Hormonal Responses to a Potent Gonadotropin Hormone-Releasing Hormone Antagonist in Normal Elderly Men*

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ABSTRACT. GnRH analogs, both agonists and antagonists, have potential use in androgen-dependent diseases of older men, such as prostatic cancer and benign prostatic hyperplasia. Previous experience with agonists of GnRH has suggested that GnRH analogs may be more effective in aged men than in young men, but little is known about GnRH antagonists in older men. Therefore, we evaluated the hormonal effects of a single dose and a short course of a GnRH antagonist (Nal-Glu) in normal elderly men. Six young men (25-34 yr old) and six older men (60-76 yr) each received single morning injections of Nal-Glu (25, 75, and 250 μg/kg), separated by 2 weeks. Serum levels of testosterone (T), immunoreactive LH (LRHRIA) and FSH (FSHRIA), and bioactive LH (LH BIO) and bioactive FSH were evaluated periodically for 7 days after each injection. In addition, six elderly men received 25 and 15 μg/kg/day Nal-Glu for 10 consecutive mornings each, and serum levels of T, inhibin, LRHRIA, LH BIO, FSHRIA, and bioactive FSH were evaluated.

Nal-Glu in all three single doses caused a significant (P < 0.01) decline in serum levels of T and gonadotropins that was similar in extent in the elderly and young men. For example, T declined to a level of 19% of baseline after the 250 μg/kg dose of Nal-Glu in both age groups. For both the young and elderly men, the major effect of increasing the Nal-Glu dose was a prolongation of the period of suppression. Multiple Nal-Glu injections in the elderly men also resulted in a rapid decline in T, inhibin, and bioactive and immunoreactive gonadotropins. For both LH and FSH, bioactivity decreased to a greater extent than immunoreactivity. Local side-effects of Nal-Glu tended to be fewer and of less intensity in the elderly men compared to those in the young men.

These results demonstrate that the response to Nal-Glu in healthy elderly men is similar to that in younger men, and extended administration of Nal-Glu in elderly men effectively suppresses gonadal and pituitary function. These results suggest that the role of GnRH antagonists in the effective treatment of androgen-dependent disease in the aging male needs to be explored further. (J Clin Endocrinol Metab 71: 881-886, 1990)

The development of GnRH analogs has offered the potential of alternative therapies for prevalent age-related androgen-dependent diseases, such as prostatic carcinoma and benign prostatic hyperplasia (1, 2). Agonist analogs of GnRH, although stimulating an initial increase in gonadotropins and testosterone (T), eventually lead to suppression of pituitary and gonadal function as a result of pituitary desensitization (1, 3). Studies using GnRH agonist analogs in patients with metastatic prostatic cancer have shown their effectiveness in stabilization and/or regression of the disease (4-6), and there are a few reports of the efficacy of these compounds in treatment of symptomatic BPH (2, 7-9). However, one drawback to using GnRH agonists alone in the treatment of prostate disease is that these agents cause an initial physiological and biochemical exacerbation of the disease (10-12).

More recently, antagonist analogs of GnRH have become available for testing. The GnRH antagonists compete with endogenous GnRH for binding to pituitary receptors (13), and their suppressive effects on pituitary and gonadal hormones occur almost immediately. In animals, GnRH antagonists cause a rapid and profound suppression of serum levels of gonadotropins and T without causing an initial "flare" reaction (14-16), making them more attractive than agonist analogs in the treatment of diseases such as prostate cancer.

Experience with GnRH agonist administration in aging men with prostate diseases suggests that GnRH analogs may be more effective in suppressing hormone levels in older men than in young men (1). However, although there have been several reports of single dose

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or short course treatment with GnRH antagonists in young men (17–22), there are no data on their use in elderly men. The purposes of this study are to compare, in elderly and young men, the hormonal effects of a single injection of a potent GnRH antagonist, Nal-Glu, and to characterize, in the elderly men, the effects of a 10-day course of this same GnRH antagonist.

Nal-Glu is a second generation GnRH antagonist (23) which retains ovulatory inhibition potency and suppresses spermatogenesis in rats (14). Chronic administration of this compound has been shown to be efficacious in decreasing gonadal function in monkeys (24). Unlike other second generation GnRH antagonists, Nal-Glu has less in vitro histamine-releasing activity than the first generation antagonists, but local allergic reactions have been reported (20). The terminal serum half-life of Nal-Glu in the adult male has been reported to be 12.8 ± 2.7 h (18).

