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Use of testosterone alone as hormonal male contraceptive

Utilisation de la testostérone seule comme contraception masculine hormonale

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Abstract The world population continues to grow rapidly while resources for sustainable living dwindle and man-made ecological problems increase proportionally to the overpopulation. Family planning is required to reduce population growth in developing countries and to stabilize populations in developed countries. Contraception makes abortion superfluous and provides the key to family planning. Women increasingly demand that men share the burden and risks of contraception and – as opinion polls show – men would be willing to use contraceptives if they were available. Research has established the principle of hormonal male contraception based on suppression of gonadotropins and spermatogenesis. All hormonal male contraceptives use testosterone, but in East Asian men, testosterone alone can suppress spermatogenesis to a level compatible with contraceptive protection. In Caucasians additional agents are required of which progestins are favoured.

Keywords World population · Family planning · Male contraception · Spermatogenesis suppression · Testosterone preparations · Synthetic androgens.

Résumé La croissance de la population mondiale se poursuit rapidement alors que les ressources pour un développement durable s'amenuisent et que les problèmes écologiques issus de l'activité humaine augmentent proportionnellement à la surpopulation. Une planification familiale est nécessaire pour réduire la croissance de la population dans les pays en développement et pour stabiliser celle des pays développés. La contraception rend l'avortement superflu et fournit les clés d'une planification familiale. Les femmes demandent de plus en plus que les hommes partagent le poids et les risques de la contraception, et — comme le montrent les enquêtes d'opinion — les hommes seraient prêts à utiliser des contraceptifs s'ils étaient disponibles. La recherche a établi le principe d'une contraception masculine hormonale basée sur la suppression des gonadotrophines et de la spermatogenèse. Toute contraception masculine hormonale utilise la testostérone, mais la testostérone seule ne peut réduire la spermatogenèse à un niveau compatible avec une protection contraceptive que chez les hommes d'Extrême-Orient (Asie de l'Est). Chez les Caucasiens, des substances additionnelles sont nécessaires pour atteindre ce niveau, parmi lesquelles les progestatifs sont privilégiés.

Mots clés Population mondiale · Planification familiale · Contraception masculine · Suppression de la spermatogenèse · Formes de testostérone · Androgènes de synthèse

Introduction

Men have more and more expectation and the will to share the responsibility of family planning by using contraceptive methods. Considering the disadvantages of traditional male contraceptive methods (i.e. periodic abstinence, coitus interruptus, condom and vasectomy), the prerequisite for an ideal pharmacologic male contraceptive should [1]:

- be applied independently of the sexual act;
- be acceptable for both partners;
- not interfere with libido, potency, or sexual activity;
- have neither short- nor long-term toxic side effects;
- have no impact on eventual offspring;
- be rapidly effective and fully reversible;
- be as effective and as comparable to the female methods.

Of all the different experimental approaches and pharmacological methods tested so far for male contraception, hormonal methods come closest to fulfilling the criteria set out. The endocrine feedback mechanism operating between hypothalamus, pituitary and testes is the basis on which hormonal approaches to male contraception rest. Its goal is

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to suppress spermatogenesis and to reduce sperm concentration, if possible, to azoospermia or at least to a sperm concentration low enough to provide contraceptive protection as effective as oral contraceptives in women (i.e. < 1 million sperm per ml of ejaculate).

Sperm production and secretion of testicular testosterone are so closely interwoven that it has remained impossible to interrupt spermatogenesis by hormonal means without inhibiting androgen production. Inhibition of FSH alone, e.g., by antibodies, leads to reduction of sperm concentration but not to azoospermia, as monkey studies have shown [2]. Suppression of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) would indeed lead to azoospermia, but would also induce symptoms of androgen deficiency which affects libido, potency, male role behaviour and general metabolic processes (erythropoesis, protein, mineral and bone metabolism). For this reason inhibition of gonadotropins will always necessitate androgen administration.

Thus, the principle of hormonal male contraception is based on [1]:

- suppression of LH *and* FSH;
- depletion of intratesticular testosterone and atrophy of spermatogenesis;
- substitution of peripheral testosterone to maintain androgenicity.

Testosterone itself is a first choice as it simultaneously suppresses the gonadotropins and maintains androgenicity and indeed, testosterone alone was the first hormone tested for male contraception and remains part of any steroid combination to date. In this article, the trials that used testosterone alone for male contraception are summarized.

Natural testosterone

Testosterone enanthate

Soon after testosterone was synthesized and became available for clinical use in the late 1930s, its spermatogenesis-suppressing effect was recognized, but not until the 1970s did investigations start to exploit this phenomenon for male contraception. As in most hormonal male contraceptive studies to date, in the early studies sperm concentrations and counts were used as surrogate parameters for efficacy [3].

