

Original research article

Acceptability of a combination testosterone gel and depomedroxyprogesterone acetate male contraceptive regimen[☆]

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Received 1 September 2006; revised 11 November 2006; accepted 13 November 2006

Abstract

Background: Testosterone (T) gel, administered transdermally in combination with injections of depomedroxyprogesterone acetate (DMPA) every 3 months, results in effective suppression of spermatogenesis in 90% of men. Men's attitudes regarding the daily self-administration of T-gel and the impact of such a regimen on sexual function, however, are unknown. Therefore, we questioned subjects enrolled in a combination T-gel plus DMPA male contraceptive trial regarding the acceptability of T-gel for male contraception and the impact of the T-gel/DMPA regimen on sexual function and satisfaction during treatment.

Study Design: Thirty-eight healthy men, ages 18–55, were treated with T-gel (100 mg daily) + DMPA (300 mg every 3 months) for 24 weeks. Sexual function was assessed using a validated questionnaire at baseline, after 12 and 24 weeks of treatment and 12 weeks into recovery. The overall acceptability of the method and attitudes regarding the daily self-administration of T-gel were assessed by a questionnaire 12 weeks into recovery.

Results: Fifty percent of subjects were either satisfied or very satisfied with the T-gel-based contraceptive regimen, and 45% indicated they would use the regimen if it were commercially available. The T-gel was found to be easy to use by 76% of men, but a third of subjects felt that T-gel administration interfered with their daily routine. Sexual function was largely preserved during treatment; however, slight decreases in sexual function were noted during recovery.

Conclusions: The experimental male hormonal contraceptive regimen of T-gel + DMPA is acceptable to approximately one half of study volunteers, most of whom would use the method if it were commercially available. Given its appeal to a significant proportion of men, additional studies using T-gel and DMPA for male contraception are warranted.

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Keywords: Spermatogenesis; Sexual function; Male hormonal contraception; Testosterone gel

1. Introduction

Male hormonal contraception requires the administration of exogenous testosterone (T) combined with a progestogen to suppress the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. Decreased levels of LH and FSH lead to markedly

diminished sperm counts and effective contraception in approximately 90–95% of men [1]. To deliver T, most male hormonal contraceptive regimens have relied on injectable or implantable formulations of testosterone. However, the relatively frequent injections required to maintain serum T levels necessitate frequent clinic visits and can be painful. Indeed, these injections are a frequently cited reason for dissatisfaction and study discontinuation among trial subjects in male hormonal contraceptive studies [2–6].

In an effort to avoid the need for intramuscular injections of T, transdermal T patches have been tested in contraceptive trials; however, these trials were significantly less successful in terms of sperm suppression than those using intramuscular T [7–9]. This difference was thought to be due to the lower serum T levels and resulting suboptimal

[☆] This work was supported by the National Institute of Child Health and Human Development (NICHD), a division of the National Institutes of Health, through cooperative agreements U54-HD-12629 and U54 HD-42454 as part of the specialized Cooperative Centers Program in Reproductive Research and the Cooperative Contraceptive Research Centers Program. Dr. Amory is supported, in part, by the NICHD by Grant K23 HD45386.

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gonadotropin suppression achieved with the T patches. In the last several years, however, transdermal T-gels have become available for the treatment of hypogonadism [10]. T-gels result in superior serum T levels compared to T patches and are highly acceptable to patients in the treatment of testosterone deficiency [11].

Our group has recently performed a male contraceptive study using daily self-administration of T-gel in combination with injections of depomedroxyprogesterone acetate (DMPA) every 3 months in normal men [12]. This study demonstrated that the improved T delivery of the gel results in sperm suppression similar to that achieved with frequent injections of intramuscular T combined with a progestogen [13–16].

Because our study was the first use of T-gel in a male contraceptive trial, and acceptability is such an important component of compliance with any contraceptive method, we explored men’s attitudes about the acceptability of the daily self-administration of T-gel. In addition, since sexual function is closely linked to serum T levels in men, we wanted to determine the impact of this regimen on sexual function. Therefore, we asked the subjects to complete acceptability and sexual function questionnaires during the course of the study, the results of which we present herein.

