of surgical castration still remain more profound.

Ketoconazole is an antifungal imidazole derivative which has been shown to inhibit androgen production via an inhibition of 17,20-lyase activity in the testis and the adrenal cortex, while...
at higher concentrations it also suppresses glucocorticoid production (14).

Ketoconazole administered in combination with the LHRH agonist was shown in this and an earlier investigation (19) to prevent the initial LHRH agonist-induced increase of prostatic weight, while after 17 days of treatment this combination of drugs induced a significantly greater reduction of the testicular and prostatic weights than the LHRH agonist alone. The ketoconazole-induced acute blockade of 17,20-lyase activity and the ensuing blockade in androgen production result in normal toconazole-induced acute blockade of 17,20-lyase activity and prostatic weights than the LHRH agonist alone. The ketoconazole treatment resulted in an increase in the size of the adrenal gland and of the anterior pituitary in comparison with those observed after LHRH agonist administration alone. This points to blocking effects of ketoconazole on enzyme activities in the adrenal gland which is further supported by the increased circulating ACTH levels and the increased pituitary ACTH content. These changes probably reflect the ketoconazole-induced partial inhibition of corticosterone biosynthesis which was compensated for by a rise in ACTH synthesis and release and which indeed resulted in normal circulating corticosterone levels (15). LHRH analogues induce increases in plasma progesterone and decreases in 17-hydroxyprogesterone levels (see Refs. 34 and 35). Ketoconazole prevented the LHRH agonist-induced increase of progesterone secretion, probably via an additional inhibitory effect in the testes or in the adrenal gland at a "high" step in steroidogenesis, presumably the side chain cleavage of cholesterol (14, 36). However, the absence of suppressed corticosterone levels does not support the latter mechanism of action of ketoconazole.

Cyproterone acetate has powerful inhibitory effects on androgen action while it also inhibits gonadotropin release (16). The drug can be classified as a partial agonist/antagonist, because it was shown to have slight androgenic activity in castrated animals (37). In addition it has prostaglandin and glucocorticoid activities (16). In the present study cyproterone acetate was shown to prevent the LHRH-induced initial increase of the prostatic weight, while it significantly further decreased the testicular and prostatic weights after 10 and 17 days. The antigenadotrophic properties of the compound did not help to prevent the LHRH agonist-induced initial marked increase of the plasma LH levels after 2 days, and it also did not increase the speed at which the circulating LH concentrations and the pituitary LH content were suppressed. Cyproterone acetate administration resulted in a significant decrease of the circulating corticosterone levels, of the ACTH content of the pituitary gland, and of the adrenal gland weight, effects probably mediated via the glucocorticoid-like effects of the compound (17, 38). Its discrepant effects on circulating progesterone and 17-hydroxyprogesterone levels are difficult to interpret because of cross-reactivity of the drug in the radioimmunoassays used. We suggest that the decrease in plasma progesterone levels in comparison with the effect of LHRH-A alone might be caused by the glucocorticoid-like suppressive effects of cyproterone acetate on the adrenal gland, while the unexpected high 17-hydroxyprogesterone levels are probably caused by the cross-reactivity of the drug in the radioimmunoassay. The glucocorticoid-like effects of cyproterone acetate have also been observed in humans. They became manifest during high-dose cyproterone acetate therapy of children with precocious puberty, but no signs of adrenal insufficiency have been reported in adult men (17, 39).

Finally the effects of the combination of the LHRH agonist with a "pure" antiandrogen were investigated. In this study we used RU 23908, a compound which is from a pharmacological viewpoint quite similar to other compounds like flutamide (40). Antiandrogens of this type specifically block the action of androgens at all target sites. Blockade of the pituitary androgen receptors interferes with the feedback mechanism which controls testosterone secretion (see Refs. 21 and 41). Consequently these compounds increase testicular androgen production, which in turn counteracts the antiandrogen effect in the peripheral organs like the prostate (41). In the case of RU 23908 the antiandrogenic activity of the compound on the prostate indeed is fully manifest in castrated animals only but is weakened in intact animals by the compensatory increase of testosterone secretion which follows from the interference with the hypothalamic-pituitary-gonadal axis (21, 41).

In the present study it was shown that RU 23908 not only prevented the initial LHRH agonist-induced increase in prostatic weight but even suppressed it after only 4 days. Similar observations were reported previously (21). The combination of the LHRH agonist and RU 23908 caused after 10 and 17 days a similar further decrease in testicular and prostatic weight as observed after the combination with cyproterone acetate. The RU 23908-induced reduction of the feedback of testosterone on pituitary gonadotropin secretion did not interfere with the LHRH agonist-induced early depletion of the pituitary LH content or with the course of plasma LH concentrations. In addition there was no interference observed of RU 23908 with adrenocortical function, neither with regard to adrenal gland weights, plasma and pituitary ACTH, and corticosterone levels nor with regard to the LHRH agonist-induced changes in circulating progesterone and 17-hydroxyprogesterone levels.

In conclusion we showed in this study that the new depot formulation of the LHRH analogue used rapidly induces a decrease in circulating testosterone levels and eventually significantly suppressed LH levels. This contrasts to earlier studies in rats with intermittent LHRH agonist injections in which this goal was not reached. In parallel recent studies in humans also showed this long-term (21–28 days) effectivity of the depot Zoladex preparation without the often described tendency of the gonadotropins or of testosterone to escape during intermittent (p.o.) administration of LHRH agonists (42). All three "antiandrogenic" compounds used prevented the LHRH agonist-induced initial increase of the prostatic weight. However, there were profound differences in the mechanism of action of the drugs used. It is obvious from our study that the first choice of treatment of metastatic prostatic cancer in humans should be the combination of a LHRH agonist with a "pure" antiandrogen like RU 23908, because this combination not only prevents the initial increase of prostatic weight observed after the administration of the LHRH agonist but also actually decreases the prostatic weight after only 4 days. No interaction of RU 23908 administration with the desensitizing effect of the LHRH-A on pituitary gonadotropins was observed, while no action on the pituitary-adrenocortical axis occurred. The drug was well tolerated as evidenced by the increase in body weight which was similar with that observed after LHRH agonist administration alone.

Our study showed that surgical castration induced a significantly more rapid decrease in the weight of the ventral prostate.
than the combination of LHRH-A and RU 23908, but this difference had disappeared after 10 and 17 days. No data are available with regard to a longer follow-up. It is possible that after a longer period of time ventral prostate weight would have been identically suppressed with all therapeutic regimens used. A shortcoming of the present study is that the additive inhibitory effects of the three antiandrogenic drugs after 10 and 17 days on the LHRH analogue-induced decrease in the prostatic weight might not pertain to men, inasmuch as in patients a complete suppression of LH and testosterone levels to those observed after surgical castration is more easily reached during LHRH analogue therapy.

A second shortcoming of our study with regard to potential extrapolation to the human situation is the fact that the adrenal gland of the rat does not produce androgens. This is in sharp contrast to the human adrenal gland which produces significant concentrations of androstenedione, testosterone, and also dehydroepiandrosterone and its sulfate (12).

REFERENCES


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