Materials and Methods

Subjects

Healthy young (age range, 25–34 yr) and elderly (age range, 66–76 yr) men were recruited for study from the community. Before entry, all men signed an informed consent approved by the University of Washington Human Subjects Committee. All men were non-smokers on no medications, and health was determined by medical history and physical examination as well as by normal complete blood count, urinalysis, and blood chemistry screen. Before acceptance into the study, each man was tested for sensitivity to a 10-μg intradermal dose of the GnRH antagonist. Each individual received repeat blood screening tests on the last day of the entire protocol regimen. All testing was performed at the Clinical Research Center (CRC) of the University of Washington.

Drug preparation

The GnRH antagonist (AcD2Nal1,p4ClPhe3,p3PAl3,Arg5, D-Glu6(AA),D-Ala10-GnRH), Nal-Glu, previously tested for pyrogens, was dissolved in bacteriostatic water plus 4% mannitol to a concentration of approximately 10 mg/mL and then passed through a 0.22-μm filter into sterile vials. Once in solution, the purity and concentration of the compound solution were confirmed by high pressure liquid chromatographic evaluation. Vials were stored at −20°C until use; once thawed, the individual vials were kept at 4°C.

Experimental protocol

Single dose studies. Six young and six elderly men were admitted to the CRC for 24 h on each of four separate occasions (each admission separated by at least 2 weeks) to receive, in random order, vehicle injection or one of three doses (25, 75, and 250 μg/kg BW) of Nal-Glu antagonist, administered sc in the abdominal wall sometime between 0800–1000 h. For each injection, blood was drawn 30 min before and just before the injection, and again 30, 60, 90, and 120 min and 3, 4, 6, 8, 12, and 24 h after the injection. Once discharged from the CRC, subjects returned for blood sampling in the mornings (0800–1000 h) on days 2, 3, 4, and 7 (day 0 = day of injection). Blood was allowed to clot at room temperature, serum was separated, and the sample was frozen and stored at −20°C until assayed.

10-day studies. Six elderly men received two dosage courses (25 and 75 μg/kg BW-day) of Nal-Glu antagonist as abdominal wall sc injections in the mornings (0800–1000 h) daily for 10 consecutive days. The two dosage regimens were separated by at least 3 weeks, and half of the men received the lower dosage regimen first. Blood was drawn just before daily injection on days 0 (day of the first injection), 1, 2, 3, 4, 7, 9, 11, and 16 (day 16 being the seventh recovery day) and processed as in the single dose protocol.

All serum samples were assayed in duplicate for T, LH, and FSH by RIA. LH bioactivity was measured in duplicate in the 0, 6, 12, and 24 h, day 2, and day 3 samples from the single dose studies and in all the samples from the higher dosage (75 μg/kg BW-day) 10-day study. FSH bioactivity was assayed in triplicate, and immunoreactive inhibin was assayed in duplicate in all samples from the 75 μg/kg-day 10-day study. For each hormone, all samples from one man were analyzed in the same assay.

Hormone assays

The RIAs for serum LH and FSH have been described previously (25). LER-907 was used as the reference standard for both assays. Reagents were supplied by the National Hormone and Pituitary Program, except for the tracers [125I]LH and [125I]FSH, which were obtained commercially (Diagnostic Products, Los Angeles, CA). The limit of detectability of the LH assay was 3 μg/L, and the intra- and interassay variabilities were 5.5% and 8.4%, respectively. The FSH assay limit of detectability was 25 μg/L, with intra- and interassay variabilities of 7.3% and 9.7%, respectively. The normal range in adult men for LH is 10–80 μg/L, and for FSH is 30–230 μg/L. Serum gonadotropin levels in men with idiopathic hypogonadotropic hypogonadism are undetectable in the assay.

The RIA for serum T used reagents from the WHO Matching Reagent Program, and the methodology has been reported previously (26). T was separated from serum by ether extraction, and separation of bound from free hormone was accomplished by dextran-coated charcoal. The assay sensitivity was 0.35 nmol/L (0.1 ng/mL), and the intra- and interassay variabilities were 5.1% and 9.8%, respectively. The normal range of serum total T in normal adult men is 12.1–34.7 nmol/L.

