An investigation of the effectiveness of testosterone implants in combination with the prolactin inhibitor quinagolide in the suppression of spermatogenesis in men

W.Morton Hair¹, Frederick C.W.Wu² and Gerald A.Lincoln¹,³

¹MRC Human Reproductive Sciences Unit, The University of Edinburgh, The Chancellor’s Building, 49 Little France Crescent, Edinburgh EH16 4SB and ²University Department of Endocrinology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK
³To whom correspondence should be addressed. E-mail: g.lincoln@hrsu.mrc.ac.uk

BACKGROUND: Administration of testosterone inhibits gonadotrophin secretion and spermatogenesis in men but the degree of response is highly variable. This treatment also stimulates prolactin, itself a progonadal hormone in animals. This study investigated whether concomitant suppression of prolactin (PRL) with the non-ergot, dopamine receptor agonist quinagolide (Q), would enhance the efficacy of testosterone in its inhibition of spermatogenesis in healthy eugonadal men. METHODS: A total of 46 men were randomized to three treatment groups: Group 1, T1200: 1200 mg testosterone implant plus daily oral placebo; Group 2, T1200 + Q: 1200 mg testosterone plus oral Q 75 mg/day; Group 3, T800 + Q: testosterone 800 mg plus oral Q 75 µg/day. After an initial pre-treatment period of 4 weeks, subjects were treated for 24 weeks followed by an 8-week recovery period. RESULTS: The total numbers of subjects that achieved severe oligospermia (<10⁶/ml including azoospermia) from weeks 8–16 were 11/13 (85%), 11/12 (92%), 8/13 (61.5%) in the three groups respectively. CONCLUSIONS: The results show that inhibition of PRL does not confer additional efficacy in spermatogenic suppression in men. However, Q did not totally block PRL secretion in the subjects, possibly because testosterone replacement itself stimulated PRL by a direct action on the lactotroph, thus the effectiveness of dual inhibition of gonadotrophin and PRL could not be fully investigated.

Key words: prolactin inhibition/quinagolide/spermatogenesis/testosterone

Introduction

Androgen administration aimed at producing a reversible contraceptive for men acts by inhibition of FSH and LH secretion to suppress spermatogenesis. It does not however suppress PRL secretion, which, at least in animal models, is a weak gonadotrophin (Bartke et al., 1975; Oughtit et al., 1993; Lincoln et al., 1996; Jabbour and Lincoln, 1999). Initial studies showed that long-term treatments with testosterone esters, even at high doses, induce azoospermia in only a proportion (~65%) of subjects with notable differences between ethnic groups (World Health Organization Task Force, 1990; Handelsman et al., 1992; Sundaram et al., 1993; Behre et al., 1995). More recently, steroid treatments involving testosterone combined with progestins, have been shown to be more effective in the suppression of spermatogenesis (Bebb et al., 1996; Handelsman et al., 1996; Meriggiola et al., 1996; Wu et al., 1999; Martin et al., 2000). A number of suggestions have been proposed to explain the heterogeneity in the contraceptive response to steroid treatments. These include differing sex hormone-binding globulin (SHBG) levels and responsiveness to gonadotrophin suppression (Behre et al., 1995; Wang et al., 1998), differing 5-alpha reductase activity in the testis and its impact on intra-testicular androgen levels (Anderson et al., 1996), structural differences in testicular morphology between ethnic groups (Zhengwei et al., 1998) and possible differences in sex steroid metabolism and/or diet (Santner et al., 1998).