2. Methods

2.1. Subjects

Forty-four healthy men, ages 18–55, were recruited by newspaper advertisement and posted flyers. In brief, this was an open-label, two-arm, randomized male contraceptive study consisting of a 1- to 2-month control period, 24 weeks of treatment and a recovery period. After informed consent was obtained, subjects were randomly assigned to either (1) T-gel (100 mg topically daily) + DMPA (300 mg im every 12 weeks) or (2) T-gel + DMPA + a GnRH antagonist acyline (300 µg/kg sc every 2 weeks for the first 12 weeks) [12,17]. All subjects agreed to use a marketed and effective form of contraception during the study. After the treatment period was completed, subjects were followed up for 3–6 months until sperm parameters had normalized. Thirty-eight men completed the protocol: 21 in the T + DMPA group and 17 in the T + DMPA + acyline group. Compliance with T-gel administration exceeded 98%. Baseline information regarding relationship status and current method of contraception was obtained through a medical history form. The Institutional Review Board at the University of Washington approved all procedures involving human subjects. Complete information on the study design and the results of this regimen on sperm and hormone parameters has been recently published [12].

2.2. Questionnaires

For the assessment of sexual function during treatment, we used the validated sexual function inventory developed and reported by O’Leary and colleagues [18]. This 4-point

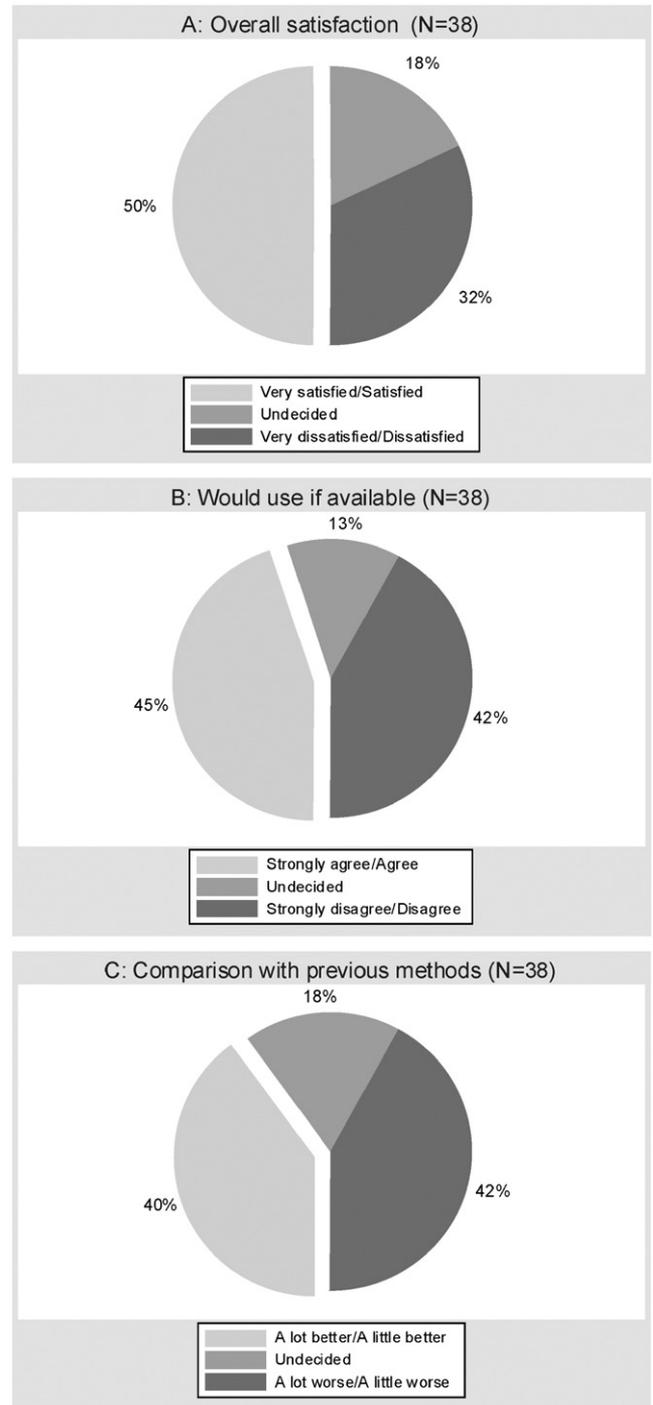


Fig. 1. Responses (%) given by study volunteers to the following statements: (A) “Overall, I was satisfied with this method of contraception”; (B) “If available today, I would use this method of contraception as my primary method”; and (C) “How would you compare this method of contraception to the one you have used most often”.

