Urol Res (1986) 14:261–264

Urological Research

Effects of a Potent LHRH-Agonist on the Pituitary Gonadal Axis With and Without Testosterone Substitution

J. Frick and W. Aulitzky

Urological Department, General Hospital, Salzburg, Austria

Accepted: April 18, 1986

Summary. In this study we investigated the effect of low and high dosages of a potent LHRH agonist on the pituitary-gonadal axis with special consideration to the effect on the tubular compartment of the testis. Included were 3 treatment groups: the probands in Group I were treated with 3 x 50 μg HOE 766/week intranasally for 5 months; in Group II with 3 x 100 μg HOE 766 intranasally/day for 6 months and in Group III with 3 x 200 μg HOE 766 intranasally plus 5 mg fluoxymesterone orally/day for 5 months. With the low dose (Group I) no changes in the seminal parameters measured could be observed whereas LH and FSH levels increased in plasma, testosterone showed no change compared to preatreatment values. When high dosages/day of a potent LHRH agonist were administered without androgen replacement (Group II) pronounced decrease of LH and FSH took place, the testosterone plasma levels approached the female range. Spermatogenesis was arrested. The agonist plus androgen replacement (Group III) counteracted the suppression of spermatogenesis.

Key words: LHRH agonist, Effect on pituitary-gonadal axis, Different application regimen, With and without testosterone substitution.

LHRH or its potent agonists regulate pituitary function in two different ways: low dosages and regular pulses cause an activation resulting in increasing LH/FSH plasma levels whereas high dosages, frequent pulses and/or constant dose infusion result, in desensitization [2]. This paradoxical effect of LHRH agonists was suggested for the development of new methods of fertility control [6, 8, 9, 17]. It is well documented that the chronic administration of potent LHRH agonists exert degenerative effects on testicular function in different animal models [7, 15, 16, 20] acting by down-regulation of the pituitary and testicular receptors [1] or by a direct action on the Leydig cells [6, 18]. Preliminary clinical trials have been performed [3, 8, 9, 11–14, 19] with variable results but if testosterone substitution were counterproductive it might therefore sustain spermatogenesis.

The aim of this study was to investigate the effects i) of low and high dosages of a potent LHRH agonist on the pituitary gonadal axis with special consideration of the tubular compartment of the testis and ii) with and without androgen replacement. The data obtained might produce some insight into the hormone interaction between the pituitary and its target organs.

Material and Methods

D-Ser-(TBu)^6-LHRH-ethylamide (HOE 766) as nasal spray was administered as agonist and in one group of probands Fluoxymesterone was administered as an androgen replacement.

The probands were divided in 3 groups

Group I: 6 men, aged 21–41 years, were treated with 3 x 50 μg HOE 766/week intranasally for 5 months.

Group II: 4 men, aged 34–44 years, were treated with 3 x 100 μg HOE 766 intranasally/day for 6 months.

Group III: 4 men, aged 26–50 years, administered 3 x 200 μg HOE-766 intranasally plus 5 mg Fluoxymesterone orally/day for 5 months.

Before initiation of therapy and every 4 weeks during treatment and posttreatment the following examinations were carried out: 1. Clinical check. 2. Plasma hormones for LH, FSH, testosterone (T), E_2 and prolactin. 3. Semen analysis. 4. In a few probands SMA 12. The hormone determinations were performed as published previously [5], the semen analyses were carried out according to the requirements of Eliasson [4].

All probands were instructed to have sexual abstinence (five days) prior to each visit. It was planned to maintain the treatment for at least 5–6 months. The assessment of libido and potency was based on the subjective report of the probands.