The first efficacy study of testosterone-based hormonal male contraception was sponsored by the WHO and included 10 centres on four continents [4]. Healthy fertile participants were given 200 mg of the longer-acting testosterone enanthate weekly by intramuscular injection. One hundred fifty-seven men (70%) reached azoospermia after 6 months of treatment and entered the efficacy phase for a further year, during which no other contraceptive was used by the couple. Only one pregnancy was reported in this first proof-of-principle study. Although the efficacy of this study was very high, it cannot be used to determine the overall efficacy of testosterone alone as a contraceptive because only men who became azoospermic could enter the efficacy phase while the others were excluded.

In order to clarify the question whether men developing oligozoospermia can be considered infertile, a second worldwide multicentre efficacy study involving 357 couples followed [5]. In this study azoospermia again proved to be a most effective prerequisite for contraception. If sperm concentration, however, failed to drop below 3 million/mL of ejaculate, resulting pregnancy rates were higher than when using condoms. When sperm concentrations decreased below 3 million/mL, which was the case in 98% of the participants, then protection was not as effective as for azoospermic men, but was better than that offered by condoms.

From these two WHO trials it became clear that East Asian men responded with a higher rate of azoospermia than Caucasian men. Although this phenomenon could not be fully explained to date it formed the basis for very effective trials in Chinese couples using testosterone undecanoate alone as described below.

Even if these WHO studies represented a breakthrough by confirming the principle of action, they did not offer a practicable method. For a method requiring weekly intra muscular injections is not acceptable for broad use. Moreover, several months, often up to one year, are required before sperm production reaches significant suppression. For this reason, current research is concentrating on the development of long-acting testosterone preparations and on methods to hasten the onset of effectiveness.

Testosterone buciclate

As long-acting testosterone preparations appeared more promising in terms of practicability and acceptability, WHO and the NIH initiated a synthesis program for such preparations [6] through which the long-acting testosterone ester testosterone buciclate was identified. This molecule showed a half-life of 29.5 days when tested in hypogonadal men, much longer than the 4.5 days of testosterone enanthate [7]. Suppression of spermatogenesis was comparable to that of weekly testosterone enanthate injections, reaching azoospermia in three out of eight volunteers after a single injection of 1200 mg of testosterone buciclate [8]. Despite its promising pharmacokinetic profile, no industrial partner could be found to undertake development of this preparation.

Testosterone pellets

Pellets consisting of pure testosterone are used for substitution in hypogonadism in some countries. In male

contraceptive studies, the sperm-suppressing effect was comparable to weekly testosterone enanthate injections [9]. The disadvantage of minor surgery required for insertion under the abdominal skin is compensated by their low price. Spontaneous extrusion may be a disadvantage.

Testosterone undecanoate

Oral testosterone undecanoate

Initially, testosterone undecanoate was studied as an oral preparation in volunteers of Caucasian origin [10]. Subjects were given a daily dose of 240 mg over a period of 12 weeks, but only one out of seven volunteers reduced sperm output sufficiently for contraception. This low effectiveness is probably due to the short half-life of testosterone undecanoate when given orally. Even if administered four times a day, the peaks are not sufficient to suppress gonadotropins consistently and thereby to achieve azoospermia.

Intramuscular testosterone undecanoate (TU)

• TU in tea seed oil

While testosterone undecanoate had been developed as an oral preparation in Europe, it was turned into an injection in China, using tea seed oil as a vehicle and is used as such in China for hypogonadism and in trials for male contraception. Back in Europe, the half-life of this Chinese preparation could be extended even further when dissolved in castor oil and is now available for clinical use in 1000 mg depot injections [11].

In the clinical trials in China, testosterone undecanoate alone administered every 4 weeks resulted in azoospermia in all Chinese men who received a dose of 1000 mg and in azoospermia or severe oligozoospermia in 95% of Chinese men who received a dose of 500 mg during a 4–6 month suppression phase [12]. In the ensuing Phase III study involving 305 couples, an efficacy phase followed the suppression phase and no pregnancies were initiated by men exhibiting azoospermia or severe oligozoospermia [13]. However, reappearance of sperm occurred in six men during the efficacy phase; one pregnancy was attributed to "sperm rebound". Side effects observed in subjects were all typical of elevated testosterone serum levels.

The largest efficacy study to date was also performed in China, based on a loading dose of 1000 mg followed by monthly injections of 500 mg testosterone undecanoate. When sperm counts had fallen below 1 million sperm/mL, 898 men entered the efficacy phase during which only 9 pregnancies were recorded. This represents a pregnancy rate of 1.1/100 person-years [14]. Thus, in China, testosterone undecanoate provides better protection against pregnancy than condom use. Although injection intervals of four weeks appeared to be an achievement over the weekly injections of testosterone enanthate, the participants in a Chinese study considered the frequency of injections the most inconvenient part of this regimen [15]. If testosterone undecanoate in castor oil were to be used in China, this complaint could certainly be overcome.

