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Testosterone Release From a Subcutaneous, Biodegradable Microcapsule Formulation (Viatrel) in Hypogonadal Men

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ABSTRACT: Men with hypogonadism require testosterone replacement for optimal health. In the United States, testosterone is currently administered by daily transdermal patches, topical gels or intramuscular injections every 1–3 weeks. Biodegradable polylactide-co-glycolide microcapsules are currently used for long-term drug delivery in humans. Such microcapsules that contain testosterone could provide a better means of long-term testosterone therapy. We therefore studied the pharmacokinetics and pharmacodynamics of testosterone release from testosterone microcapsules in men with hypogonadism. Fourteen men who had been treated previously with testosterone were enrolled in an open-label, prospective study of testosterone microcapsule administration. Subjects were enrolled if 2 consecutive serum total testosterone levels were lower than 8.7 nmol/L after a 4-week washout from testosterone therapy. Subjects were injected with a single dose of either 267 mg (n = 7) or 534 mg (n = 7) of (Viatrel) testosterone microcapsule, and serum total testosterone, dihydrotestosterone, estradiol, sex-hormone binding globulin, luteinizing hormone, and follicle-stimulating hormone levels were determined at days −14, −7, and 0 before the injection; at days 1, 2, and 7 after the injection; and then weekly thereafter for 8–12 weeks. Mean serum total testosterone levels peaked immediately following injection on day 1 at 25.2 ± 2.6 nmol/L in the 267 mg group and 34.7 ± 2.4 nmol/L in the 534 mg group. Total serum testosterone levels declined gradually and fell below 8.7 nmol/L at 42 days after injection in the 267 mg group, and 70 days after injection in the 534 mg group. Estradiol and dihydrotestosterone levels followed a similar pattern. Mean serum free testosterone also peaked immediately following injection on day 1 at 0.51 ± 0.05 nmol/L in the 267 mg group and 0.97 ± 0.08 nmol/L in the 534 mg group. No significant adverse reactions were seen, although 2 subjects complained of transient tenderness and fullness at their injection sites. We conclude that a single injection of 534 mg of testosterone microcapsules to men with hypogonadism normalizes serum hormone levels for up to 10–11 weeks, albeit with a pronounced early peak and a relatively long period of low-normal serum total testosterone. Subcutaneously administered testosterone microcapsules may provide a safe and convenient method for the long-term treatment of male hypogonadism or testosterone replacement in male contraceptive regimens.

Key words: Hypogonadism, poly-lactide-co-glycolide, pharmacokinetics, androgen, dihydrotestosterone, estradiol.

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Men with hypogonadism require testosterone replacement therapy to maintain normal bone and muscle mass, strength, and sexual function (Katznelson et al, 1996; Behre et al, 1997; Bhasin and Bremner, 1997; Snyder et al, 2000; Wang et al, 2000). In the United States, testosterone is administered by intramuscular injections, patches, or a recently approved transdermal gel. Each of these modes of testosterone delivery, however, have drawbacks. Injections, although inexpensive, must be given deeply into a large muscle every 1–3 weeks to maintain normal serum testosterone levels and are uncomfortable and occasionally painful (Fossa et al, 1999). Patches must either be applied daily to a shaved scrotum (Testoderm, Alza Pharmaceuticals, Palo Alto, Calif) or to body skin (Androderm [Smithkline Beecham, Philadelphia, Pa]; Testoderm TTS [Alza Pharmaceuticals]; Amory and Matsumoto, 1998). However, the nonscrotal patches (Androderm) can cause moderately severe skin reactions in more than half of subjects due to the vehicles that facilitate testosterone absorption across the skin, or adhere poorly to skin and deliver testosterone less efficiently (Testoderm TTS). The newly available testosterone gel appears safe and effective in early trials (Swerdloff et al, 2000), but it is expensive, must be applied daily, and care must be taken to avoid inadvertent vicarious exposure to women and children.

Biodegradable polylactide-co-glycolide (PLGA) microcapsules have been approved by the US Food and Drug Administration and are currently used safely and effectively via subcutaneous injection for long-term drug delivery in humans (Jain, 2000). Zoladex (Zeneca Phar-

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Viatrel is a trademark of Biotek, Inc, Woburn, Mass.