An additional explanation for the failure to induce complete azoospermia is that it may be necessary to inhibit PRL, in addition to the classical gonadotrophins, to fully block spermatogenesis. This is because PRL potentially acts in the testis to stimulate both androgenic and spermatogenic functions, based on studies in rodents (Hondo et al., 1995). In man the progonadal role of PRL is less clear. Early studies using I125-PRL failed to demonstrate PRL binding in the human testis, in contrast to the situation in the rat (Wahlstrom et al., 1983). More recently, mRNA for the PRL receptor has been
characterized in the human testis (Kline et al., 1999), and immunocytochemistry has revealed that PRL receptors are weakly expressed in the Leydig cells in the interstitial tissue and more strongly expressed in germ cells undergoing spermatogenesis in the seminiferous tubules (Hair et al., 2002). Functional activation of these receptors and their secondary messenger systems JAK-STAT and the extracellular signal-regulated kinase (ERK) by PRL has also been demonstrated in human testis and vas deferens. Furthermore, there is clinical data indicating that PRL may promote spermatogenesis. In one study, treatment with exogenous PRL, or a dopamine antagonist to increase circulating PRL concentrations was shown to restore testicular function and fertility in hypoprolactinaemic infertile men (Ufearo and Orisakwe, 1995), and in another study, combined suppression of gonadotrophins and PRL in eugonadal men treated for prostatic carcinoma produced a more marked reduction in testicular weight than gonadotrophin suppression alone (Huhtaniemi et al., 1991). Based on these observations, and the demonstration that the administration of testosterone and oral progestin stimulates PRL secretion (Bellis and Wu, 1998), we infer that suppression of PRL may enhance the effectiveness of sex steroid in inducing spermatogenic suppression in man.

The purpose of the present study was to test this hypothesis. Healthy male volunteers were treated orally with the non-ergot dopamine receptor agonist quinagolide (Q), to chronically suppress PRL secretion. This drug has been shown to inhibit PRL production with minimal effects on the gastrointestinal tract and on nausea, mood and sleep behaviours (Brownell et al., 1996). At the start of the treatment, the volunteers also received s.c. implants of testosterone to suppress gonadotrophin secretion. Implants were used rather than intermittent injections to provide a smooth androgen profile with less inconvenience to the subjects. A high and an intermediate dose of testosterone was selected to establish whether PRL inhibition would act in synergy with the degree of gonadotrophin suppression and perhaps allow use of a lower dose of androgen to induce azoospermia in men.

A preliminary report on this study has been published as an abstract (Hair et al., 2000).

Materials and methods

Subjects

The study medication and design, information for volunteers, method of recruitment and the reimbursement of expenses were all approved by the Central Manchester Ethical Committee for Medical Research and by the Medical Research Council. Prospective volunteers were recruited from the community through local media advertising. Written and verbal information as to the nature of the study was provided to 480 men. Prospective candidates were then interviewed during which a full medical history was obtained and thereafter underwent physical examination. Routine haematology, biochemistry and semen analysis were then performed as screening tests on two occasions 2 weeks apart, to determine if subjects met the inclusion criteria. The subjects were required to be within the age range 19–50 years, free of chronic disease, on no long-term medication, with normal haematology and biochemical screening tests and a normal semen profile based on World Health Organization (WHO) guidelines (World Health Organization, 1999). The subjects were also required to be willing to continue with their existing contraceptive method. Following recruitment, 46 volunteers entered the study.

Medications

Quinagolide (Q) was used to chronically inhibit PRL secretion in the volunteers. The drug tablets were supplied by Novartis (Norprolac; Novartis Pharmaceuticals UK Ltd, Frimley, Surrey, UK). Subjects initially received a Starter Pack containing two tablets each of 25, 50 and 75 µg of Q to allow graded introduction of the medication. Following the introduction over 6 days, the subjects took one 75 µg tablet per day. This dose was selected based on manufacturer’s recommendations in the treatment of hyperprolactinaemia to effectively suppress PRL secretion and minimize side effects. A small pilot study in five normal men was also conducted. This demonstrated that daily administration of 75 µg Q suppressed blood plasma PRL concentration by >80% for the 9 day treatment period with a carryover effect for 3 days. For the main clinical trial, tablets were taken after food and before bed. Placebo tablets supplied by our hospital pharmacy were taken by one group of subjects as a control.

Crystalline testosterone implants (200 mg) were generously donated by Organon (Product licence No. 0065/5084R; NV Organon, Oss, Netherlands). Implants were inserted using a trocar with sterile technique in the s.c. fat of the anterior abdominal wall with local anaesthesia using 1% lignocaine. In the high dose treatment the subjects received six implants (1200 mg), and in the lower dose they received four implants (800 mg). These doses were selected on the basis that 1200 mg testosterone produces severe oligospermia in normal men, while 800 mg testosterone less completely suppresses sperm numbers.

