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Single-dose administration of the gonadotropin-releasing hormone antagonist, Nal-Lys (antide) to healthy men*

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Objective: To evaluate the ability the Nal-Lys GnRH antagonist ([N-Ac-Nal (2)[1], 4ClDPhe[2], D_3Pal[3], Lys (Nic)[5], D-Lys(Nic)[6], Lys (iPr)[8], D-Ala[10]] to suppress gonadotropins and T in humans and to assess its duration of action and its local effects.

Design: Placebo-controlled clinical study.

Setting: A university community.

Subjects: Seven normal male volunteers.

Interventions: We administered single injections of Nal-Lys (0, 10, 25, and 50 μg/kg body weight). Blood samples were collected before and at frequent time intervals after injection.

Results: Nal-Lys caused only minor local effects. At the higher doses (25 and 50 μg/kg), serum LH and T levels were suppressed to 50% to 70% of baseline; serum FSH levels were suppressed to 70% to 80% of baseline, and levels of all three hormones returned to basal values within 24 hours after injection.

Conclusions: In humans, Nal-Lys has similar potency and duration of action to other antagonists and produces fewer local side effects. However, the utility of Nal-Lys is limited by formulation difficulties; current efforts are directed at improving the formulation in order to explore the potential clinical uses of this peptide. Fertil Steril 1993;60:680–5

Key Words: GnRH, gonadotropins, male contraception, GnRH antagonist

Gonadotropin-releasing hormone antagonists are synthetic analogues of GnRH that compete with endogenous GnRH for pituitary binding sites and cause immediate suppression of gonadotropin secretion and, secondarily, of gonadal steroid secretion in animals and in men (1). They are potentially useful in a variety of clinical situations, including ovulation induction, prostate disease, and contraceptive development. We and others have shown that when these compounds are given to men on a daily basis, the suppression of hormone levels is maintained throughout the treatment period (2–5). In addition, when GnRH antagonists are combined with T replacement, azoospermia or severe oligospermia is induced in monkeys (6–9) and in normal men (10–12). However, the utility of first and second generation GnRH antagonists has been limited by their local effects. In humans, administration of antagonists such as Nal-Glu results in local erythema, pruritus, and subcutaneous nodule formation at the injection site. The local effects are thought to be due in part to histamine release; this process can be quantified in vitro. Recently, the GnRH antagonist ([N-Ac-Nal (2)[1], 4ClDPhe[2],

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D_3Pal^3, Lys (Nic)^5, D-Lys(Nic)^6, Lys (iPr)^8, D-Ala^{10}] (Nal-Lys) has been synthesized (13, 14). This compound, which has acetylated Lys residues in the fifth and sixth positions, has potency similar to previous antagonists, but it has much less histamine-releasing potential (13, 14).

Nal-Lys has been administered to rats and to nonhuman primates (15–21). Early studies in ovariectomized monkeys showed that a single subcutaneous or intravenous bolus could suppress serum LH levels to below detectable limits within 24 hours (15); depending on the dosage administered, gonadotropin suppression was sustained for 2 to 11 days (15). Studies in male monkeys showed that single injections of 3 to 10 mg/kg would suppress serum T levels for 2 days to nearly 10 weeks (16). Binding of the antagonist to serum proteins has been proposed as one potential mechanism subserving the long-acting effects of a single injection (17, 18).

The characteristics of long duration of action plus low histamine-releasing effects have made Nal-Lys a potentially attractive GnRH antagonist; however, no data are available using this antagonist in humans. We therefore designed a study to administer single doses of Nal-Lys to healthy young men to test its ability to suppress gonadotropins and T, to evaluate its duration of action, and to assess its local effects at the site of injection.

MATERIALS AND METHODS

Subjects

Seven healthy men, ages 21 to 36, participated in the study. All subjects signed a consent form approved by the Human Subjects Committee of the University of Washington. Each of the men had a normal medical history, physical examination, and screening blood tests and was within 20% of ideal body weight. All of the men were nonsmokers who took no regular medications, and none of the men abused alcohol. All subjects were tested for sensitivity to a 10 μg intradermal dose of Nal-Lys before acceptance into the study.