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Table 1. *Patient characteristics and cause of hypogonadism*

Patient	Dose	Diagnosis	Age (yr)	LH* (IU/L)	FSH* (IU/L)	Testosterone* (nmol/L)
1	267 mg	Kallmann syndrome	28	0.9	0.8	1.07
2	267 mg	Primary testicular failure	48	14.3	18.7	5.76
3	267 mg	Pituitary adenoma	43	0.3	0.8	1.46
4	267 mg	Kallmann syndrome	37	0.9	0.7	2.08
5	267 mg	Idiopathic hypogonadotropic hypogonadism	44	5.2	10.2	6.7
6	267 mg	Kallmann syndrome	28	0.7	0.3	1.42
7	267 mg	Idiopathic hypogonadotropic hypogonadism	49	4.9	8.0	5.63
8	534 mg	Kallmann syndrome	24	0.4	0.3	1.42
9	534 mg	Primary testicular failure	49	12.0	22.4	5.83
10	534 mg	CNS sarcoidosis	37	0.3	0.3	2.08
11	534 mg	Idiopathic hypogonadotropic hypogonadism	47	1.0	3.2	7.64
12	534 mg	Idiopathic hypogonadotropic hypogonadism	46	2.1	4.0	6.28
13	534 mg	Idiopathic hypogonadotropic hypogonadism	40	1.0	2.1	4.96
14	534 mg	Kallmann syndrome	19	0.2	0.2	1.12

* Gonadotropin and testosterone levels are taken after 4-week washout from androgen therapy and immediately prior to injection with testosterone microcapsule.

maceuticals, Wilmington, Del), a gonadotropin-releasing hormone analogue compounded to a PLGA, is effectively administered by subcutaneous injection every 3 months without adverse side effects (Cockshott, 2000). Periodic subcutaneous injection of biodegradable PLGA microcapsules containing testosterone have the potential to provide a better means of long-term testosterone therapy by decreasing injection frequency and obviating the need for deep intramuscular injections. Microcapsules containing testosterone have been tested previously both in animals (Peacock et al, 1993) and men with hypogonadism (Bhasin et al, 1992). The human studies demonstrated that testosterone microcapsules were able to maintain serum testosterone levels within the normal range for 10–11 weeks. This formulation of microspheres, however, required 2 painful, large-volume (2.5 mL) intramuscular injections, that limit its appeal for long-term testosterone replacement. We have reformulated testosterone microcapsules to permit subcutaneous administration, which we believe may be more successful as a means of long-term testosterone administration, and herein present our initial human trial results of these microcapsules.

Materials and Methods

Testosterone Microcapsule Formulation and Injection

The Viatrel testosterone microcapsule formulation suitable for subcutaneous administration was formulated and developed by Biotek, Inc (Boston, Mass). Testosterone was encapsulated in a biodegradable matrix composed of 85/15 lactide/glycolide copolymer. Testosterone is released from the microcapsules by diffusion and leaching from the matrix followed by eventual degradation of the polymer during the treatment period. The microcapsules were placed in vials prior to sterilization by irradiation. A proprietary suspending medium was added to the testosterone microcapsules and the suspension was vortexed for 30 seconds. Suspended testosterone microcapsule (2.5 mL, corresponding to 267 mg testosterone) was injected in the subcutaneous fat tissue lateral to the umbilicus. The procedure was performed twice for a 534 mg injection, with injections on both sides of the abdomen for a total of 5.0 mL of injected microcapsule.

Subjects

Fourteen men with hypogonadism, who had been previously treated with testosterone, were studied. The characteristics of these patients can be seen in Table 1. All had a normal physical examination (except many had small testis size, gynecomastia, or both), hematologic and blood chemistry studies, serum cholesterol and triglyceride levels, and urinalysis. Subjects were instructed to discontinue their usual testosterone replacement therapy for 4 weeks (ie, the screening period) during which hormone levels (testosterone, dihydrotestosterone [DHT], luteinizing hormone [LH], follicle-stimulating hormone [FSH], sex-hormone binding globulin [SHBG], and estradiol [E_2]) were measured weekly. After subjects had 2 consecutive weekly total testosterone levels of less than 8.7 nmol/L (250 ng/dL), a baseline blood sample (day 0) was obtained, and testosterone microcapsule was then administered by subcutaneous injection. Subjects returned for blood draws on days 1, 2, 4, and 7, and weekly thereafter for 7 more weeks (the 267 mg group), and 11 more weeks (the 534 mg group). Physical examinations were performed at weeks 4, 8, and 12. Fifteen subjects (1 subject each enrolled in the 267 mg and 534 mg groups with a 4-week washout between) were

administered testosterone microcapsules, and 14 subjects completed the study. One subject failed to make his postinjection blood draw appointments and was excluded from the study. This excluded subject had a normal examination at the end of the study and remains in good health. The University of Washington Human Subjects Review Committee and the Veteran's Affairs Puget Sound Health Care System Research and Development Committee approved the study protocol and all subjects gave informed consent.