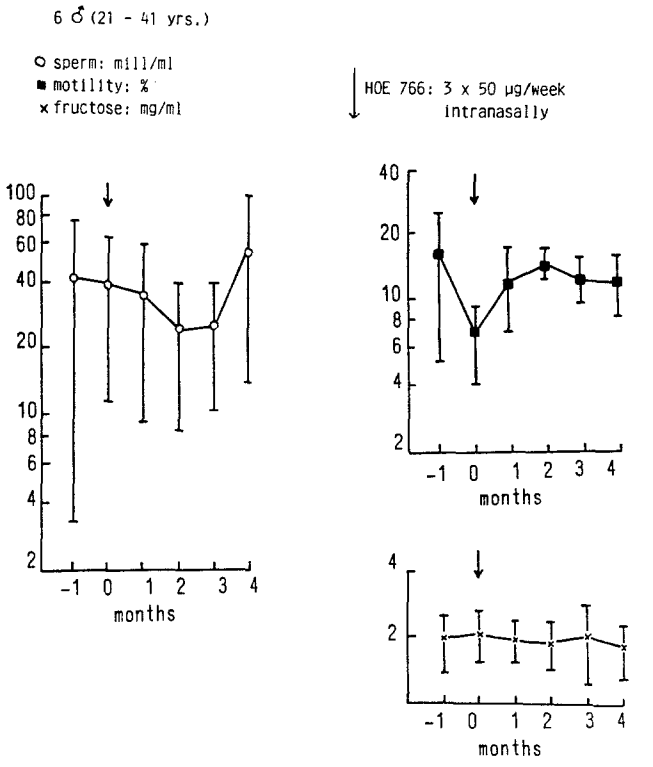

Fig. 1. Means ± SD for sperm density, progressive motility and seminal plasma fructose content in 6 men, aged 21–41, before and during treatment with HOE 766 intranasally 3 x 50 µg/week (Group I)

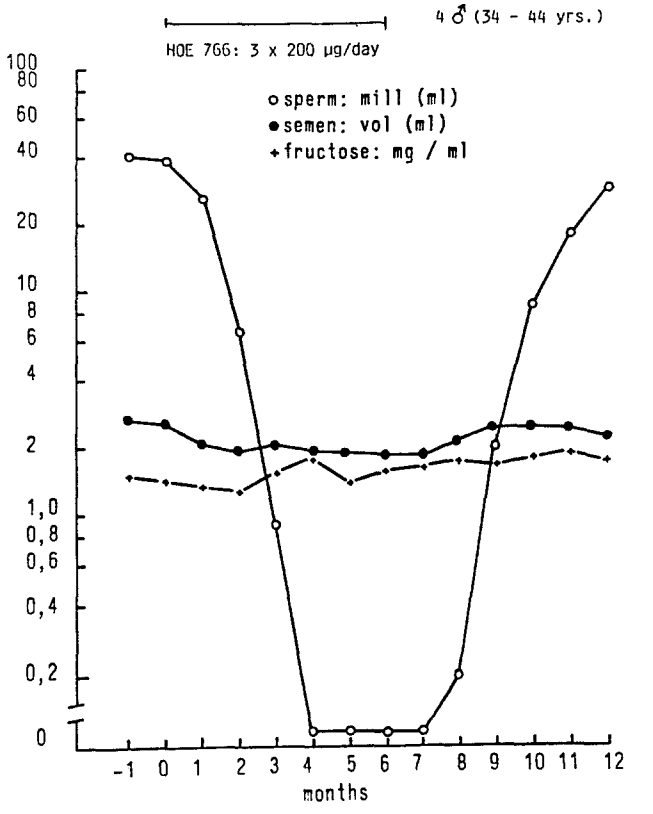

Fig. 2. Mean values of sperm density, semen volume and seminal plasma fructose from 4 subjects of treatment Group II during the whole observation period

Results

Effect on the Tubular Compartment of Testis

Group I: The data for sperm densitiy, progressive motility and seminal plasma fructose content are shown in Fig. 1. In none of the measured parameters a significant change was found when comparing pre- and posttreatment values.