Antagonist Preparation

The GnRH antagonist, Nal-Lys, was dissolved in bacteriostatic water with 5% alcohol and 3% mannitol to a concentration of 2 mg/mL. The solution was then passed through a 0.22-μm filter into sterile vials. Vials were stored at −20°C until use.

Clinical Protocol

Each man was admitted to the Clinical Research Center of the University of Washington on four separate occasions ≥ 21 days apart. On each occasion, each subject received one of four test doses of antagonist: 0, 10, 25, and 50 μg/kg body weight. Each subject received all four doses. None of the men received the 50 μg/kg dose on the first admission; the doses were otherwise administered in random order. On each admission, baseline blood samples were collected 30 minutes and 5 minutes before the injection. At time 0 (between 7:30 and 9:00 A.M.), Nal-Lys was administered subcutaneously into the abdomen. Injections of ≤1 mL volume or less were administered as one injection; injections requiring >1 mL volume were administered as two separate injections, one on each side of the abdomen. Blood samples were drawn at 30, 60, 90, and 120 minutes after injection and then at 3, 4, 6, 8, 12, and 24 hours after injection. Subjects were discharged after 24 hours and returned to the research center for blood sampling on days 2, 3, 4, 7, 10, and 14 after injection. Vital signs were monitored at the time of each blood sample for the first 24 hours after injection. Subjects were examined for erythema and induration at 1 hour, 24 hours, and 14 days after each injection; subjective symptoms were also recorded at these times.

Levels of LH, FSH, and T were measured on each blood sample collected. Serum levels of Nal-Lys were measured on blood samples collected from six of the seven men during the 50 μg/kg study. The seventh man did not give permission for testing for hepatitis B and human immunodeficiency virus, which were required for the measurement of serum Nal-Lys levels.

Hormone Assays

Serum T levels were measured by RIA using reagents from the World Health Organization Matched Reagent Program by methods previously described (22). Testosterone was separated from serum by ether extraction; bound and free hormone were separated by dextran-coated charcoal. The assay sensitivity was 0.35 nmol/L; the interassay and intra-assay variabilities were 4.1% and 8.1%, respectively. Serum levels of LH and FSH were measured by an immunoradiometric method (MAIA clone; Serono Laboratories, Geneva, Switzerland). The limits of detectability for each assay were 0.5 IU/L. The interassay variabilities for LH and FSH were 10% and 11%, respectively. The intra-assay variabilities were 4.8% and 7.0% for LH and FSH, respectively.

Nal-Lys levels were measured by RIA. The assay contained 300 μL of sample (diluted) or standard (25 to 300 ng), 200 μL of tracer ($I^{125}Tyr^{0}$-Antide, 15,000 to 20,000 cpm) and 100 μL diluted antiserum (final tube titer, 1:10,000; Woods Assay, Iowa City, IA). No detectable displacement of antibody-bound $I^{125}Tyr^{0}$-Antide was observed with synthetic fragments of Nal-Lys, natural GnRH, other GnRH analogues, or a variety of peptide and steroid hormones. This solution was incubated at 8°C for 20 hours and then diluted carrier rabbit serum was added (in 200 μL), followed by 200 μL titered anti-rabbit globulin. This second solution was allowed to incubate for an additional 8 hours and was then centrifuged at 2,000 × *g*. The supernatant fraction was aspirated, and the radioactivity in the pellet was determined by spectroscopy. The minimal detectable dose in the assay was approximately 8 pg/tube, and the intra-assay and interassay variances were <5% and 7%, respectively. Data were reduced by four parameter logistic fit.

Statistics

The mean hormone levels at each time point were calculated for all men at each dose. Values were expressed as absolute levels and as percentage of the baseline level. The baseline level was considered to be the average of the two samples drawn before injection of Nal-Lys. The time effects on hormone concentration were determined by analysis of variance with repeated measures. For each hormone, the area under the curve at each of the four doses was determined using Simms' rule.

