SUCCESSFUL INHIBITION OF SPERMATOGENESIS
IN MAN WITHOUT LOSS OF LIBIDO:
A POTENTIAL NEW APPROACH TO MALE CONTRACEPTION

E.M. Coutinho and J.F. Melo
Maternidade Climerio de Oliveira
Federal University of Bahia
Bahia, Brazil

ABSTRACT

Marked reduction of sperm count occurred in eight fertile men bearing subdermal Silastic capsules containing testosterone who received 50 mg of either norgestriene or R 2323 twice weekly per os. Four other men also bearing testosterone implants who received an equivalent dose of norethindrone have not shown a similar drop in sperm count. None of the patients who received either norgestriene or R 2323 reported loss of libido or potency. These results suggest one of these nor-steroids may be used for a male contraceptive pill.

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INTRODUCTION

With the advent of the steroid contraceptives, the control of conception has become primarily the responsibility of the woman. One reason for the unavailability of a male contraceptive pill based on the same biological principles as the female pill lies in the difficulties of achieving suppression of fertility in the male without interfering with his sexual drive and potency (1). Some progestins are active in the male as they are in the female in suppressing gonadotropin production (2). With appropriate doses and repeated administration, the inhibitory effect on gonadotropin secretion may be prolonged in such a way as to cause progressive loss of testicular function (3). Unfortunately, both the germinal and endocrine functions of the testes depend upon gonadotropin stimulation; and as spermatogenesis is suppressed, androgen secretion is also depressed.

Recently, however, it has been shown in castrates and in hypogonadal men that a major endocrine function of the testes can be replaced by the use of subdermal Silastic capsules containing testosterone (4). The capsules are designed to release slowly, but continuously, an amount of testosterone which is sufficient to maintain libido and potency for at least one year.

These observations suggest a possible means of preventing a major side effect of progestin-induced gonadotropin inhibition in man, thus opening the possibility that a male contraceptive method based on hormonal pituitary suppression might be feasible.

In the present report, preliminary clinical trials are described in which progestin induced suppression of spermatogenes is achieved without loss of libido and potency in healthy men implanted with long-acting testosterone Silastic capsules.

PATIENTS AND METHODS

All patients enrolled in the clinical trials were healthy, normal volunteers of 35 to 45 years of age to whom the proposed study was explained in detail. Each man had fathered at least 3 children and considered his family size to be completed.

Capsules made of Silastic tubing (Dow Corning Corp., Midland, Michigan, NM.602-235) having an outside diameter of 2.4 mm were filled with either 23 mg of finely ground testosterone* or 40 to 50 mg of one of the three non-steroids selected for this study; namely,

* Merck, Darmstadt FRG No. 24615
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noregestriennone (17α-ethynyl-17-hydroxy-estra-4,9,11, trien-3-one)**, norethindrone (NET) [19-nor-17α-ethynyltestosterone]***, and R 2323 (13-ethyl-17α-ethynyl-17-hydroxy-gona-4,9,11, trien-3-one)****. The capsules were inserted subcutaneously in the ventral aspect of the forearm of 12 men of 35 to 45 years of age through a No. 11 gauge needle following local anesthesia with 2% procaine.

Each subject had 2 or 3 capsules of testosterone and either 3 or 4 capsules of noregestriennone (4 patients), norethindrone (4 patients), or R 2323 (4 patients) implanted in a cartwheel manner through the needle. In addition to the implant, each subject received the progestogen orally beginning immediately or 8 to 12 weeks after implantation. The four patients in the noregestriennone group received 50 mg of the compound twice weekly. The patients implanted with NET capsules also received 50 mg of norethindrone twice weekly, but this dose was increased to three times weekly after 24 weeks. The patients with R 2323 capsules were given 50 mg of R 2323 per os weekly, but this dose was also increased to 50 mg twice weekly at the end of 24 weeks.

Sperm counts were performed before the capsules were implanted and every four to six weeks during the study. It was requested that the men note their coital frequency and that their wives use an oral contraceptive as long as the sperm analyses revealed active spermatogenesis.