Bioactive LH was measured by the mouse Leydig cell in vitro bioassay (27), using LER-907 as reference standard. The intra- and interassay coefficients of variation were 9.4% and 15.8%, respectively, and the assay sensitivity was 0.3 μg/L. The normal range for bioactive LH in the serum of adult men is 103–520 μg/L.

Bioactive FSH was measured using the in vitro granulosa cell bioassay (28, 29). The assay measures FSH-stimulated estrogen production by rat granulosa cells obtained from animals primed with diethylstilbestrol. The intra- and interassay variabilities for the estrogen assay were 13% and 10%, respect-
tively. The sensitivity of the FSH bioassay was 3 ng/culture well for LER-907, with inter- and intrassay variabilities of 16% and 11%, respectively. The normal range for serum bioactive FSH in adult men is 162-538 pg/L.

Serum inhibin was measured as previously described (30, 31) in a heterologous double antibody RIA using purified 31-kDa bovine follicular fluid inhibin as the tracer and antigen to generate the antiserum. Recently, a bovine follicular fluid protein (pro-αC), having no inhibin bioactivity but cross-reacting in the inhibin RIA, has been reported (32). In addition, it has been reported that recombinant α-inhibin cross-reacts in the RIA (33). How free α-subunit or other cross-reacting substances might affect the ability of the RIA to discriminate true dimeric bioactive inhibin in human serum remains unclear. However, studies of the ratio of inhibin bioactivity to immunoreactivity in women (34) suggest that the interassay variability of nonbioactive substances in the present inhibin RIA probably is small. The sensitivity (ED$_{50}$) of the inhibin RIA was 100 U/L, with an interassay variability of 10.2%. The intraassay variabilities were 9.8%, 3.3%, and 4.2% in the upper, middle, and lower ranges of male quality control serum. The normal adult male range for serum inhibin is 314-1141 U/L, while castrated men have serum inhibin levels that are undetectable in the assay.

Statistics

The mean ± se hormone levels were calculated for all men within each dose and age group. Values were expressed as both an absolute and a percentage of baseline values. For the single dose studies, baseline was the mean of seven values (−30 and 0 h on day 0 and 24 h and the morning on days 2, 3, 4, and 7) obtained after injection of vehicle only. For the longer dosing studies, baseline was the time zero value for each injection.

The dose and time effects on hormone concentration and the comparison between age groups were assessed by analysis of variance with repeated measures. Mean baseline values between age groups were compared by Student’s two-tailed t test. Side-effects were compared by Fisher’s exact test.

Results

Single dose studies

Administration of Nal-Glu in all three doses (25, 75, and 250 μg/kg) caused a significant (P < 0.001) decline within 60 min in serum T levels that was similar in both young and elderly men (Fig. 1 and Table 1). For example, 24 h after the 250 μg/kg dose, T levels were maximally suppressed (to 19% of the baseline value) in both age groups. Also, in both age groups there was a tendency for the degree of T suppression to be greater at higher doses of Nal-Glu (Table 1), and the duration of suppression was significantly (P < 0.05) longer with the higher drug doses (Fig. 1).

Within 60 min after each dose of Nal-Glu, serum immunoreactive LH (LH RIA) had decreased significantly (P < 0.001) in both age groups (Fig. 2, upper panel). Bioactive LH levels (LH BIO, Table 1) were decreased significantly (P < 0.001) in both age groups by 6 h after each dose of Nal-Glu. For both LH BIO and LH RIA, the duration of suppression was dose dependent (P < 0.001, by repeated measures), although the level of maximal suppression was not significantly dose dependent. In addition, although there was a tendency for LH BIO to be suppressed to a greater degree than LH RIA, especially in the young men, this suppression difference was not statistically significant in either age group.

For FSH RIA (Fig. 2, lower panel), administration of Nal-Glu resulted in significant (P < 0.001) declines in serum levels by 4 h after each dose in both age groups. However, the level of suppression of FSH (as a percentage of baseline) was less than that for LH for each dose of Nal-Glu (Table 1). Again, the major effect of increasing the dose of Nal-Glu appeared to be in the prolongation of the period of hormone suppression.