Hormone Measurements

Serum was obtained from whole blood by centrifugation (20 minutes at 2000 × *g*) and frozen immediately at −70°C until assayed. All samples were thawed at the study conclusion and individual hormone measurements (except for DHT) for each subject were run in the same assay. Serum levels of testosterone, LH, FSH, SHBG, and E_2 were determined using a highly specific time-resolved immunofluorometric assay (Delfia; Wallac Oy, Turku, Finland). The lower limits of detection for testosterone, LH, FSH, SHBG, and E_2 were 0.5 nmol/L, 0.05 IU/L, 0.04 IU/L, 6.25 nmol/L, and 50 pmol/L, respectively. The mean intra-assay and interassay coefficients of variation were 3.1% and 4.5% for testosterone, 2.6% and 5.4% for LH, 2.2% and 6.7% for FSH, 1.8% and 8.2% for SHBG, and 2.4% and 3.8% for E_2. Serum levels of DHT were determined by radioimmunoassay (Quest Diagnostics, San Juan Capistrano, Calif). The assay sensitivity was 150 pmol/L and the intra-assay and interassay coefficients of variation were 9.2% and 12.5%, respectively. Free and bioavailable testosterone were calculated from measurements of total testosterone, SHBG, and albumin using published methods (Sodergard et al, 1982; Vermeulen et al, 1999). The normal ranges for hormone measurements in our laboratory are as follows: testosterone, 8.7–35 nmol/L; free testosterone, 0.18–0.73 nmol/L; bioavailable testosterone, 5.2–19.8 nmol/L; LH, 1.9–6.9 IU/L; FSH, 0.7–5.7 IU/L; SHBG, 13–61 nmol/L; and E_2, 0–130 pmol/L. The normal range for DHT was 0.6–1.8 nmol/L.

Mood and Sexual Function

We collected information on mood and sexual function at baseline and 3–4 weeks after Viatrel injection using a validated questionnaire (Wang et al, 1996). Ten of the 14 subjects completed the questionnaires appropriately, and responses from this subset were analyzed.

Statistical Analysis

Hormone measurements from the 14 subjects who completed the study were averaged for each time point to obtain the mean and standard errors of the mean (SEM). Changes over time and between groups after testosterone microcapsule injection were analyzed by one-way repeated analysis of variance with the Duncan post-hoc correction, and standard deviations and SEM were calculated. Area-under-the curve (AUC) and maximum concentration (C_{max}) were calculated using the Legrange polynomial association (GraphPad Software, San Diego, Calif), and the individual patient values using the trapezoid rule from t = 0 to the last measured level for each subject without smoothing or curve fitting. The average concentration (C_{avg}) and half-life ($T_{1/2}$) were calculated for all subjects from t = 1 to the last measured level. Results of responses to the sexual questionnaire were compared between baseline and 3–4 weeks after Viatrel injection using a Wilcoxon rank-sign test.

Results

Serum Total Testosterone

Immediately prior to testosterone microcapsule injection, serum total testosterone levels were well below the normal range, averaging 3.1 ± 1.0 nmol/L in the 267 mg group and 4.7 ± 1.1 nmol/L in the 534 mg group. After testosterone microcapsule injection, serum total testosterone levels increased rapidly to a mean maximum concentration of 25.5 ± 2.2 nmol/L (731 ± 62.3 ng/dL) on day 2 in the 267 mg testosterone microcapsule group and 34.7 ± 2.5 nmol/L (995 ± 71 ng/dL) on day 1 in the 534 mg group (Figure 1A). Serum total testosterone levels declined slowly over the next several weeks, falling below 8.7 nmol/L (250 ng/dL) after 42 days in the 267 mg group and 70 days in the 534 mg group. The AUC for total testosterone in the 267 mg group was 737 ± 84 nmol/days-L and 1235 ± 78 nmol/days-L for the 534 mg group (Table 2; $P < .05$). No subject who received 267 mg of testosterone microcapsule had serum total testosterone concentrations above the upper limit of normal during the first week of treatment, but 4 of 7 subjects who received 534 mg of testosterone microcapsule had serum total testosterone measurements above the upper limit of normal during this period.