Group II: As demonstrated on Fig. 2 the treatment period (3 x 100 µg HOE 766/day) lasted for 6 months, the probands became virtually azoospermic around the 4th month of treatment, two months after cessation of therapy the recovery of spermatogenesis began gradually and by the 6th month sperm densitiy was approaching pretreatment levels. Semen volume and seminal plasma fructose content showed no changes throughout the observation period.

Group III: Figure 3 shows the seminal parameters of 4 probands treated with the combination of HOE 766 (3 x 200 µg HOE 766/day) and Fluoxymesterone (5 mg/day) for 5 months. None of the measured parameters (sperm densitiy, volume, fructose content) showed marked changes throughout the observation period.

Plasma Hormone Levels

In Group I (Fig. 4) there was a marked increase in LH and a moderate increase in FSH secretion during the treatment period whereas prolactin, E_2 and T-levels little changes.

The endocrine profiles in Group II (Fig. 5) gave clear evidence of a down regulation during the treatment phase as LH, FSH and T-values decreased far below the low normal range; following cessation of therapy there was a restoration of the hormonal parameters to pretreatment values within 6 months E_2 and prolactin levels were not influenced by the therapy.

In Group III (Fig. 6) the down regulatory effect of the drug combination was much less pronounced compared to Group II. LH, FSH and T remained above the lower limit of normal range. The prolactin values showed a moderate increase throughout the observation period.

Clinical Pharmacology

SMA 12 and urine analyses were performed for all subjects at monthly intervals during treatment and during the recovery phase. For all parameters, values remained within normal range.

Clinical Findings and Side Effects

Blood pressure and testicle size were measured monthly in each subject during treatment and recovery. Neither parameter showed any pronounced increase or decrease. Regular palpation of the prostate revealed no abnormalities. The probands in Group II, however, complained of marked de-

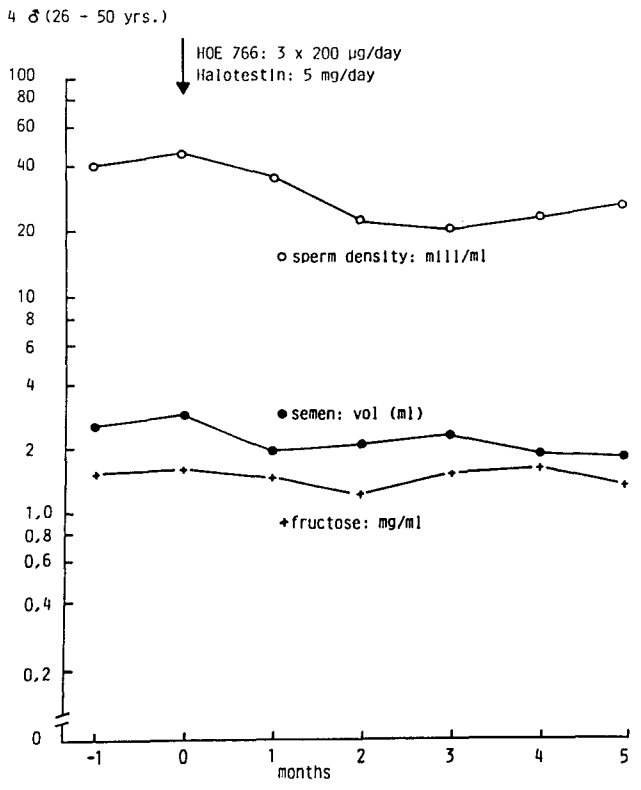

Fig. 3. Mean values of sperm density, semen volume and seminal plasma fructose from 4 subjects of treatment Group III during the whole observation time