Study design

Subjects were randomized to one of three treatment groups in a single blind parallel group design: Group 1; testosterone 1200 mg plus daily oral placebo (T1200); Group 2: testosterone 1200 mg plus oral Q 75 µg/day (T1200 + Q); and Group 3: testosterone 800 mg plus oral Q 75 µg/day (T800 + Q). A more balanced design would have utilized a T800 + placebo group but this was not included due to constraints on the number of volunteers and the power calculation requirement of no fewer than 12 subjects per group. The protocol involved a pre-treatment phase of 4 weeks, a treatment phase of 24 weeks and a recovery phase of 8–12 weeks (see Figure 1). The treatment phase was initiated by the insertion, on one occasion, of either four or six testosterone implants according to treatment-group. The subjects also commenced daily oral Q, or placebo tablets, which were dispensed monthly at the clinical monitoring visit. Treatment of the subjects did not occur simultaneously but was staggered according to time of recruitment. The recovery phase was determined by the time to re-attainment of the pre-treatment sperm concentration in the ejaculate, or to two consecutive sperm counts >20×10⁶/ml.

Clinical monitoring

Every 4 weeks throughout the study each subject was weighed and pulse and blood pressure measured. They were then interviewed to record evidence of compliance, unused tablets were returned and any notable effects of the treatment were recorded. A blood sample was obtained for hormone measurements, and a semen sample was produced for analysis. The blood samples were heparinized, centrifuged within 30 min of collection and stored at −20°C until analysis on completion of the full study. Every 8 weeks, additional blood samples were obtained for monitoring of haematological parameters, renal and liver function tests and serum lipid concentrations. Testis size was measured using an orchidometer. At the
beginning and end of the study a standard rectal examination of the prostate was carried out.

**Semen analysis**

Semen samples were obtained by masturbation after 48 h abstinence and analysis of semen volume, pH, sperm concentration, motility and morphology was carried out within 60 min of collection according to WHO guidelines (World Health Organization, 1999). Azoospermia was verified by centrifugation of the whole semen sample and microscopic examination of the re-suspended pellet residue.

**Blood analysis**

Full blood counts, glucose, HbA1c, urea, electrolytes, liver enzymes and lipid profiles were measured by a hospital auto-analyser. Low-density lipoprotein (LDL) cholesterol was derived using the Friedwald formula. On completion of the clinical study the blood plasma concentrations of prolactin (PRL), FSH and LH were assayed in all subjects by highly sensitive immunofluorometric assays (Delfia, Pharmacia-Wallac, Turku, Finland) with an assay sensitivity of 9.0, 0.125 and 0.125 IU/l, respectively. Total testosterone was determined by previously described radioimmunoassay (Corker and Davidson, 1978) with a detection limit of 0.3 nmol/l.

**Statistical analysis**

Results are expressed as group mean ± SEM. Data were analysed by two-way ANOVA with repeated measures using Statistica software (version 4.0) to identify significant time-by-group interactions with Tukey's post-hoc comparisons. In addition, ANOVA with repeated measures was performed within each group to detect significant effects of treatment. Baseline levels for each variable were defined as the arithmetic mean of the two pre-treatment samples. Recovery levels were defined as those obtained at 4–12 weeks following completion of treatment according to time at which the recovery criteria were met. Severe oligospermia was defined as a specimen with sperm present in the ejaculate but at a concentration of <1×10⁶/ml. Testis volume was defined as the sum of volume measurements for the left and right testis. The 8–20 week period was selected as the period of maximum sperm suppression.

**Results**

**Subjects**

Of the 46 men who entered, 38 completed the study. Five men failed to attend regular clinical appointments and were lost to follow-up after 4–20 weeks without explanation. One man was withdrawn from the study due to extrusion of two testosterone implants and due to his lack of compliance with oral Q. Two subjects did not tolerate oral Q: in one case, the treatment caused symptoms of nausea and vomiting during the first few days of treatment and in the second case the treatment caused perceived effects on mood and libido from week 4 and the subject subsequently withdrew at week 16. After these losses the group sizes were 13, 12 and 13 for T1200, T1200 + Q and T800 + Q treatments respectively.