RESULTS

Serum Nal-Lys Levels

Nal-Lys levels were measured in six of the men. The seventh man did not give permission to have his blood tested for Nal-Lys. Serum Nal-Lys levels were undetectable before injection in five of the six men. In the sixth man, baseline Nal-Lys levels at times −30 and −5 minutes were 0.24 and 0.29 ng/mL, respectively. This subject had received the 25 μg/kg dose 21 days previously. Serum Nal-Lys levels after injection of the 50 μg/kg dose rose rapidly; the peak value of 18.3 ng/mL occurred at 30 minutes (Fig. 1). Nal-Lys levels fell quickly during the first 24 hours after injection but remained elevated above the baseline range for the duration of the blood-sampling period; the mean Nal-Lys level on day 14 was 0.54 ng/mL.

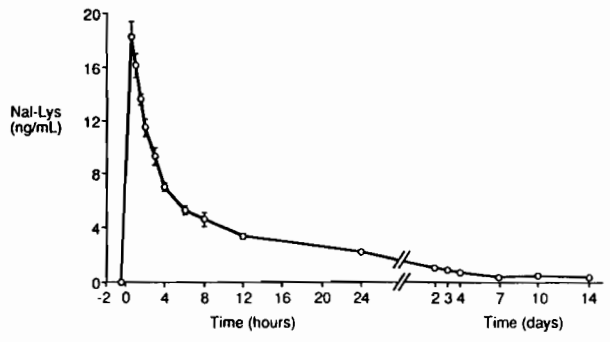

Figure 1 Serum Nal-Lys levels (mean ± SEM) in six men after administration of Nal-Lys, 50 μg/kg.

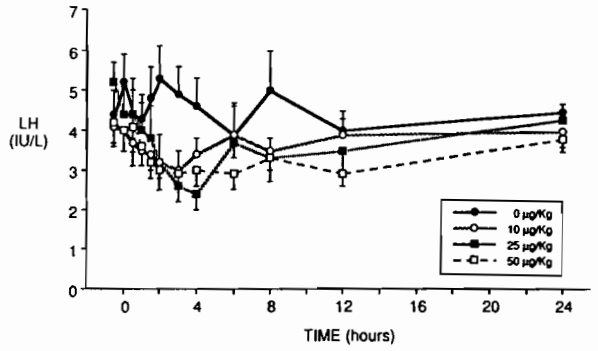

Figure 2 Serum LH levels (mean ± SEM) in seven healthy men during the first 24 hours after administration of the Nal-Lys GnRH antagonist at doses of 0, 10, 25, and 50 μg/kg.

Serum LH

Mean baseline LH values were similar during all four studies. During the placebo study and after administration of 10 μg/kg Nal-Lys, mean serum LH levels did not change significantly (Fig. 2). After administration of 25 μg/kg, significant suppression of mean serum LH occurred within 120 minutes (Fig. 2; $P < 0.05$). Mean serum LH levels were maximally suppressed 4 hours after injection (2.5 ± 0.4 IU/L, 52% ± 6% of the baseline level, $P < 0.05$). Baseline levels were re-established by 24 hours. After administration of 50 μg/kg of Nal-Lys, there was significant suppression of mean serum LH within 90 minutes (Fig. 2). Mean serum LH levels were maximally suppressed 6 hours after injection, decreasing from 4.0 ± 0.5 to 2.9 ± 0.4 IU/L (70% ± 5% of the baseline level, $P < 0.05$). Baseline levels were reachieved by 24 hours after injection. The areas under the curve during the first 24 hours of the placebo and 50 μg/kg studies differed significantly ($P < 0.05$).