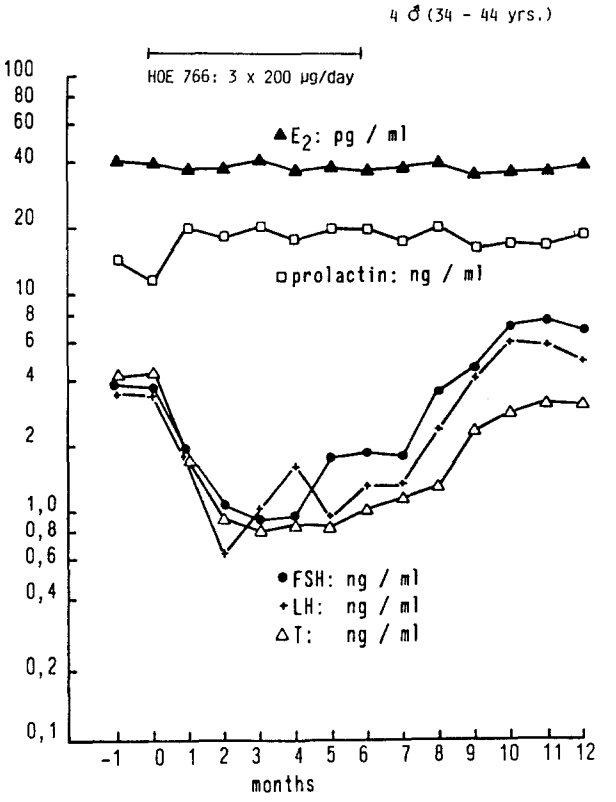

Fig. 5. Mean plasma levels of E_2, prolactin, FSH, LH and T from 4 subjects in treatment Group II during the whole observation time

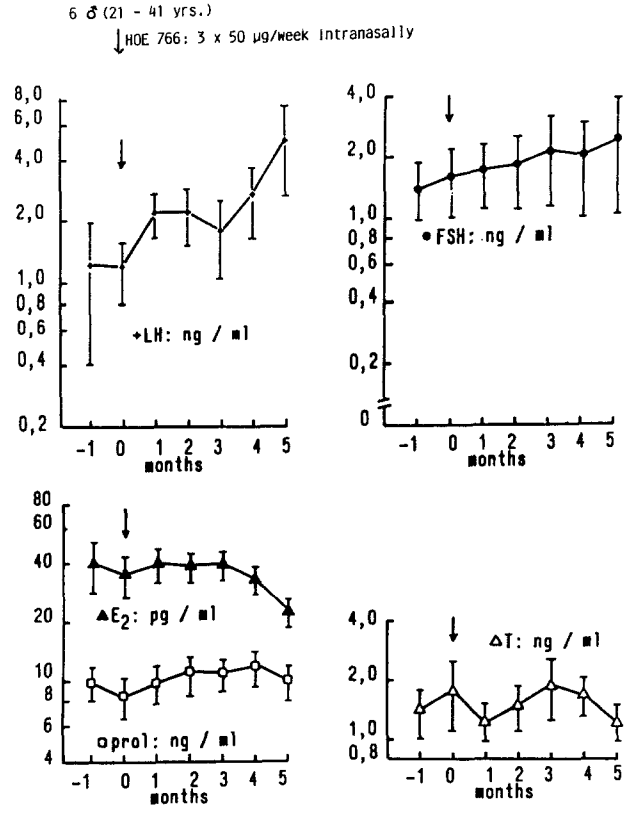

Fig. 4. Mean plasma levels ± SD of LH, FSH, T, E_2 and prolactin from 6 subjects in treatment Group I during the whole observation time