In the 38 men who completed the study, the oral Q and testosterone implants were generally well tolerated and there were no serious adverse effects reported by the participants. Transient morning nausea in the first week was reported by two subjects taking oral Q and by one subject taking the placebo. Mild acne was reported in four subjects and increased libido at the start of the study was reported in 16 subjects. There was no apparent difference in these symptoms in the three treatment groups. The men did not differ significantly between groups in age (Group T1200 + placebo, 30.77 ± 1.99 years; Group T1200 + Q, 33.36 ± 1.5 years and Group T800 + Q, 34.75 ±
follows: 43.5

The mean PRL concentrations for the treatment period were as
T800 + Q groups, compared with the T1200 + placebo group.
throughout the treatment period) in the T1200 + Q and
were significantly \( (P < 0.05) \) time-by-treatment interaction. PRL concentrations were significantly \( (P < 0.05) \) decreased at weeks 4–24 (throughout the treatment period) in the T1200 + Q and T800 + Q groups, compared with the T1200 + placebo group. The mean PRL concentrations for the treatment period were as follows: 43.5 ± 18.6, 52.6 ± 21.4 and 162.3 ± 14.9 mIU/l for the T1200 + Q, T800 + Q and T1200 + placebo groups respectively. There was no significant difference in the PRL concentrations between the two groups that received Q. PRL was suppressed by at least 80% (compared to pre-treatment values) in 9/12 (75%) subjects in the T1200 + Q group, and in 9/13 (69%) subjects in the T800 + Q group. The remaining subjects suppressed to a mean 47.73 ± 8.26% (range 11.2–72.2%). There was no disclosed non-compliance to explain this variability in PRL suppression.

There was also evidence that testosterone alone increased PRL secretion. In the testosterone 1200 + placebo group, plasma PRL concentrations increased significantly \( (P < 0.05) \) relative to pre-treatment values at week 4 following insertion of the testosterone implants. In the testosterone 1200 + Q and T800 + Q groups, PRL concentrations also increased significantly \( (P < 0.05) \) above the placebo group at week 28, as a rebound response to cessation of Q.

**Testosterone implantation**

After insertion of the testosterone implants, total testosterone concentration increased above baseline for 4–8 weeks in all groups (Figure 1, upper right panel). The analysis of the total testosterone concentration in blood plasma showed a significant \( (P < 0.001) \) effect of time but no statistical differences between groups, although plasma concentrations of testosterone were lower in the T800 + Q group.

**Gonadotrophin suppression**

Plasma LH and FSH concentrations were markedly suppressed by the testosterone treatment in all groups (Figure 1, lower panels). Concentrations were lowest at week 4 and remained suppressed until week 12 before increasing to pre-treatment values by week 24. The analysis revealed a significant \( (P < 0.001) \) time-by-treatment interaction; the plasma LH and FSH concentrations were significantly \( (P < 0.05) \) lower in both T1200 groups compared with the T800 + Q group from weeks 4–16. There was no significant difference in gonadotrophin concentrations between the T1200 + placebo and the testosterone 1200 + Q groups during the phases of suppression and recovery.

Figure 2. Long term changes in sperm density in the ejaculate of groups of male volunteers treated with testosterone (T) implants with either quinagolide (Q) or placebo as follows: (i) T1200 mg + daily oral placebo (open square symbol), (ii) T1200 mg + 75 µg daily oral Q (closed square symbol), (iii) T800 mg + 75 µg daily oral Q (open round symbol). The testosterone implants were inserted once only at week 0 and the Q treatment was continued for 24 weeks (horizontal bar = treatment period). Values are mean ± SEM. \( n = 13, 12 \) and 13 for the three groups respectively.

**Sperm suppression and recovery**

Pre-treatment sperm concentrations in the ejaculate were similar in the three treatment groups (group means: 55.19 ± 8.09, 40.62 ± 6.97, 51.08 ± 9.36 millions/ml for T1200 + placebo, T1200 + Q and T800 + Q respectively) (Figure 2). Sperm concentration fell sharply in all groups by week 4 of treatment and continued to decline until weeks 12–16 before increasing by week 24. Sperm concentrations returned to pre-treatment values by weeks 28–32. The analysis demonstrated a significant \( (P < 0.001) \) time-by-treatment interaction, with sperm concentrations significantly \( (P < 0.05) \) reduced in both T1200 groups, compared with the T800 + Q group from weeks 12–20. There was no significant difference in sperm concentrations between the T1200 + placebo and the testosterone 1200 + Q groups during the phases of suppression and recovery.