• TU in castor oil

In a first contraceptive trial of testosterone undecanoate in castor oil 1000 mg were injected into 14 Caucasian volunteers at 6-week intervals. Eight of 14 men achieved azoospermia [16]. Although this rate of azoospermia is not different from that achieved with testosterone enanthate alone, the longer injection interval represents a significant advantage. A later pharmacokinetic study concluded that 8-week intervals of 1000 mg injections would be sufficient for contraceptive purposes [17].

Considering that 10 to 14-week intervals between 1000 mg testosterone undecanoate injections are required for substitution of hypogonadal men, about 1/3 more testosterone is required for contraception in normal volunteers.

• TU in men with subnormal semen values

Clinical studies to date have only included volunteers with "normal" semen values considered by WHO standards. As a male contraceptive should be available to all interested men regardless of their semen parameters, how volunteers with subnormal semen parameters respond to hormonal male contraception has recently been investigated [18]. During a 34-week treatment phase, the volunteers received injections of 1000 mg testosterone undecanoate in weeks 0, 6, 14 and 24. This was followed by a 24-week recovery and follow-up period. As it was not known whether men with subnormal semen parameters would recover to starting levels, cryopreservation of semen was offered to all subnormal volunteers.

Twenty-three men with normal semen parameters and 18 with sperm counts below 20 million completed the trial. The normal volunteers showed the expected response with 17 suppressing sperm counts below 1 million/ejaculate (13 showing azoospermia) and 6 not-suppressing below 1 million sperm/ejaculate. By the end of the recovery period all sperm counts had returned to the range of starting values. The subnormal group showed a similar pattern with 13/18 (=72%) men suppressing below 1 million/ejaculate (8/18 = 44% showing azoospermia) and the remaining 5/18 (=28%) not-suppressing sperm counts below 1 million/ejaculate. All sperm counts returned to the starting range. This demonstrated that regarding suppressibility and reversibility, volunteers with normal and subnormal sperm counts display the same pattern.

The study confirmed that in Caucasian men with normal sperm counts as well as in men with subnormal sperm counts testosterone alone can produce azoospermia in about half and suppression below 1 million in about two thirds of the volunteers. The same proportion of men in both groups appears to require an additional gestagen for full contraceptive protection. These results have a significant impact on the eligibility of men for hormonal contraception as those with subnormal semen parameters do not need to be treated separately from those with normal parameters.

Synthetic androgens

19-nortestosterone

When searching for preparations with longer-lasting effectiveness, 19-nortestosterone-hexoxyphenylpropionate was tested. Its spectrum of effects is very similar to that of testosterone and it has been used as an anabolic steroid since the 1960s. The 19-nortestosterone ester injected every 3 weeks enabled azoospermia to be reached by as many men as by testosterone enanthate [19]. Thus, the 19-nortestosterone ester is as effective as testosterone enanthate but allows a longer interval between injections. However, as 19-nortestosterone is a synthetic androgen and testosterone undecanoate has the advantage of a longer half-life and being natural testosterone, 19-nortestosterone has not been tested further.

7α-methyl-19-nortestosterone (MENT)

The synthetic androgen 7α-methyl-19-nortestosterone (MENT) offers an approximately 10-fold higher potency to suppress pituitary gonadotropins than testosterone. In contrast to testosterone, there is no 5α-reduction so that effects on the prostate could be minimal. A first dose-finding study showed that MENT administered in subcutaneous implants was as effective as testosterone given alone in suppressing spermatogenesis [20]. The potential of these implants either alone or in combination with gestagen implants is currently being investigated by the Population Council (New York).

Conclusion

Minimal serious adverse events were registered in the trials with testosterone alone. In all studies, sperm counts returned to normal levels, as a review of major studies also revealed, so that one of the prime goals of male hormonal contraception, i.e., reversibility, is met [21]. In addition, a self-applicable oral or/and transdermal application form would be desirable as shown by the combination of transdermal testosterone with oral gestagens [22,23]. However, long-term studies extending over three or more years to ascertain safety parameters especially in regard to the cardiovascular system and to the prostate have not yet been performed. As currently no pharmaceutical company is engaged in the development of hormonal male contraception, clinical trials sponsored by WHO and the Population Council or on a smaller academic level will continue, but the “struggle for hormonal male contraception” will continue for an undetermined time period [24].

Conflit d’intérêt : l’auteur déclare ne pas avoir de conflit d’intérêt.

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