Multiple dosing studies

Mean serum T levels for the six elderly men, who received two dosage regimens of Nal-Glu injections daily for 10 days, are shown in Fig. 3 (top panel). For the 75 μg/kg BW·day dose, mean T levels decreased significantly (P < 0.001) from 16.9 ± 1.6 nmol/L on day 0 to 2.1 ± 0.3 nmol/L (12% of baseline) on day 2. After day 2, mean T levels increased significantly (P < 0.005) to a maximum level on day 4 of 5.2 ± 0.7 nmol/L, after which T levels gradually declined again to a level on day 9 of 2.4 ± 0.7 nmol/L. After completion of the 10 daily Nal-

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**Fig. 1.** Mean (±SE) serum T levels in six young (A) and six elderly (B) men after single dose injections of vehicle ( ), or 25 μg/kg ( ), 75 μg/kg ( ), and 250 μg/kg ( ) Nal-Glu. Time zero is the time of injection.
GLU injections, serum T levels increased and returned to near-baseline levels by day 16 (no blood sampling was performed on days 12–15). Results with the 25 µg/kg BW·day dosage regimen were similar, although the maximum suppression was not as marked (8.7 ± 1.3 nmol/L on day 2) as that seen with the higher dosage regimen (Fig. 3, top panel).

With the 75 µg/kg BW·day dose of NA²-Glu, serum inhibin levels in the elderly men decreased significantly (P < 0.01) from 507 ± 58 U/L on day 0 to a nadir of 272 ± 38 U/L (54% of baseline) on day 7 (Fig. 3, lower panel). Unlike the results for serum T levels, serum inhibin levels did not show a significant spontaneous increase during the NA²-Glu treatment. The lower NA²-Glu dosage regimen also led to a significant (P < 0.01) decline in serum inhibin levels, but the maximal level of suppression (355 ± 66 U/L on day 3) was not as great as that with the higher NA²-Glu dose. For both dosage regimens, inhibin levels returned to baseline levels by day 16.

Mean serum levels of LH RIA (Fig. 4A) in the elderly men declined significantly (P < 0.001) during both 10-day dosage regimens of NA²-Glu. For the higher NA²-Glu dose, LH RIA declined from 28 ± 6 µg/L on day 0 to a nadir of 6 ± 1 µg/L (21% of baseline) on day 2. This decline in LH RIA was followed by a significant spontaneous increase in serum levels to 12 ± 2 µg/L (42% of baseline) on day 4 before the serum levels again declined (Fig. 4A). With the lower NA²-Glu dosage regimen, LH RIA was suppressed to 41% of baseline by day 1, but then gradually increased to 76% of baseline by day 9. Seven days after cessation of NA²-Glu injections (day 16), LH RIA had returned to baseline levels or above.

Serum levels of LH BIO generally paralleled those of LH RIA (Fig. 4B). LH BIO was 447 ± 103 µg/L at baseline; after 75 µg/day NA²-Glu injections, LH BIO declined to 10% of baseline (to 43 ± 3 µg/L) by day 2. On days 3–4, LH BIO levels were significantly increased (P < 0.05) over the day 1 value, increasing to 31% of baseline levels; subsequently, LH BIO levels again declined to low levels (17% of baseline) on day 9 and returned to baseline levels by 1 week (day 16) after NA²-Glu injections ceased.

During NA²-Glu administration, the ratio of serum LH BIO to LH RIA (B/I) significantly declined (P = 0.003, Fig. 4E). At baseline, LH B/I was 19.7 ± 5.1; this declined rapidly, and by day 1, the ratio was 6.8 ± 0.4 (35% of
baseline). By day 4, the LH B/I had increased to 11.7 ± 2.2 and remained at that level until the antagonist was discontinued.

Serum FSH RIA levels decreased significantly ($P < 0.001$) after both dosage regimens of Nal-Glu (Fig. 4C). However, the declines in serum FSH RIA were not as large as those in LH RIA. For example, the maximum suppression of FSH RIA after the 25 µg/kg BW Nal-Glu dosage regimen was to a level of $147 ± 28 µg/L$ on day 1, a 27% decline from baseline. After the higher Nal-Glu dose, FSH RIA levels declined to as low as $95 ± 15 µg/L$ (48% of baseline) on day 9 (Fig. 4C). FSH RIA levels returned to baseline by 1 week after the last Nal-Glu injection in both dose regimens.