Serum Free Testosterone

Immediately prior to injection, serum free testosterone levels were very low, averaging 0.06 ± 0.02 nmol/L in the 267 mg group and 0.11 ± 0.03 nmol/L in the 534 mg group. After testosterone microcapsule injection, serum free testosterone increased rapidly, peaking on day 1 after injection at 0.51 ± 0.05 nmol/L in the 267 mg group and 0.97 ± 0.08 nmol/L in the 534 mg group (Figure 1B). Serum free testosterone levels decreased slowly but remained significantly elevated over baseline levels for 49 days in the 267 mg group and 84 days in the 534 mg group. Serum free testosterone averaged between 1% and 3% of total serum testosterone throughout the study period. The AUC for serum free testosterone was 15.2 ± 2.2 nmol/days-L for the 267 mg group and 31.7 ± 1.6 nmol/days-L for the 534 mg group (Table 2; $P < .05$).

Serum Bioavailable Testosterone

Prior to injection, serum bioavailable testosterone levels were very low, averaging 1.8 ± 0.8 nmol/L in the 267 mg group and 1.5 ± 0.4 nmol/L in the 534 mg group. After testosterone microcapsule injection, serum bioavail-

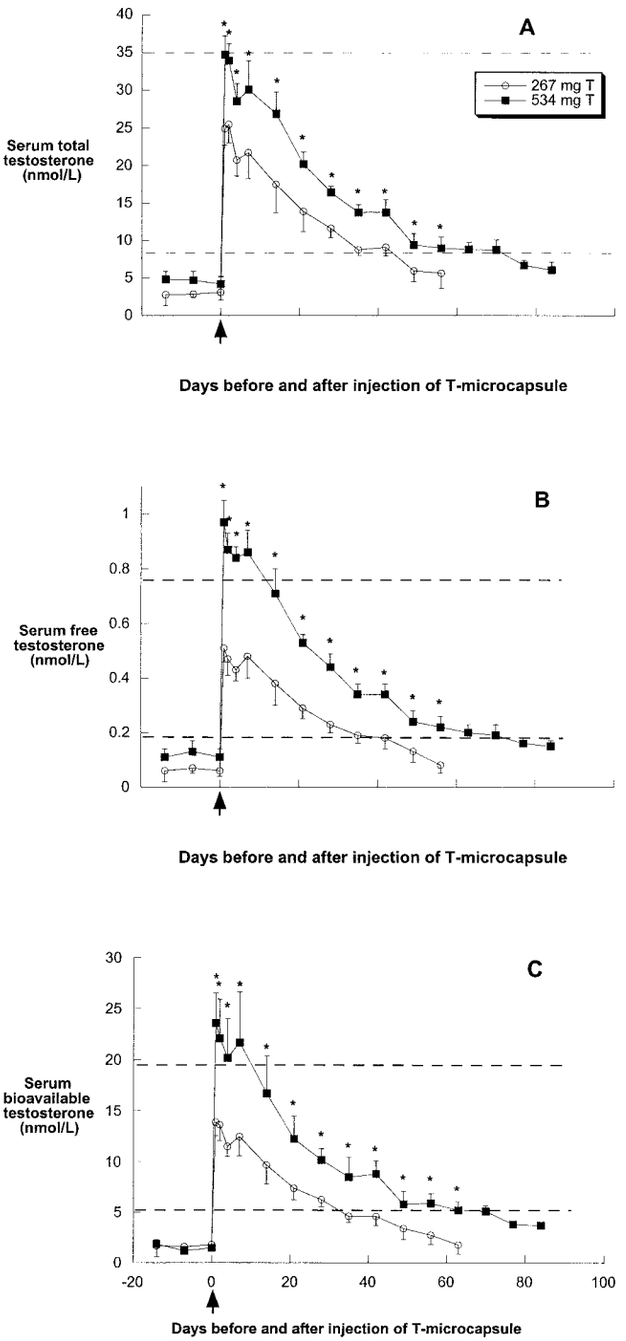

Figure 1. Serum total testosterone **(A)**, free testosterone **(B)**, and bioavailable testosterone **(C)** before and after injection of 267 mg (n = 7) and 534 mg (n = 7) of testosterone microcapsule. Data are means ± SEM. Dashed lines represent the normal range. *$P < .05$ between groups. Conversion for testosterone: 1 nmol/L = 288 pg/mL.