Serum FSH Levels

Mean baseline FSH levels were similar during each of the four studies. During the placebo study,

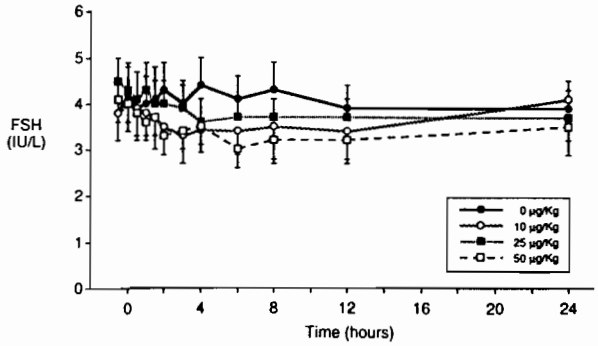

Figure 3 Serum FSH levels (mean ± SEM) in seven healthy men during the first 24 hours after administration of the Nal-Lys GnRH antagonist at doses of 0, 10, 25, and 50 μg/kg.

mean serum FSH levels did not change significantly. Three hours after administration of 10 μg/kg Nal-Lys, the degree of suppression of serum FSH reached statistical significance (3.9 ± 0.6 IU/L to 3.3 ± 0.6 IU/L, $P < 0.05$; Fig. 3). After administration of 25 μg/kg, significant suppression of serum FSH occurred within 180 minutes ($P < 0.05$). Maximal suppression of FSH occurred 6 hours after injection, at which time mean serum FSH was 3.6 ± 0.5 IU/L (81% ± 6% of baseline, $P < 0.05$); at 24 hours, hormone levels had returned to baseline. After administration of 50 μg/kg of Nal-Lys, there was significant suppression of mean serum FSH within 120 minutes. Maximal suppression of FSH occurred at 6 hours, when mean serum FSH was 3.0 ± 0.4 IU/L (73% ± 10% of baseline, $P < 0.05$). Baseline levels were re-established by 24 hours after injection. The area under the curve during the first 24 hours of the placebo study differed significantly ($P < 0.05$) from the areas under the curve during each of the 10, 25, and 50 μg/kg studies.

Serum T Levels

There were no statistical differences in the baseline T values during any of the four studies. During the placebo study, a normal circadian rhythm was observed; the lowest T levels occurred in the late afternoon and early evening (Fig. 4). Mean serum T levels during the 10 μg/kg study were generally lower than during the placebo study. Mean T levels were maximally suppressed after 6 hours (Fig. 4). After administration of 25 μg/kg Nal-Lys, significant suppression of mean serum T occurred within 4 hours (Fig. 4). Maximum suppression occurred at 12 hours after injection, at which time mean serum T was suppressed from 5.79 ± 0.27 ng/mL (20.1 ± 0.93 nmol/L) to 3.89 ± 0.27 mg/mL (13.5 ± 1.6 nmol/L; 66% ± 7% of the baseline level; $P < 0.05$). Baseline levels were re-established by 24 hours. Serum T levels decreased significantly within 4 hours after injection of the 50 μg/kg dose of Nal-Lys (Fig. 4). Maximal suppression occurred 6 hours after injection; mean serum T at this time was 3.48 ± 0.49 ng/mL (12.07 ± 1.7 nmol/L; 59 ± 6% of the baseline level, $P < 0.05$). By 24 hours after injection, baseline levels were re-established. The areas under the curve during the first 24 hours of each of the 10, 25, and 50 μg/kg studies differed significantly ($P < 0.05$) from the area under the curve of the placebo study. There were no significant differences among the areas under the curve for the 10, 25, and 50 μg/kg doses.

Side Effects

There were no changes in vital signs in any of the men during any of the four studies. None of the men experienced erythema, tenderness, or induration at the injection site after injection of placebo; transient erythema was noted in two men after the 10 μg/kg dose. Four men had minimal induration (1 to 3 mm) accompanied by slight local tenderness that developed 24 hours to several days after injection of the 25 and 50 μg/kg doses; the induration and tenderness lasted 2 to 3 days. Erythema was present at the injection site for 1 to 2 hours after injection of the higher doses.