RESULTS

As long as the subjects received no oral treatment, the changes in total sperm count were negligible. Men who received 2 testosterone and 4 noregestriennone capsules had no significant changes in sperm count for as long as 16 weeks (subjects Number 1 and 2). In subject Number 1 whose sperm count was in the range of 90 million/ml before the treatment began, a count of 60 million/ml was observed 34 weeks after the insertion of the capsules. In both subjects No. 1 and No. 2, however, a rapid and marked drop in sperm count took place 5 to 8 weeks following the initiation of oral administration of 100 mg of noregestriennone weekly. In subject No. 1, the sperm count dropped from 60 million/ml to 14 million/ml in 5 weeks. In subject No. 2, the drop was even more abrupt as illustrated in Figure 1. In patients 3 and 4 who received noregestriennone from the onset of treatment, the drop in sperm count occurred 5 and 6 weeks after the treatment started (Figure 2).

In the patients with NET implants prior to commencement of the oral treatment, the changes in sperm count were negligible and even during oral administration of 25 mg of the compound twice weekly, the sperm count was not markedly lowered. In subject No. 5 there

** Laboratories Roussel, France
*** Syntex, Palo Alto
**** Roussel UCLA F, France
Figure 1. The effect of nonpessistronone (50 mg twice weekly) on sperm count (million/ml) and sperm motility of a 42-year-old man bearing submental Sertoli canals containing testosterone (2) and nonpessistronone (4). Note the marked drop in both sperm count and sperm motility which takes place 8 weeks after initiation of oral therapy.
Figure 2. The effect of norgestrienone (50 mg twice weekly) on sperm count (millions/ml) of two men bearing 3 subdermal Silastic capsules containing testosterone. Note the rapid drop in the sperm count of both subjects six weeks after initiation of therapy.
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was a change from an initial count of 170 million/ml to 120 million/ml over a period of 12 weeks. In the other three subjects (Nos. 6, 7, 8), there was almost no change in sperm count over a similar period of 12 weeks. In two of these subjects (Nos. 6 and 8), oral administration of 100 mg weekly of NET was started at the end of the initial 12-week period and maintained for an additional 12-week period. In subject No. 6 there was no significant change in sperm count, whereas in subject No. 8 a change from 160 million/ml to 110 million/ml was recorded over the 12-week period of oral treatment. In subject No. 8 the oral dose of NET was then further increased to 50 mg daily. At the end of six weeks on this higher dosage, the sperm count dropped to 1 million/ml. The treatment had to be discontinued, however, because the patient developed gynecomastia. Figure 3 shows the changes in sperm count in the 4 patients on NET.

In subjects who received R 2323 implants, the response was similar to that observed for those receiving norgestriennone. Almost no change in sperm count occurred over a 12-week period before oral treatment was started. However, 6 to 12 weeks following the administration of 50 mg of R 2323 orally twice weekly, the total sperm counts dropped markedly. In patient No. 9, the initial sperm count of 80 million/ml dropped to 1 million/ml after six weeks of oral treatment, and azoospermia resulted at the end of 10 weeks. In patient No. 10 an initial count of 127 million/ml which had been reduced to 100 million/ml over the initial 12-week period dropped to 40 million/ml over a period of 10 weeks following the start of the oral treatment. Azoospermia occurred 6 weeks later. Figure 4 shows the effect of the treatment on the sperm counts of these two patients.

In subject No. 11, oral treatment with R 2323 was started simultaneously with the insertion of the R 2323 implants. The patient’s initial count of 87 million/ml dropped to 50 million/ml over a period of 6 weeks and to 1 million/ml in another 6 weeks. A dramatic drop in sperm motility occurred in the first six weeks from 60% spermatozoa with normal motility when the count was 87 million/ml to zero motile sperm when the count had dropped to 50 million/ml. After exhibiting near azoospermia, this subject discontinued oral R 2323 for 12 weeks while retaining his implants. At the end of this period his sperm count was found to be 20 million/ml and sperm motility was restored to 30%. Oral therapy was then re-established and at the end of 7 weeks the count had again dropped to 1 million/ml and sperm motility was again zero (Figure 5). Subject No. 12 who received no oral treatment failed to show any change in sperm count for as long as 18 weeks.