Likert scale, 11-question inventory assesses three domains of male sexual function: sexual drive, erectile function and ejaculatory function, and also queries subjects about their perception of problems in each area (“freedom from

Table 1
Baseline current relationship and contraceptive characteristics of study subjects (N=38)

Characteristic	n (%)	Age range (years)
Current relationship		
Married	11 (29)	27–51
Steady dating	11 (29)	19–55
Cohabiting	10 (26)	21–46
Casual relationship(s)	3 (8)	31–46
No current partner	3 (8)	35
Current contraception		
Condoms	13 (34)	21–47
Female pill	16 (42)	19–51
Depo-Provera	3 (8)	28–38
IUD	3 (8)	26–35
None	2 (5)	29–55
Female sterilization	1 (3)	51
Satisfaction with current method of contraception		
Very satisfied	7 (18)	22–51
Mostly satisfied	20 (53)	19–47
Neutral or mixed	10 (26)	22–55
Dissatisfied/very dissatisfied	1 (3)	29

problems”), as well as including a question regarding overall satisfaction with global sexual function. For purposes of analysis, domain subscores are calculated and can be compared over time. Subjects completed this questionnaire at clinic visits at baseline, after 12 and 24 weeks of treatment and 12 weeks into the recovery period.

As there are no validated instruments for the assessment of male contraceptive method acceptability, we modeled our acceptability questions on those found in previously published studies of male contraceptive acceptability [2–6]. Twelve weeks into recovery, the subjects were asked to select *strongly disagree*, *disagree*, *undecided*, *agree* or *strongly agree* in response to the following questions: (1) “Overall, I was satisfied with the method of contraception,” (2) “If available today, I would use this method of contraception as my primary method.” In addition, subjects were asked to select *a lot better*, *a little better*, *about the same*, *a little worse* or *a lot worse* in response to the question: “How would you compare this method of contraception to the one you have used most often.” Lastly, to determine subject’s response to the self-administration of the daily gel, subjects were asked to select *strongly disagree*, *disagree*, *undecided*, *agree* or *strongly agree* in response to the following questions: “The gel was easy to use,” “The gel smelled good,” “The gel dried quickly on my skin,” “The gel left my skin feeling sticky,” “Applying the gel interfered with my daily routine,” “The gel was messy to use,” “The gel irritated my skin,” and “The gel interfered with my sexual activities.”

2.3. Statistical analyses

There were no significant differences in subject’s responses between the two study groups for any question; so responses from all 38 subjects who completed the study

were combined for analysis. All questionnaires were completed. Since subject’s attitudes about the acceptability of the regimen and the ease of gel self-administration were queried only 12 weeks into recovery, this information is presented in a descriptive fashion. For ease of presentation, “agree/satisfied” and “strongly agree/very satisfied” as well as “strongly disagree/very dissatisfied” and “disagree/dissatisfied” categories are combined. Categorical outcomes were compared using a chi-square test and the association between age and outcomes scores was compared using Spearman’s correlation. For analysis of the sexual function data, mean scores and standard deviations were computed. A repeated measures ANOVA was used to assess trends in mean responses, followed by paired *t* tests to identify measurements that differed significantly compared with baseline scores. For all comparisons, an alpha of <.05 was considered significant. Statistical analyses were performed using STATA version 8.0 (College Park, TX).

3. Results

3.1. Baseline characteristics

Of the 44 men enrolled in the study, 38 completed all study procedures. The mean age of the subjects was 34±8 years. Of the six subjects who failed to complete the study, in only one case was this due to an adverse event (rash from T-gel). Baseline contraceptive and relationship characteristics of the study subjects are shown in Table 1. The majority of the subjects (84%) were in stable relationships during the study, in which female hormonal contraceptives were the most common form of contraception (42%); however, condoms were being used by approximately one third of study subjects. Most respondents (71%) reported satisfaction with their current method of contraception, with the highest levels of satisfaction seen with the use of IUDs, female sterilization and DMPA, and lower levels of satisfaction associated with use of condoms and female oral contraceptives.

Table 2
Impressions of the testosterone gel during treatment, n (%)

Statement	Strongly disagree/Disagree	Undecided	Agree/Strongly agree
Gel was easy to use	9 (19)	3 (8)	28 (74)
Gel smelled good	12 (32)	12 (31)	14 (37)
Gel dried quickly on my skin	14 (37)	3 (8)	21 (55)
Gel left my skin feeling sticky	3 (8)	4 (11)	31 (81)
Gel interfered with my daily routine	17 (45)	8 (21)	13 (34)
Gel was messy to use	17 (37)	8 (21)	16 (42)
Gel irritated my skin	29 (76)	4 (11)	5 (14)
Gel interfered with my sexual activities	28 (73)	5 (13)	5 (14)

Subjects were asked whether they agreed or disagreed with the above statements.