DISCUSSION

We administered single doses of the GnRH antagonist Nal-Lys to healthy young men; with the higher doses, we observed suppression of serum LH and T levels to 50% to 70% of their respective base-

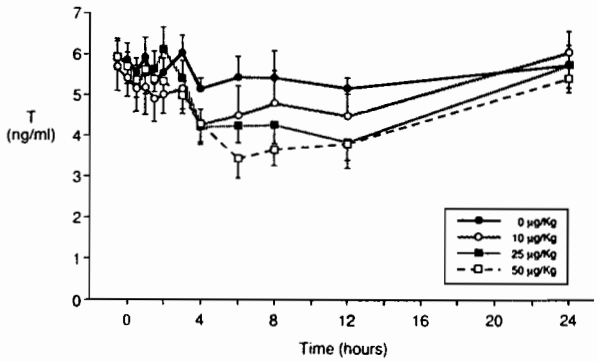

Figure 4 Serum T levels (mean ± SEM) in seven healthy men during the first 24 hours after administration of the Nal-Lys GnRH antagonist at doses of 0, 10, 25, and 50 μg/kg.

line levels; FSH levels were suppressed to 70% to 80% of baseline. These decreases were completely reversed within 24 hours, although Nal-Lys levels in the serum remained elevated. Administration of Nal-Lys was accompanied by minimal local side effects. Our results show that Nal-Lys has fewer local effects than GnRH antagonists previously administered to humans and that the potency and duration of action of Nal-Lys are similar to those of previous antagonists. However, because gonadotropins and T were only partially suppressed, the data suggest that higher doses of Nal-Lys must be tested in humans to find a dosing level to be used in longer studies. If such a dose can be formulated, Nal-Lys may ultimately have more clinical utility than GnRH antagonists that have been tested in the past.

Previous studies using Nal-Lys have been conducted in rats and in nonhuman primates (15–21). In these studies, doses of 0.3 to 15 mg/kg have been administered using a vehicle (propylene glycol, which cannot be administered safely to humans) different from the vehicle used in this study. In the animal studies, marked suppression of gonadotropins and gonadal steroids have been observed over periods lasting as long as several weeks. The maximum dose we administered, 50 μg/kg, is sixfold lower than the lowest dose used in animal studies, and it is 60 to 200 times lower than doses typically used. It is therefore not surprising that the magnitude and duration of gonadotropin and T suppression we observed was considerably less than in animal studies. Differences in the vehicle used (water with alcohol and mannitol versus propylene glycol) and the mode or rapidity of excretion of Nal-Lys may also contribute to the differing effects of the antagonist in animal and human studies. Interestingly, however, the peak Nal-Lys level we observed (18.3 ng/mL) was not markedly different from that reported by Gordon et al. (19) after injection of 0.3 mg/kg Nal-Lys in intact female monkeys. In that study, however, Nal-Lys was detectable in the serum at levels of 4 to 5 ng/mL at the time of subsequent ovulation 50 to 60 days after injection. In our men, Nal-Lys was detectable in all of the men 14 days after injection, but the levels were <1 ng/mL at this time. The prolonged duration of detectable Nal-Lys in serum may be due to the formation of a local depot of peptide at the site of injection; alternatively, it may be due to a binding protein present in serum that results in a long half-life of the drug (17, 18).

We previously have administered single doses of the Nal-Glu GnRH antagonist ([AcD2Nal[1], D4ClPhe[2], D3Pal[3], Arg[5], DGlu [6](AA), DAla[10]] GnRH) to healthy young men at doses of 25, 75, and 250 μg/kg (2). When Nal-Glu was administered at the 25 μg/kg dosage, serum T levels were suppressed to 38% of the baseline value; in the present study, T levels were suppressed to only 66% of the baseline level after the 25 μg/kg dose. In contrast, the maximal suppression of serum LH and FSH were similar after injection of the two antagonists. Serum LH levels were suppressed to 54% and 52% of the baseline level by Nal-Glu and Nal-Lys, respectively, whereas FSH levels were suppressed to 72% and 81% of the baseline levels by Nal-Glu and Nal-Lys, respectively. The reason for the enhanced suppression of T by Nal-Glu is not clear; however, it is possible that levels of biologically active LH were suppressed more completely by Nal-Glu (2), leading to more suppression of T levels by this antagonist. Because we were unable to test doses of Nal-Lys > 50 μg/kg, it is not possible to compare the two antagonists fully.