able testosterone increased rapidly, peaking on day 1 after injection at 13.9 ± 1.4 nmol/L in the 267 mg group and 23.7 ± 2.9 nmol/L in the 534 mg group (Figure 1C). Thereafter, serum bioavailable testosterone decreased slowly but remained significantly elevated over baseline

Table 2. *Pharmacokinetic parameters of testosterone microcapsule administration for total and free testosterone*

	267 mg (n = 7)	534 mg (n = 7)
Total T-AUC (nmol/day-L)*	737 ± 84†	1235 ± 78†
C_{max} (nmol/L)	25.5 ± 2.2†	34.7 ± 2.5†
C_{avg} (nmol/L)	14.33 ± 1.4†	18.1 ± 1.1†
$T_{½}$ (days)	20.4	22.3
Free T-AUC (nmol/day-L)	15.1 ± 2.2†	31.7 ± 1.6†
C_{max} (nmol/L)	0.51 ± 0.05†	0.97 ± 0.08†
C_{avg} (nmol/L)	0.30 ± 0.02†	0.48 ± 0.02†
$T_{½}$ (days)	22.5	25.0

*All comparisons between 267 mg and 534 mg group are significant at $P < .05$. AUC indicates area-under the curve; C_{max}, maximum concentration; C_{avg}, average concentration; $T_{½}$, half-life.
† Data are means ± SEM.

levels for 49 days in the 267 mg group and 84 days in the 534 mg group. Serum bioavailable testosterone averaged between 55% and 70% of serum total testosterone throughout the study period.

Serum Estradiol and Dihydrotestosterone

Prior to testosterone microcapsule administration, serum E_2 was within the normal range in both groups: 54 ± 19 pmol/L in the 267 mg group and 81 ± 23 pmol/L in the 534 mg group. Serum E_2 peaked 4 days after injection in both groups: 105 ± 21 pmol/L in the 267 mg group and 168 ± 28 pmol/L in the 534 mg group (Figure 2A). Prior to testosterone microcapsule administration, DHT levels were below the lower limit of normal in both groups: 0.63 ± 0.09 nmol/L in the 267 mg group and 0.34 ± 0.04 nmol/L in the 534 mg group. Serum DHT levels peaked 3 days after injection at 1.23 ± 0.21 nmol/L in the 267 mg group and on day 7 at 1.03 ± 0.16 nmol/L in the 534 mg group (Figure 2B).

Sex-Hormone Binding Globulin

Serum SHBG differed nonsignificantly between the 2 groups at baseline (33.4 ± 6.6 nmol/L for the 267 mg group and 24.6 ± 7.5 nmol/L for the 534 mg group; $P = .28$) and throughout the study period (Figure 3). For both groups, serum SHBG levels were highest immediately prior to injection of testosterone microcapsule. By 1 week after testosterone microcapsule administration, serum SHBG levels had decreased by 16% in the 267 mg group and by 24% in the 534 mg group. SHBG levels slowly increased thereafter slowly, and returned to baseline by 70 days after injection in both groups.

Serum Gonadotropins

Seven subjects (3 in the 267 mg group and 4 in the 534 mg group) had normal or elevated levels of gonadotropins at baseline, whereas the remaining 7 subjects had severe hypogonadotropic hypogonadism (Table 1). In the sub-