The proportion of subjects in each group who achieved severe oligospermia/azoospermia (sperm concentration <1×10⁶/ml) for at least 4 weeks was 11/13 (85%), 11/12 (92%), 8/13 (61.5%) in T1200 + placebo, T1200 + Q and T800 + Q groups respectively. The corresponding numbers achieving azoospermia were 5/13 (38%), 6/12 (50%) and 5/13 (38%). The group profiles for the incidence of oligospermia and azoospermia are summarized in Figure 3. Inhibition was maximal at weeks 8–16 with a similar pattern in the three treatment groups; the incidence of sustained oligo/azoospermia was least in the testosterone 800 + Q group. In this group, the subjects in which PRL secretion was maximally inhibited (suppression >80% of pre-treatment, \( n = 9 \)), the degree of spermatogenic suppression was notably greater than in those subjects in whom PRL was inadequately suppressed (\( n = 4 \)). Severe oligospermia/azoospermia was achieved in 78% of the PRL inhibited group but only 25% in the poorly inhibited
group; this apparent association between PRL and sperm production was not evident in the testosterone 1200 + Q group. Progressive motility (WHO categories, a + b) was unaffected by treatment in the three groups. Ejaculate volume was marginally decreased in the three treatment groups from weeks 12±20 (range 8±29%) with no difference between groups. Semen pH was unaffected by treatment.

Metabolic, haematological and general effects of treatment
Blood plasma concentration of high-density lipoprotein (HDL) cholesterol was decreased at week 12±20 during treatment with no significant differences between the three groups. Concentrations had not returned to pre-treatment values by the end of the recovery period. Total cholesterol, triglycerides and LDL cholesterol concentrations were not affected by the treatments. Body weight, blood pressure, pulse, liver function tests (albumin, aspartate amino transferase, alanine amino transferase, alkaline phosphatase and albumin), glucose metabolism (fasted blood glucose, HbA1c) and renal function (electrolytes, urea, creatinine) were also unaffected by the treatments. Haemoglobin concentrations were significantly ($P < 0.01$) increased at week 12 in all groups, in parallel with experimentally induced changes in testosterone, but were otherwise unaffected. Other haematology indices (white blood cell count and platelets) were unaffected. Prostate examination revealed no changes related to any treatment.

Discussion
The aim of this study was to establish whether suppression of PRL enhances the effectiveness of exogenous testosterone in inhibiting sperm production in normal men. This was based on the potential progonadal effects of PRL, and the presumption that the simultaneous suppression of both PRL, and the classical gonadotrophins LH and FSH, would induce more complete spermatogenic arrest. The overall results do not support the hypothesis. The degree of spermatogenic arrest and the period of induced azoospermia was similar in the T1200 and T1200 + Q groups, and the effects in the T800 + Q group were comparable to those previously reported for men receiving this dose of testosterone alone (Handelsman et al., 1992). There was, therefore, no significant effect on the spermatogenic profiles associated with the chronic treatment with our selected dose of Q.

The current experiment was designed to compare treatments with and without Q in the presence of a standardized high dose of testosterone (T1200 mg). This was based on the expectation that this level of testosterone would produce sub-maximal sperm suppression and allow us to detect an additional effect due to Q. However, the T1200 mg treatments in this study produced a very high degree of sperm suppression, leaving little scope to observe an additional effect of Q during the treatment phase. We therefore looked for an effect of the PRL manipulation on the pattern of recovery at the time when the testosterone implants were becoming exhausted (weeks 12–24) and daily Q treatment continued. Again, there was no significant difference between the T1200 + placebo and T1200 + Q groups in this pattern of recovery, although the T1200 + Q subjects were the last to return to pre-treatment values, and there was a period at weeks 24–28 where there was no overlap in sperm concentrations between the two groups, that is suggestive of a marginal effect. The only evidence that the Q treatment may have had some androgen dose-sparing effect was obtained from the T800 + Q group. In this group, there was marked individual variation in the degree of inhibition of PRL and degree of spermatogenic suppression. In the subjects in which PRL secretion was maximally inhibited (suppression >80% of pre-treatment, $n = 9$), the degree of spermatogenic suppression was greater than in those subjects in whom PRL was inadequately suppressed ($n = 4$). Severe oligospermia was achieved in 78% of the PRL inhibited group, which was comparable with 85% for the T1200 + placebo group. This provides minimal support for the view that only in partial hypogonadotrophic states when gonadotrophin concentrations are sub-maximally reduced (as in the T800 group), is it possible to observe any concomitant effect of PRL.
withdrawal. A subtle interactive effect of PRL and gonadotrophin status has previously been described in animal models where the effects of LH and FSH on testicular physiology always predominate (Bartke, 1999; Lincoln et al., 2001).