Nal-Lys is less soluble than several other GnRH antagonists; it can be dissolved to a concentration of only 2 mg/mL in formulations developed to date, whereas Nal-Glu can be dissolved to a concentration of 10 mg/mL. Because of its relative insolubility, larger volumes of vehicle are required for injection of Nal-Lys than for Nal-Glu or other antagonists, and this factor limits the dose of Nal-Lys that can currently be administered subcutaneously. It is likely that a higher dose of Nal-Lys (such as 100 μg/kg) would suppress gonadotropins and T to the castrate or near-castrate range, as do doses of 75 to 100 μg/kg of Nal-Glu. At the present time we are unable to test this hypothesis, however.

At present, there is no hormonal contraceptive method available for widespread usage in men. A recent study by the World Health Organization (23) has shown that exogenous T enanthate has an efficacy rate at least as great as that of female hormonal regimens; however, only 50% to 70% of men achieve azoospermia on this regimen (23). Recent studies suggest that some combination of GnRH antagonist and T may induce azoospermia in a greater percentage of men. However, the Nal-Glu antagonist used in these long-term studies is limited by its local effects, and fewer than 30 men have participated in long-term studies on antagonist and T. To conduct the larger trials needed to establish the utility of such a regimen, a potent agent with fewer local effects is needed. If a more soluble formulation of Nal-Lys could be developed and an effective dose established, this would allow for

larger studies on antagonist/T regimens to be conducted.