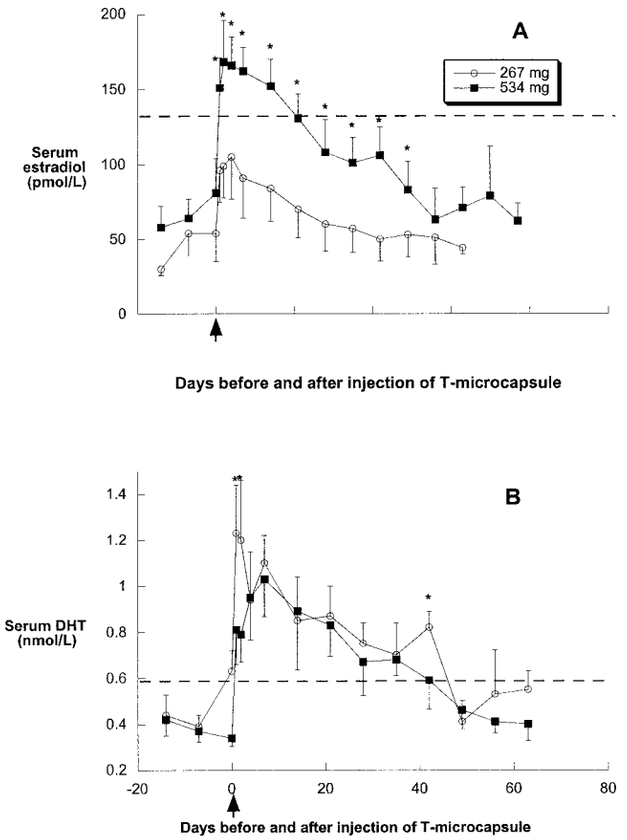

Figure 2. Serum E_2 **(A)** and DHT **(B)** before and after injection of 267 mg (n = 7) and 534 mg (n = 7) of testosterone microcapsule. Data are means ± SEM. Dashed lines represent the normal range. *$P < .05$ between groups. Conversion for E_2: 1 nmol/L = 272 pg/mL.

jects with normal or elevated serum gonadotropins at baseline, there were no significant differences in gonadotropin levels between groups prior to testosterone microcapsule administration: serum LH was 6.0 ± 2.5 IU/L and FSH was 10.1 ± 2.7 in the 267 mg group; and LH was 3.4 ± 1.8 IU/L and FSH was 6.2 ± 3.9 IU/L in the 534 mg group. After testosterone microcapsule administration, FSH and LH levels fell below the normal range in both groups. Serum LH reached a nadir in week 4 in the 267 mg group at 1.3 ± 0.5 IU/L and in week 6 at 0.07 ± 0.03 IU/L in the 534 mg group, whereas serum FSH reached a nadir at week 2 in the 267 mg group at 3.9 ± 1.4 IU/L, and at week 6 at 0.4 ± 0.3 IU/L in the 534 mg group ($P < .05$ compared with the 267 mg group; Figure 4A and B).

In the subjects with severe hypogonadotropic hypogonadism, serum gonadotropin levels were below the normal range at baseline: serum LH was 0.27 ± 0.09 IU/L and FSH was 0.52 ± 0.1 IU/L in the 267 mg group; LH was 0.1 ± 0.07 IU/L and FSH was 0.42 ± 0.27 in the 534 mg group. LH and FSH levels were extremely low throughout the study period, but did suppress after testosterone microcapsule administration, with serum LH reaching a nadir in week 3 in the 267 mg group at 0.09 ± 0.04 IU/L, and in week 6 at 0.02 ± 0.01 IU/L in the 534 mg group; and serum FSH reaching a nadir in week

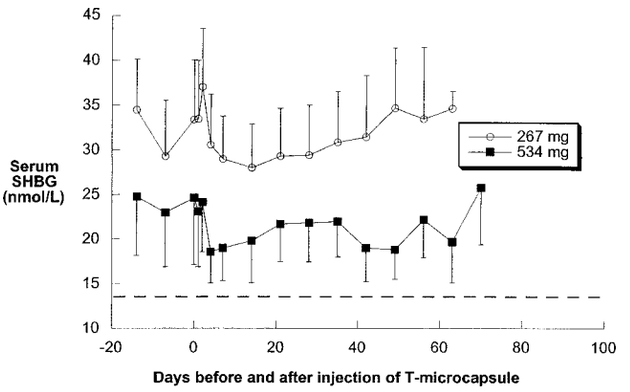

Figure 3. Serum SHBG before and after injection of 267 mg (n = 7) and 534 mg (n = 7) of testosterone microcapsule. Data are means ± SEM. Dashed lines represent the normal range. *$P < .05$ between groups.