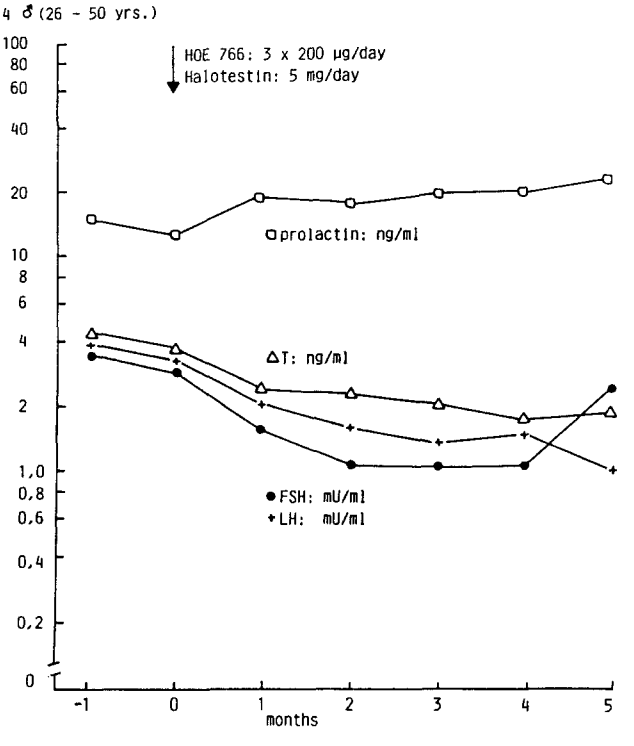

Fig. 6. Mean plasma values of prolactin, T, LH and FSH from 4 subjects in treatment Group III during the whole observation time

crease of libido and some changes in sexual behaviour beginning at the end of the second month of treatment and lasting until the third month after cessation of drug administeration whereas the subjects in Group I and Group III presented normal libido and erections throughout the observation time.

Discussion

With the low dose administration of HOE 766 (50 μg, 3 x/week) no change in sperm density or progressive motility could be observed. LH exhibited a marked and FSH a moderate increase during treatment for 5 months whereas T did not change compared to pretreatment levels. Libido and erection remained normal.

When high and multiple dosages per day of a potent LHRH agonist are administered without androgen replacement our results demonstrate clearly a pronounced decrease of LH and FSH, T-values reach almost female levels but basal testosterone secretion was still found 6 months after onset of treatment [8]. The effect on the tubular compartment resulted in arrest of spermatogenesis after 4 months of treatment which was proven by multiple sperm analyses. The inhibitory effect was reversible after cessation of treatment.

The assessment of libido and potency was based on the subjective reports of the probands and must, therefore, be interpreted cautiously. The participants receiving the agonist alone (Group II) reported marked decrease of libido by the 8th treatment week and lasting until the third month after cessation of drug administration, whereas the probands receiving the agonist plus fluoxymesterone reported normal libido and sexual behaviour. Androgen replacement caused a blockade of the antifertility effect of HOE 766 as demonstrated when administered alone. In none of the subjects in Group III was there demonstrable inhibition of spermatogenesis after 6 months of treatment. The administration of one fluoxymesterone tablet/day may produce one or two testosterone peaks which may have been sufficient to counteract the suppression of spermatogenesis achieved by the inhibitory effect of the LHRH analogue [13]. To overcome this problem a constant release preparation would be necessary to maintain a sufficiently high plasma concentration.

Acknowledgements. The financial support provided by the International Development Research Centre of Canada, the U.S. Agency for International Development (Grant AID/pha-G-1116), the Ford Foundation, the Rockefeller Foundation, and the Geo. J. Hecht Fund is gratefully acknowledged.