Table 3
Self-reported sexual function during treatment (N=38)

Domain	Baseline	Treatment		Recovery	p Value (trend)
		Week 12	Week 24		
Sex drive (0–8) ^a	6.4±1.3	6.6±1.6	6.3±1.7	5.9±1.7	.15
Erectile function (0–12) ^b	10.7±1.7	11.0±1.4	10.4±1.8	10.6±1.7	.20
Ejaculatory function (0–8) ^c	7.6±0.6	7.4±0.8	7.2±1.0*	7.1±1.5*	.06
Freedom from problems with sexual activity (0–12) ^d	11.4±1.1	11.1±1.5	10.7±1.8*	10.8±1.9*	.04
Overall satisfaction with sexual activity (0–4) ^e	3.2±1.0	3.2±0.9	3.1±1.1	2.9±0.9*	<.001

Values are means±SD. Higher values represent greater levels of satisfaction.

^a Sum of two 4-point Likert scale responses to questions regarding frequency and level of sexual drive.

^b Sum of three 4-point Likert scale responses to questions regarding frequency of erections, firmness of erections and ease of sexual activity with erections.

^c Sum of two 4-point Likert scale responses to questions regarding ease of ejaculation and volume of ejaculate.

^d Sum of three 4-point Likert scale responses to questions regarding lack of problems associated with sex drive, erectile and ejaculatory function.

^e A single 4-point Likert scale response to question regarding overall level of satisfaction with sex life in the preceding 30 days.

* p<.05 compared with baseline.

3.2. Overall acceptability

The survey results from the acceptability questionnaire are depicted in Fig. 1. The overall acceptability of the T-gel plus DMPA contraceptive regimen used in this study was 50% (Fig. 1A), with 32% of subjects finding the method unsatisfactory. Similarly, 45% of subjects indicated a willingness to use this regimen if it were commercially available, while 42% of subjects indicated that they would not (Fig. 1B). Lastly, 40% of subjects found the regimen preferable to their previous methods, while 42% did not (Fig. 1C). There was a significant interaction between current contraceptive use and acceptability, with subjects whose partners were currently using intrauterine devices being more likely to be dissatisfied or strongly dissatisfied with the regimen compared with couples using other methods of contraception (p=.03). In addition, older men were more likely to rate the method favorably, compared to younger users (p=.02).

3.3. T-gel acceptability

The results of the questionnaire regarding the acceptability of the T-gel are listed in Table 2. A large majority of subjects (74%) found the gel easy to use and thought that it dried quickly (55%), but a large majority felt it left their skin feeling sticky (81%). Opinion was nearly equally divided regarding the smell of the gel and the extent to which it interfered with one's daily routine. Most subjects did not find the gel irritating to their skin (76%). However, there was a clear association between subjects who found that the gel interfered with daily routines and dissatisfaction with the method overall, with only 2 (15%) of 13 subjects who felt that the gel interfered with their daily routines rating the method as satisfactory (p=.01).

3.4. Sexual function

The results of the self-reported sexual function questionnaires are reported in Table 3. Most subjects scored highly on the questionnaire at baseline. After 24 weeks of treatment, there were mild, if significant, decreases in ejaculatory

function and the subjects' assessment of whether they considered their sexual function problematic. Mild nonsignificant decreases in sex drive and erectile function were noted at the end of treatment and during recovery. A significant decrease trend in overall sexual satisfaction was noted during recovery (p<.001), mainly due to a decrease after treatment ended. However, there was no association between subjects with reduced sexual satisfaction and overall method acceptability (p=.35).

4. Discussion

In this report we demonstrate that T-gel, when combined with injections of DMPA every 3 months, is an acceptable form of male contraception for roughly one half of subjects in an experimental male contraceptive trial. Given the ability of this regimen to markedly inhibit spermatogenesis [12], its acceptability to study subjects is of great interest, since further development of this regimen would be pointless in the absence of a reasonable degree of appeal to men. Indeed, one of the main reasons the development of injectable hormonal contraceptive has been slow has been dislike of the frequent intramuscular T injections necessitated by most of these regimens [2–6].

Previous male hormonal contraceptive studies utilizing transdermal T administration with patches resulted in suboptimal suppression of spermatogenesis, and frequent patch-related dermatitis [7–9]. No information about acceptability of these regimens to study subjects was published; however, the low efficacy and frequency of skin reactions in normal men has led to the abandonment of T patches for male hormonal contraception.

Therefore, we were interested in determining the response of our normal population of study subjects to daily self-administration of T-gel as part of a male hormonal contraceptive regimen. The gel proved to be easy to use for a large majority of men, and skin irritation was uncommon. More frequently, subjects complained of the gel being messy, or leaving their skin feeling sticky. Subjects who felt that the gel interfered with their daily routine were

significantly more likely to rate the acceptability of the regimen poorly. Such individuals would be unlikely to use the gel for long-term contraception.