Serum FSH BIO measured during the 75 µg/kg BW/day dosage regimen of Nal-Glu is shown in Fig. 4D. FSH BIO levels fell rapidly with Nal-Glu injections, reaching a nadir of $142 µg/L$ (26% of baseline) on day 3, and remained low throughout the injection period. FSH BIO levels returned to baseline values by 7 days after cessation of Nal-Glu.

FSH B/I declined with antagonist administration (Fig. 4F). At baseline, FSH B/I was 2.5 ± 0.1. By day 4, the FSH B/I was 1.1 ± 0.1, a significant 56% decline from baseline ($P < 0.001$). FSH B/I remained low until cessation of Nal-Glu, at which time values returned to baseline by day 16.

Side-effects of Nal-Glu were localized to the site of sc injection and included temporary erythema, pruritus, and nontender sc induration. In the single dose studies, these local side-effects, in general, appeared to be dose related, occurring with greater frequency and intensity as the...
Nal-Glu dosage increased (Table 2). Also, in the single dose studies, the elderly men tended to have fewer local side-effects than the younger men, although, due to small numbers of men in the sample size, the differences did not reach statistical significance (Table 2).

For the multiple dosing regimens, all the elderly men experienced local erythema after the majority of injections, and a third of the men experienced sc induration lasting from 24 h to 2 weeks. Local site reactions did not appear to be any more frequent in the latter part of the regimen than after the first several injections. After the completion of each dosage regimen each man was questioned as to whether he had experienced any changes in libido or hot flashes during the study. These potential side-effects had been discussed before study entry. However, none of the elderly men complained of either decreased libido or hot flashes during the 10-day Nal-Glu dosing regimens, and none of the men withdrew from the study because of side-effects.

Discussion

We compared the effects of several single dose injections of Nal-Glu GnRH antagonist on the pituitary and testicular function of normal elderly and young adult men. Then, in elderly men we evaluated the pituitary and testicular suppressive effects of two 10-day courses with two different dosage regimens of Nal-Glu. Our results showed that healthy elderly and young men had similar suppression of pituitary and testicular function after single dose treatment with the GnRH antagonist. In addition, in the older men, significant and sustained pituitary and testicular suppression could be accomplished with the longer term antagonist treatment regimen. Although the healthy older men did not appear to be more sensitive to the testicular suppressive effects of the Nal-Glu GnRH antagonist than were the younger men, the older men tended to have fewer local side-effects from the drug injections. Overall, these results suggest that GnRH antagonists may have a role in the treatment of age-related androgen-dependent disease, such as prostate cancer.

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<thead>
<tr>
<th>Young (n = 6)</th>
<th>Elderly (n = 6)</th>
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<tbody>
<tr>
<td>Nal-Glu dose (ug/kg BW)</td>
<td>0 25 75 200</td>
</tr>
<tr>
<td>No. of men experiencing</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>0 6 8 0 4 4 5</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0 3 4 0 1 2 2</td>
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<td>SC induration</td>
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*Injection of vehicle only.

Our single dose Nal-Glu data in the elderly and young men are similar to those reported from studies of young men using Nal-Glu (17, 18) or other GnRH antagonists (19-21). With Nal-Glu, serum T levels were suppressed up to 81% in both older and younger men, while others have reported serum T suppressions between 76-91% using similar dosages in young men (17, 18). In both age groups, T suppression was rapid, with a decline beginning within 1 h after injection. In addition, as reported for young men (17, 18), increasing the dosage of antagonist led to a longer duration of T suppression rather than a more profound degree of suppression.

There was not a significant difference between the two age groups in the level of Nal-Glu-induced suppression of serum immunoreactive gonadotropins or BIO LH. Both elderly and younger men suppressed LH RIA more than FSH RIA, in agreement with other data from young men (17-19).

During the 10-day multiple dosing course of Nal-Glu, the older men demonstrated a rapid and sustained decline in serum T levels, with the maximum level of suppression being more profound at the higher Nal-Glu dose (75 ug/kg BW). On days 3 and 4 there was a minor increase in serum T levels. This T escape from suppression was small in magnitude and not sustained; by day 7 the levels of T suppression were again at a low level. These data agree well with data previously reported in young men, in regards to both the extent of suppression (18, 22) and the partial escape in the early course of treatment (18).