References

1. Auclair C, Kelly PA, Labrie F, Coy DH, Schally AV (1877) Inhibition of testicular LH6hCG receptor level by treatment with a potent LHRH agonist of HCG. Biochem Biophys Res Commun 76:855–860
2. Crowley WF, Comite F, Vale W, Rivier J, Loriaux DL, Cutler GB (1981) Therapeutic use of pituitary densitization with a long-acting LHRH agonist: A potential new treatment for idiopathic precocious puberty. J Clin Endocrinol Metab 52:2, 370–372
3. Doelle GC, Alexander AN, Evans RM, Linde R, Rivier J, Vale W, Rabin D (1983) Combined treatment with an LHRH agonist and testosterone in man: reversible oligospermia without impotence. J Androl 4:298–302
4. Eliasson R (1971) Standard for investigation of human semen. Andrologia 3:49–56
5. Frick J, Danner CH, Joos H, Kunit G, Luukkainen T (1981) Spermatogenesis in men treated with subcutaneous application of levonorgestrel and oestrone rods. J Androl 2:331–338
6. Hsueh AJW, Erickson GF (1979) Extrapituitary inhibition of testicular function by luteinizing hormone-releasing hormone. Nature 281:66–67
7. Labrie F, Auclair C, Cusan L, Kelly PA, Pelletier G, Ferland L (1978) Inhibitory effect of LHRH and its agonists on testicular gonadotropin receptors and spermatogenesis in the rat. Int J Androl [Suppl] 2:303–318
8. Labrie F, Cusan L, Séguin C, Bélanger A, Pelletier G, Reeves J, Kelly PA, Lemay A, Raynaud JP (1980) Antifertility effects of LHRH agonists in the male rat and inhibition of testicular steroidogenesis in man. Int J Fertil 25:157–170
9. Labrie F, Belanger A, Pelletier G, Seguin C, Cusan L, Kelly PA, Lemay A, Auclair C, Raynaud JP (1980) LHRH agonists: inhibition of testicular function and possible clinical applications. In: Cunningham GR, Schill WB, Hafez ESE (eds) Regulation of male fertility. Martinus Nijhoff, The Hague, The Netherlands
10. Linde R, Doelle GC, Alexander N, Kirchner F, Vale W, Rivier J, Rabin D (1981) Reversible inhibition of testicular steroidogenesis and spermatogenesis by a potent gonadotropin-releasing hormone agonist in normal men. N Engl J Med 305:663–667
11. Michel E, Bents H, Akhtar FB, Hönigl W, Sandow J, Nieschlag E (1985) Failure of high-dose sustained release GnRH agonist plus testosterone to suppress male fertility. Abstract 3rd Int Congr Androl, Post Graduate Course, Boston, Massachusetts
12. Nieschlag E, Hoogen H, Bölk M, Schuster H, Wickings EJ (1978) Clinical trial with testosterone undecanoate for male fertility control. Contraception 18:607–611
13. Nieschlag E, Michel E, Knuth UA (1985) Endocrine approach to male fertility regulation. In: Recent advances in Andrology. 3rd Int Congr of Androl, Post Graduate Course, Boston, Massachusetts
14. Nillius SJ, Bergquist C, Wide L (1980) Chronic treatment with the gonadotropin-releasing hormone agonist D-Ser (TBU)^6-EA^{10}-LRH for contraception in women and men. Int J Fertil 25:239–246
15. Sandow J, Hahn M (1978) Chronic treatment with LHRH in golden hamsters. Acta Endocrinol (Copenh) 88:601–610
16. Sandow J, Rechenberg W, Baeder C, Engelbart K (1980) Antifertility effects of an LH-RH analogue in male rats and dogs. Int J Fertil 25:213–221
17. Schally AV, Kastin AJ, Coy DH (1976) LH-releasing hormone and its analogue: recent basic and clinical investigations. Int J Fertil 21:1–30
18. Séguin C, Cusan L, Bélanger A, Kelly PA, Labrie F (1980) Direct effect of LH-RH-agonists on testicular LH receptors in hypophysectomized rats. Proceedings of the Sixth Intern Congr Endocrinol, pp 773–777
19. Swerdloff RS, Bhasin S (1984) Suppression of gonadal function by constant infusion of GnRH agonist in the human male (Abstract). J Steroid Biochem 20/6B:1374–1379
20. Wickings EJ, Zaidi P, Nieschlag E (1981) Effects of chronic, high-dose LHRH-agonist treatment on pituitary and testicular functions in rhesus monkeys. J Androl 2:72–79

Dr. J. Frick
Urologische Abteilung
Landeskrankenanstalten
A-5020 Salzburg
Austria