More importantly, sexual function was well preserved during the study, with slight decreases noted at the end of treatment and during recovery. The decrease in sexual function during recovery may be due to a delay in recovery of the hypothalamic–pituitary axis after the discontinuation of the daily T-gel, or it may reflect residual effects from the DMPA injection. The decreases noted at the end of treatment are unlikely to be hormonal, as serum T levels were elevated during this period [12]. Therefore, other effects of the study, such as the requirement for twice monthly scheduled ejaculations may play a role. In the absence of a placebo group, it is difficult to determine the cause or significance of this decrease. Nevertheless, no subject discontinued the study secondary to sexual complaints, and it appears unlikely that changes in sexual functioning will account for much, if any, dissatisfaction with this method of male contraception. Future studies of sexual function in male contraceptive studies should include assessment of sexual function 4 to 6 months after treatment is completed to determine if the slight declines seen in sexual function during recovery in this study persist, as has been suggested for female hormonal contraceptives [19].

It is noteworthy that the acceptability of this regimen is slightly lower than that reported in other male hormonal contraceptive studies. For example, in one recent study, Meriggiola and colleagues [6] reported that 66% of subjects questioned during recovery in a study of a newer long-acting injectable T/progestogen combination found the regimen acceptable and would consider using it if it were commercially available. The lower rate of acceptability in our study may reflect different study populations or true differences between the appeal of the long-acting injectable T and the T-gel preparation. Alternatively, subjects in this recent study of intramuscular injections knew ahead of time they would be receiving injections, so individuals who were averse to injections would be unlikely to enroll. If so, the overall appeal of contraceptive regimens to all men based on injectable formulations of T may be lower than reported. In addition, cultural factors may play a role in the acceptability of a route of T administration. In a recent multinational survey of men's preferences for male hormonal contraception, a gel-based approach was more appealing than injections in South American countries and less appealing than injections in Europe and North America [20].

We did not specifically examine the subject's responses to the DMPA and acyline injections; however, it seems unlikely that either injection played a large role in subject's perceptions of the acceptability of the regimen. The similarity in the responses between the two groups suggests that randomization to the acyline group did not influence the results. This may be due to the fact that by the time the acceptability questionnaire was administered, 12 weeks into recovery, subjects had not received an acyline injection for over 6 months. Since this was also the case for the DMPA

injection, it also seems unlikely that the DMPA injection played a large role in the subjects' attitudes regarding the regimen; however, this was not directly assessed.

A second limitation to our study is that study volunteers may not reflect the attitudes of all men using contraception. In addition, a large majority of the men in our study were in a stable relationship and may not accurately reflect the opinions of single men with multiple sexual partners. However, since male hormonal contraception would not afford protection against sexually transmitted infections, this population is not considered to be the targeted users of such a method in any case. In addition, we did not determine the acceptability of this method of contraception to women, who might have strong feelings both about their potential exposures to the T-gel and/or relying on their male sexual partner for contraception. Surveys asking women for their opinion of a male contraceptive have been encouraging [21], but only one study has solicited the input of the subject's partners in a trial setting [5]. Such assessment should be considered in future studies of contraceptive acceptability. Lastly, as in other trials of male hormonal contraception, roughly 10% of men failed to suppress their sperm counts to levels associated with effective contraception [12]. If this were the case with a marketed contraceptive regimen, and additional sperm count testing were necessary to see if a man could stop all other contraception before relying solely on the hormonal method, the overall acceptability would likely be lower than the values presented here.

In conclusion, this study demonstrates that the male hormonal contraceptive regimen of daily T-gel + DMPA injected every 3 months is acceptable to roughly one half of men, most of whom would use the method if it became commercially available. The T-gel is relatively easy for men to use and is less irritating to the skin than T patches, but some men perceive that the T-gel interferes with their daily activities; these men would be less likely to use a T-gel-based method if it were commercially available. Nevertheless, T-gel-based contraceptive approaches appear sufficiently appealing to enough men to warrant additional study, which may ultimately lead to the development of a safe, effective and popular form of reversible contraception for men.

Acknowledgments

We thank Ms. Kathy Winter, Ms. Marilyn Busher, Ms. Janet Gilchrest, and Ms. Kimberly Anable for assistance with the clinical aspects of the study, Ms. Consuelo Pete for seminal fluid analyses, Ms. Dorothy McGuinness for performance of hormone assays, and Ms. Lindsey Bunk for assistance in questionnaire design. In addition, we would like to thank Auxilium Pharmaceuticals for the donation of the T-gel.

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