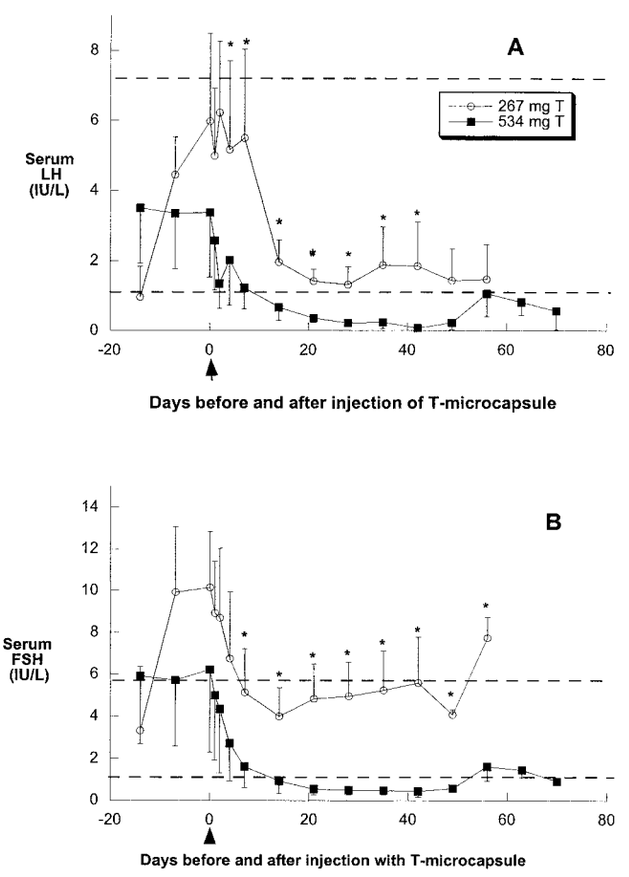

Figure 4. Serum LH **(A)** and FSH **(B)** before and after injection of 267 mg (n = 4) and 534 mg (n = 3) of testosterone microcapsule in subjects with normal or high serum gonadotropins at baseline. Data are means ± SEM. Dashed lines represent the normal range. *$P < .05$ between groups.

Table 3. *Serum hematocrit, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and PSA at baseline and end of treatment with testosterone microcapsule*

	267 mg (n = 7)		534 ng (n = 7)	
	Baseline*	8 weeks postinjection*	Baseline*	12 weeks postinjection*
Hematocrit (%)	46.4 ± 1.3	42.9 ± 1.1	46.9 ± 1.8	43.6 ± 1.3
Total cholesterol (ng/dL)	199.6 ± 16.8	203.9 ± 16.0	213.7 ± 15.2	207.3 ± 21.0
HDL cholesterol (ng/dL)	40.7 ± 4.0	46.1 ± 4.5	45.6 ± 4.5	44.1 ± 3.6
LDL cholesterol (ng/dL)	108.7 ± 15.7	106.5 ± 14.4	120.3 ± 14.7	115.3 ± 19.7
Triglycerides (ng/dL)	279.0 ± 72.2	263.7 ± 62.2	239.1 ± 46.7	268.1 ± 54.8
PSA (ng/dL)	0.8 ± 0.2	0.6 ± 0.2	0.7 ± 0.3	0.6 ± 0.3

* Data are means ± SEM.

3 in the 267 mg group at 0.28 ± 0.12 IU/L, and in week 5 at 0.09 ± 0.06 in the 534 mg group.

Mood and Sexual Function

Improvements were seen in the 10 men who completed their questionnaires in self-assessed feelings of irritability ($P = .05$ compared with baseline) and the quality ($P = .05$) and duration of erections ($P = .02$). Trends toward improvements in reported number of sexual interactions per day, number of orgasms, ejaculations, and episodes of intercourse were also noted during treatment as compared with baseline reporting.

Adverse Reactions, Safety, and Tolerability

There were no major adverse effects in any subjects who received testosterone microcapsule. Two of the subjects complained of pain for 5–10 minutes, associated with mild erythema at the injection site. In addition, the injection area was palpable as a small, indurated area under the skin for several weeks after the injection, however, by 12 weeks postinjection the induration was gone. No new gynecomastia or breast tenderness was noted after injection. Serum total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, prostate-specific antigen, and hematocrit did not change significantly during the study (Table 3).

Discussion

In summary, we have demonstrated that subcutaneous administration of PLGA microcapsules containing testosterone (Viatrel) appears to be a safe and effective long-acting mode of testosterone therapy for men with hypogonadism. With the 534 mg dose, serum total testosterone remains within the normal range for up to 10–11 weeks. This compares favorably to intramuscular injection of testosterone esters such as testosterone undecanoate, which must be given every 6–8 weeks (Nieschlag et al, 1999), and is similar to the duration of testosterone release seen in prior studies with intramuscular testosterone microcapsules (Bhasin et al, 1992). Testosterone delivered by microcapsule also results in appropriate elevations of free testosterone, serum estradiol, and DHT levels. Finally, a single-dose of testosterone microcapsule exhibited the predicted pharmacodynamic androgenic suppressive effects on serum SHBG, LH, and FSH while maintaining mood, energy, and sexual function, and without inducing any measurable effects of androgen excess such as polycythemia or suppression of high-density lipoprotein cholesterol.