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REFERENCES

1. Karten MJ, Rivier JE. Gonadotropin releasing hormone analog design. Structure function studies toward the development of agonists and antagonists: rationale and perspective. Endocr Rev 1986;7:44–66.
2. Tenover JS, Dahl KD, Vale WW, Rivier JE, Bremner WJ. Hormonal responses to a potent gonadotropin hormone-releasing hormone antagonist in normal young and elderly men. J Clin Endocrinol Metab 1990;71:881–8.
3. Bagatell CJ, McLachlan RI, deKretser DM, Burger HG, Vale WW, Rivier JE, et al. A comparison of the suppressive effects of testosterone and a potent new gonadotropin-releasing hormone antagonist on gonadotropin and inhibin levels in normal men. J Clin Endocrinol Metab 1989;69:43–8.
4. Pavlou SN, Interlandi JW, Wakefield G, Island DP, Rivier J, Vale W, et al. Gonadotropins and testosterone escape from suppression during luteinizing hormone-releasing hormone antagonist administration in normal men. J Clin Endocrinol Metab 1987;64:1070–4.
5. Pavlou SN, Wakefield G, Schlechter NL, Lindner J, Souza KH, Kamilaris TC, et al. Mode of suppression of pituitary and gonadal function after acute or prolonged administration of a luteinizing hormone-releasing hormone antagonist in normal men. J Clin Endocrinol Metab 1989;68:446–54.
6. Bremner WJ, Bagatell CJ, Steiner RA. GnRH antagonist plus testosterone: a potential male contraceptive. J Clin Endocrinol Metab 1991;73:465–9.
7. Weinbauer GF, Surmann FJ, Akhtar FB, Shah GV, Vickery BH, Nieschlag E. Reversible inhibition of testicular function by a gonadotropin-releasing hormone antagonist in monkeys (*Macaca fascicularis*). Fertil Steril 1984;42:906–14.
8. Weinbauer GF, Gockeler E, Nieschlag E. Testosterone prevents the complete suppression of spermatogenesis in the gonadotropin-releasing hormone antagonist-treated nonhuman primate (*Macaca fascicularis*). J Clin Endocrinol Metab 1988;67:284–90.
9. Weinbauer GF, Surrmann FJ, Nieschlag E. Suppression of spermatogenesis in a nonhuman primate (*Macaca fascicularis*) by concomitant gonadotropin-releasing hormone antagonist and testosterone treatment. Acta Endocinol (Copenh) 1987;114:138–46.
10. Pavlou SN, Brewer K, Lindner J, Farley MG, Bastias MC, Roger BJ, et al. Combined administration of a GnRH antagonist plus testosterone in men induces reversible azoospermia without loss of libido. J Clin Endocrinol Metab 1991;73:1360–9.
11. Tom L, Bhasin S, Salameh W, Steiner B, Peterson M, Zokol RZ, et al. Induction of azoospermia in normal men with combined Nal-Glu gonadotropin-releasing hormone antagonist and testosterone enanthate. J Clin Endocrinol Metab 1992;75:476–83.
12. Bagatell CJ, Christensen RB, Matsumoto AM, Bremner WJ. Comparison of a gonadotropin releasing hormone antagonist plus testosterone (T) versus T alone as potential male contraceptive regimens. J Clin Endocrinol Metab 1993;77:427–32.
13. Ljungqvist A, Feng DM, Hook W, Shen ZX, Bowers CY, Folkers K. Antide and related antagonists of luteinizing hormone release with long action and oral activity. Proc Natl Acad Sci USA 1988;86:8236–40.
14. Folkers K, Bowers C, Tang PFL, Feng D, Okamoto D, Zhang Y, et al. Specificity of design to achieve antagonists of LHRH of increasing effectiveness in therapeutic activity. In: Vickery BH, Nestor JJ, editors. LHRH and its analogs, part 2. Lancaster, UK: MTP Press, Ltd., 1987:25–36.
15. Leal JA, Williams RF, Danforth DR, Gordon K, Hodgen GD. Prolonged duration of gonadotropin inhibition by a third generation GnRH antagonist. J Clin Endocrinol Metab 1988;67:1325–7.
16. Edelstein MC, Gordon K, Williams RF, Danforth DR, Hodgen GD. Single dose long-term suppression of testosterone secretion by a gonadotropin releasing hormone antagonist (Antide) in male monkeys. Contraception 1990;42:209–14.
17. Danforth DR, Gordon K, Leal JA, Williams RF, Hodgen GD. Extended presence of Antide (Nal-Lys) GnRH antagonist in circulation: prolonged duration of gonadotropin inhibition may derive from antide binding to serum proteins. J Clin Endocrinol Metab 1990;70:554–6.
18. Danforth DR, Williams RF, Gordon K, Leal JA, Hodgen GD. Inhibition of pituitary gonadotropin secretion by the gonadotropin releasing hormone antagonist, Antide. II. Development of an in vitro bioassay for characterization of pharmacokinetics of Antide in circulation. Endocrinology 1991;128:2041–4.
19. Gordon K, Williams RF, Danforth DR, Hodgen GD. Antide-induced suppression of pituitary gonadotropin and ovarian steroid secretion in cynomolgus monkeys: premature luteolysis and prolonged inhibition of folliculogenesis following single treatment. Biol Reprod 1991;44:701–6.
20. Habenicht UF, Schneider MR, El Etreby MF. Induction of chemical castration in male rats by a long-acting LHRH-antagonist. The Prostate 1990;17:69–83.
21. Habenicht U, Schneider MR, El Etreby MF. Effect of the new, potent LHRH antagonist Antide. J Steroid Biochem Mol Biol 1990;37:937–42.
22. Matsumoto AM, Paulsen CA, Hopper BR, Rebar RW, Bremner WJ. Human chorionic gonadotropin and testicular function: stimulation of testosterone, testosterone precursors, and sperm production despite high estradiol levels. J Clin Endocrinol Metab 1983;56:720–8.
23. World Health Organization Task Force on methods for the regulation of male fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet 1990;336:955–9.