The unexpected finding in our trial was that the oral Q was not fully effective at blocking PRL and there was marked variability in the degree of PRL suppression between subjects in both the T800 + Q and T1200 + Q groups. This was despite the findings of the short pilot study clearly showing that oral Q at 75μg/day markedly suppressed blood PRL concentrations towards the minimum assay detection limit. There are several possible explanations to account for this anomaly. The first is that the subjects failed to comply with the experimental protocol of taking daily Q. However, monthly tablet returns and rigorous questioning at the monthly clinical monitoring did not suggest a significant level of non-compliance. Given that the elimination half-life of quinagolide is 17.5 h (Brownell et al., 1996), the omission of occasional tablets is unlikely to have had a significant long-term effect on PRL control. Moreover, at the end of the treatment period, there was a notable increase in PRL concentrations in all subjects that received Q. This is a rebound response to chronic dopamine receptor agonist withdrawal and further supports our contention that subject compliance was good. The second explanation is that chronic Q treatment resulted in the development of refractoriness to PRL inhibition. Q is routinely used clinically is that chronic dopamine receptor agonist withdrawal and further supports our contention that subject compliance was good. The second explanation is that chronic Q treatment resulted in the development of refractoriness to PRL inhibition. Q is routinely used clinically in the treatment of hyperprolactinaemia in both men and women without clear evidence of long-term loss of responsiveness (Homburg et al., 1990; Schultz et al., 2000). Such refractoriness, however, may only in the suppression of PRL in men with normal physiological concentrations of PRL (Rana et al., 1995).

The third, and perhaps most important factor, is that the testosterone treatments themselves activated PRL secretion, thus rendering the Q less effective. Previous work has shown that plasma PRL concentrations are significantly increased in men treated with testosterone enanthate injections (Bellis et al., 1998). In the current study, blood PRL concentrations were significantly increased in the placebo treated subjects 4 weeks after the administration of the 1200 mg testosterone implants. Furthermore, it is well known from pituitary cell culture studies using animal tissues that both testosterone and estradiol potently stimulate PRL synthesis and release due to a direct genomic effect on the lactotroph (Shull et al., 1985; Lambert and McLeod, 1990). This can occur independently of the inhibitory effect of dopamine receptor activation. Clinical studies also support the view that sex steroid status affects PRL secretion. For example, the efficacy of bromocriptine in the suppression of PRL secretion is reduced in hyperprolactinemic women during pregnancy when estradiol concentrations are increased and PRL secretion decreases in the menopause and after pregnancy when sex steroid concentrations decline (Karunakaran et al., 2001). Such steroid effects on PRL secretion in our trial subjects would render Q inhibition of PRL less effective. These effects of chronic treatment in normal men were not anticipated, but clearly compromised the objective of this study.

A final point is that Q was well tolerated with no serious adverse effects reported. Prolactin acts in multiple target tissues including brain, liver, skin, prostate and accessory glands. Despite this, chronic PRL suppression using Q had no demonstrable effects on semen volume, sexual behaviour and a wide range of haematological and biochemical indices demonstrating desirable specificity of action on the reproductive axis. Treatment with testosterone produced the expected effects on HDL cholesterol (Wallace and Wu, 1990), but this was not blocked or enhanced by the manipulation of PRL. There were a number of casual observations on the effect of chronic PRL suppression. The incidence of acne was lower than expected and two subjects noted an improvement in the condition of their skin and hair.

Conclusions
The current study investigated for the first time whether manipulation of PRL would enhance the efficacy of testosterone in the suppression of spermatogenesis in men. The results did not support this idea. Unexpectedly it proved difficult to achieve consistent long-term inhibition of PRL secretion in the men. Future studies will need to establish a means of totally blocking PRL release, or to utilise a cross-over design in which all subjects receive both PRL inhibitor and placebo, to test whether concomitant testosterone and PRL blockade would induce complete spermatogenic arrest. The idea of employing lower levels of testosterone, and reducing PRL due to its trophic effects on the prostate, make a combined preparation of this kind an attractive prospect in the regulation of male fertility.

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