In all subjects the drop in sperm count was found to be accompanied by a marked decrease in sperm motility. As described for subject No. 11, in most subjects the spermatozoa were observed to be immotile well before the sperm count reached zero. The changes in sperm motility appear to be faster and more marked in subjects receiving R 2323 than in those receiving norgestriennone. However, even in those patients who received norethindrone and in whom no significant change in sperm count was obtained, a decrease in sperm motility was recorded.

None of the patients receiving norgestriennone or R 2323 reported loss of libido or of potency. Two patients on R 2323 (Nos. 9 and 11) reported delayed orgasm. Two
Figure 3. The effect of norethindrone (50 mg twice weekly) on sperm count (millions/ml) of four men bearing subdermal Silastic capsules containing testosterone (2) and NET (4). Note that in only one subject was there a drop, albeit slow, in the sperm count. In patient No. 8 the dosage of NET was further increased to 50 mg daily (not shown in the figure) when the sperm count dropped to 1 million/ml.
Figure 4. The effect of R 2323 (50 mg twice weekly) on the sperm count (millions/ml) two men bearing subdermal Silastic capsules containing testosterone (3) and R 2323 (4). Note the marked drop in the sperm count of both subjects during the oral therapy. Empty circles, subject No. 9, full circles, subject No. 10.
Figure 5. The effect of R 2323 (50 mg twice weekly) on the sperm count (millions/ml) and sperm motility of a 41 year old man bearing subdermal Silastic implants containing testosterone (2) and R 2323 (4). Note that the decrease in motility is more marked than the drop in sperm count. Note also the restoration of sperm motility and, to a lesser degree, of sperm count when the treatment was discontinued. Azoospermia followed the administration of 50 mg of R 2323 three times weekly.
CONCEPTS

subjects on norgestrienone reported increased libido. Two patients receiving norethindrone reported a slight decrease in libido and one reported increased libido. No change in testicular size was observed in any of the patients. All four subjects on R 2323 increased weight (1 to 2 kg/month). The subjects on norethindrone and on noregestrienone also exhibited increase in weight but at a more moderate rate (1 to 2 kg/3 months).

COMMENTS

The present study shows that it is possible to inhibit spermatogenesis in man for up to 4 months without depressing libido and potency. Libido appears to be maintained by testosterone released continuously from the subdermal Silastic capsules at a rate which replaces or supplements endogenous testosterone. According to Frick et al. (4), testosterone capsules such as those used in this study release approximately 45 μg/24h/capsule. Three capsules release 135 μg/24hrs at a relatively constant rate for as long as 13 months, providing plasma testosterone levels which are in the range of healthy men of 20 to 40 years of age (0.52 ± 0.11 μg/100 ml of plasma). In some castrates and hypogonadal men, Frick et al. (4) have succeeded in restoring libido and potency with 3 capsules of testosterone, which is the number used in our subjects. As pointed out by these authors, however, the amount required by each subject depends at least in part on the patient’s remaining Leydig cell function. In the present series, 3 capsules appeared sufficient to provide appropriate plasma testosterone levels for the duration of the study.

The capsules of testosterone as well as those of norgestrienone are active for one year or longer. Those of R 2323 are effective for at least 9 months. Whether the progestin capsules alone have any effect on spermatogenesis or male fertility remains to be demonstrated. Four capsules of either NET, norgestrienone or R 2323 are obviously insufficient to induce rapid suppression of spermatogenesis. This is not surprising since, in women, 4 capsules of norgestrienone and as much as 6 capsules of NET do not seem to inhibit ovulation (5). Moreover, in the patients who have not received progestin implants, the oral treatment was as effective as in those who were implanted with as many as 4 progestin capsules.

Of the 3 compounds screened in this pilot study, NET is probably the least effective in suppressing spermatogenesis. Both Frick (6) and Johansson and Nygren (7) have shown, however, that daily NET administration can suppress sperm counts in some cases to azoospermic levels. The effect of NET on sperm mobility may be of interest, since it is possible that a progestin induced anti-fertility effect might be achieved without suppression of spermatogenesis.
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REFERENCES