From a pharmacokinetic standpoint, it is interesting to note that the AUC for total testosterone for the 534 mg group was only 1.67 times the AUC for the 267 mg group. This was likely due to the higher baseline SHBG levels in the 267 mg group, which increased the half-life of the total testosterone in this group. By comparison, the AUC for free testosterone in the 534 mg group was 2.08 times the AUC for the 267 mg group, as would be expected for the pharmacokinetics of unbound hormone. The pharmacokinetics seen with this subcutaneous preparation were different than those reported by Bhasin and colleagues (1992) from their intramuscular testosterone microcapsule preparation. The reason for this is unclear at present, but may represent differential rates of microcapsule decay in the subcutaneous tissue as opposed to muscle.

The peak levels of serum testosterone seen in this study are similar to those seen in trials of long-acting testosterone-esters such as testosterone-undecanoate (Zhang et al, 1998; Nieschlag et al, 1999). In these studies, the adverse effects of high peak serum testosterone levels, such as increased hematocrit and prostate volume, were minimal and less than those observed with the more frequent injections of shorter-acting esters such as testosterone enanthate (TE). Therefore, it has been suggested that the longer injection interval allowed by such preparations may be safer and better tolerated than the more rapid changes in serum testosterone seen with shorter-acting injections such as TE. The low-normal testosterone levels seen at the end of the injection interval did not cause any side

effects, and no subject complained of symptoms of inadequate testosterone replacement during this time. However, this sample may have been too small to detect such symptoms. Whether these low-normal testosterone levels seen at the end of the injection interval are sufficient to support the beneficial metabolic effects of androgenization, such as the maintenance of bone mineral density, will require further study.

DHT levels did not show the expected dose-response between the 2 doses, and the absolute values are somewhat lower than expected. It is possible that testosterone microcapsules may not lead to a proportionate increase in DHT levels, and this may be an advantage to this approach because it helps to avoid excess androgenization such as suppression of high-density lipoprotein cholesterol. Alternatively, the lack of a dose-response relationship in this instance may be that the measurement of the samples from the 267 mg group was completed several months prior to the analysis of the 534 mg samples. Therefore, the DHT levels from the 2 groups in this study should be viewed with caution.

Although no significant changes in serum hematocrit or other laboratory values were seen at the end of the injection interval, there may have been changes during the immediate postinjection period that were not appreciated by our study design. In fact, the serum hematocrit appears slightly decreased at the end of the injection interval. This is likely because by this time (8 weeks in the 267 mg group and 12 weeks in the 534 mg group), the serum total testosterone was again in the hypogonadal range. It is also important to note that despite the small sample size, improvements in both mood and sexual function were observed.

Drawbacks to the use of microcapsules for testosterone administration include a relatively pronounced peak effect 1–4 days postinjection, the presumed absence of diurnal variation in serum testosterone levels, and the discomfort experienced by some of the subjects after injection. Even in the group of subjects who received the higher dose of testosterone microcapsule, however, the mean maximum serum total testosterone concentration did not exceed the upper limit of normal, and none of the subjects complained of side effects referable to over-androgenization. In the patients who noted postinjection pain, the degree of discomfort was less or similar to that of intramuscular injections of testosterone esters. Future studies of testosterone microcapsules will focus on improving the duration of testosterone release, while minimizing the postinjection peaks and the discomfort associated with microcapsule administration.

Novel means of testosterone delivery are needed given the large number of patients who require testosterone therapy. In addition to the treatment of male hypogonadism, long-acting modes of testosterone administration may be useful for bringing the promise of male hormonal contraception to fruition (Amory and Bremner, 2000). The extended duration of action and ease of administration make testosterone microcapsules an attractive method of testosterone delivery compared with existing methods. Repeated administration of the Viatrel formulation at 70- to 80-day intervals may lead to some cumulative effects, and therefore, result in somewhat higher steady state levels. Long-term use of such a preparation in the treatment of male hypogonadism will require additional studies of the safety, efficacy, and pharmacokinetics of chronic testosterone microcapsule administration.

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