In the older men both LH RIA and LH BIO declined in parallel with serum T, increased somewhat on days 3 and 4, and decreased again to a maximum suppressed level by days 9–11. These parallel changes in serum LH and T suggest that the transient increases in serum levels of these hormones on days 3 and 4 may be secondary to a decrease in Nal-Glu suppression of LH secretion at the level of the pituitary. The decrease in Nal-Glu suppression could be due to an increase in endogenous GnRH secretion as a result of the lowered serum T levels. This possibility is supported by the finding that treatment of young men with the 4F GnRH antagonist, an antagonist that has a lower pituitary-binding affinity than Nal-Glu, results in a more profound T escape from suppression than seen with Nal-Glu (20). Furthermore, both coadministration of T with the Nal-Glu (22) and increasing the frequency of Nal-Glu injections (18) significantly blunt or eliminate the partial temporary escape of T and LH from suppression.

Inhibin, a testicular product felt to have a role in the selective suppression of pituitary FSH secretion (35), also demonstrated a rapid and sustained decline in the elderly men with Nal-Glu treatment. The amount of inhibin suppression was greater at the higher Nal-Glu.
dosage regimen used, but the degree of suppression was not as great as for serum T levels (maximum suppression to 54% for inhibin compared to 12% for T). Furthermore, FSH, by both bioassay and immunoassay, was not suppressed as much as LH by the Nar-Glu. The weaker suppression of FSH compared to LH may be related to the simultaneous decline in serum inhibin levels, or it may be due to the propensity of the pituitary to release greater amounts of FSH than LH under conditions of decreased effective GnRH secretion.

In the older men, with the multiple Nar-Glu dosing regimen both bioactive LH and FSH serum levels were suppressed to a greater extent than immunoreactive levels, thus leading to a fall in the gonadotropin B/I ratios. This decline in B/I ratio has been recognized with LH after Nar-Glu treatment in young men (18) and for FSH after treatment with another GnRH antagonist in hypogonadal women (36). It is not known if Nar-Glu treatment induces the formation of an anti-FSH, as has been described with another GnRH antagonist (38).

Overall, the healthy older men in this study demonstrated responses similar to those found of young men after single dose treatment with the Nar-Glu GnRH antagonist. In addition, our results with the 10-day course of treatment in older men showed similar responses to that previously shown in younger men (22). These results might not have been expected based on experiences with GnRH agonists in the treatment of older men with prostate disease. Older men treated with an GnRH agonist for prostatic cancer demonstrated profound T suppression (5), and testicular biopsies of older men who were treated showed spermatogenesis to be absent, whereas this was not the case with young men (37). Clearly, healthy older men do not seem to be more sensitive than young men to the suppressive effects of up to 10-day treatment with the Nar-Glu antagonist (22). This suggests that perhaps illness, such as prostate cancer, may affect the physiological response of the pituitary and testes more than does the aging process itself. Perhaps prostate cancer patients have enough testicular dysfunction secondary to their illness that they become more susceptible to the suppressive effects of the GnRH analogs (1).

Of interest is the finding that the older men as a group tended to have fewer local reactions to the Nar-Glu injections than the younger men. GnRH antagonists are mast cell secretagogues (38). Since aging has been associated with impaired contact sensitivity response (39), it may be that older men are not able to react as vigorously to the histamine-releasing effects of the Nar-Glu antagonist as younger men. This would suggest that the local side-effects of the GnRH antagonists may pose less of a treatment problem in older men. In addition, third generation GnRH antagonists are now being developed (40) that have less histamine-releasing properties.

In conclusion, Nar-Glu GnRH antagonist, whether given in single doses or daily for 10 days, results in a significant suppression of serum T, inhibin, and bioactive and immunoreactive gonadotropin levels in elderly men. In addition, the level and duration of suppression in healthy elderly men are similar to those reported in younger men. This suggests that aging per se does not seem to alter the sensitivity to the suppressive effect of GnRH analogs. However, older men may be less sensitive to the local side-effects often seen with the GnRH antagonists, and GnRH antagonist use in older men causes a decline in serum androgen levels within about an hour after administration without a phase of androgen stimulation. Both of these findings suggest that the GnRH antagonists may have an important role in the treatment of age-related androgen-dependent disorders.

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References

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