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Reexamination of Pharmacokinetics of Oral Testosterone Undecanoate in Hypogonadal Men With a New Self-Emulsifying Formulation

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Abstract

Many hypogonadal men prefer oral testosterone (T) treatment. Oral T undecanoate (TU) is available in many countries, but not in the United States. We aimed to assess the pharmacokinetics of oral TU in a new self-emulsifying drug delivery system formulation. Pharmacokinetics studies were conducted in 3 parts: 12 hypogonadal men were enrolled in 2 centers for a 1-day dosing study; 29 participants were enrolled from 3 centers for a 7-day dosing study; and 15 participants were enrolled from 1 center for a 28-day dosing study. Serial blood samples for serum sex hormone measurements by liquid chromatography–tandem mass spectrometry were drawn for up to 36 hours after oral TU administration. Mean serum T levels (C_{avg}) after oral dosing of T 200 mg as TU twice daily with food were within the adult male range in most participants in the 1-, 7-, and 28-day dosing studies but were much lower in the fasting state. The dose-proportional increase in C_{avg} of serum T after oral T 300 mg twice daily resulted in more participants with supraphysiologic serum T levels. In the 28-day study, trough serum T reached a steady state at day 7. Serum dihydrotestosterone and estradiol levels tracked serum T concentration. Dihydrotestosterone-testosterone ratios increased 3-fold after oral TU administration. Oral T 200 mg twice daily as TU in a new SEDDS formulation may be a viable therapy for hypogonadal men.

Keywords

Male hypogonadism; testosterone pharmacokinetics

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Oral testosterone (T) replacement represents an attractive option for hypogonadal men because of its convenience, ease of administration, and patient preference factors compared with T patches, gels, injections, and subcutaneous implants (Nieschlag et al, 2004; Qoubaitary et al, 2005). A buccal delivery system for T is available but not used by many hypogonadal men because the tabletlike system adheres to the gums and can be felt in the mouth, and it sometimes dislodges with meals (Wang et al, 2004c). Oral 17-alkylated androgens (ie, methyltestosterone) have been available for many years but suffer from potential hepatic toxicity (Boyer et al, 1976; Westaby et al, 1977; Bhasin et al, 2010). In addition, oral modified androgens significantly decreased high-density lipoprotein cholesterol and increased low-density lipoprotein cholesterol concentrations (Friedl et al, 1990). Despite the potential advantages of an oral testosterone formulation, extensive first-pass hepatic metabolism limits oral bioavailability of T and its esters (Tauber et al, 1986). Consequently, renewed effort has been focused on developing T prodrug formulations, such as T undecanoate (TU), to enhance delivery via intestinal lymphatics, thereby bypassing hepatic metabolism and optimizing bioavailability. TU was selected because it is highly lipophilic and is preferentially absorbed by intestinal lymphatics in contrast with other T esters, which are less lipophilic and mainly absorbed via the portal system (Horst et al, 1976). In this study, TU was formulated into a new proprietary self-emulsifying drug delivery system (SEDDS) formulation.

Although a castor oil–based oral TU preparation with an excellent safety profile in small numbers of individuals has been available in parts of the world since the 1970s (Nieschlag et al, 1975; Skakkebaek et al, 1981; Gooren, 1994), there is at present no commercially available oral TU formulation marketed in the United States. Despite the clinical improvement observed in both younger and older hypogonadal men treated with this oral TU oil-based preparation, trough serum T levels are often not elevated from low baseline levels, and serum T levels may not stay within the adult male reference range throughout the day (Nieschlag et al, 1975; Skakkebaek et al, 1981; Wittert et al, 2003; Emmelot-Vonk et al, 2008). Furthermore, it is unlikely that treatment of hypogonadal men with this TU formulation would yield average serum T levels in a sufficient percentage of men to meet the current regulatory and clinical scrutiny.

We studied the pharmacokinetics (PK) of a new oral formulation incorporating an SEDDS in hypogonadal men. This SEDDS promotes solubilization and the intestinal lymphatic absorption of lipophilic T esters, thereby reducing first-pass hepatic metabolism. Rapid deesterification of TU by nonspecific esterases in liver, blood, and tissue results in production of T. The liberated undecanoic acid moiety is metabolized via beta-oxidation. 5-Alpha reduction of TU in the gut produces dihydrotestosterone undecanoate (DHTU) and dihydrotestosterone (DHT). In this study, we report the PK of serum T, DHT, TU, and DHTU after 1-day, 7-day, and 28-day oral dosing of TU administered in SEDDS, and demonstrate that serum T levels are achieved within the physiologic range after dosing with TU 200 mg twice per day in most hypogonadal men.

Materials and Methods

Study Centers

Three centers participated in either single- or repeat-dose parts of the study: Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute in Torrance, California; and Alabama Clinical Therapeutics LLC and Alabama Internal Medicine, both in Birmingham, Alabama. The study protocol was approved by an institutional review board at each participating center.

Participants

Twelve hypogonadal men participated in a single-day study part. Twenty-nine participants received oral TU 200 and 300 mg twice per day for 7 days. In 26 participants who received TU 200 mg twice a day, serum T PK was evaluated on day 7 in the fed state and day 8 in the fasting state. A 28-day steady-state study part was conducted at one center with 15 participants. To be eligible for each study part, participants ages 18 to 66 years had baseline morning serum total T <10.4 nmol/L (<300 ng/dL, between 6 and 10 AM) on two consecutive occasions; were naive to androgen replacement; or completed a 1-week washout of oral, buccal, or transdermal T treatment or a 4-week washout of T injections. For participants with hypopituitarism or multiple endocrine deficiencies, individuals were eligible only if on stable doses of thyroid and adrenal hormonal replacement for at least 14 days prior to enrollment. Individuals were excluded from the study if they had significant chronic disease, uncontrolled diabetes mellitus (HBA1c >9%), psychiatric illness, hematocrit <.35L/L or >. 5L/L, body mass index ≥36 kg/m^2, abnormal prostate examination, prostate-specific antigen >4 mcg/L, history of prostate cancer, abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture, known malabsorptive disease, drug or alcohol abuse, a history of blood donation 12 weeks prior to the initial study dose, or if unwilling to refrain from cigarette smoking during the confinement period. All participants provided written informed consent prior to screening evaluations.

Experimental Medication

A proprietary prodrug formulation SEDDS including the active ingredient TU was developed by Clarus Therapeutics Inc (Northbrook, Illinois). Each TU capsule contains 100 mg of T equivalent to 158.3 mg of TU. The TU dose henceforth refers to the T dose equivalent. This T-ester is lipophilic, and the formulation incorporates a complex lipid matrix and an emulsifying agent.

Study Design

We conducted this PK study in three parts. The primary endpoint of for all study parts was the proportion of men with average serum T levels within the adult male reference range, predefined as 10.4 to 34.7 nmol/L (300–1000 ng/dL). This range is based on regulatory guidelines from the US Food and Drug Administration and is generally quoted as the laboratory reference range in adult men (Larsen et al, 2003). TU was administered 30 minutes after a meal unless otherwise stated. All dose-associated meals (breakfast and

dinner) provided during confinement were identical and standardized to contain 30% fat (30.3 g), 667 g total weight, 894 kcal, 139 g of carbohydrates, and 26 g of protein.

The first part was a single-dose PK study employing an open-label, 2-center, crossover design with a washout of 7 days between each treatment and follow-up employing different doses of TU (100 or 200 mg of T). The second part was a 7-day dosing study in which oral TU (200 or 300 mg of T) was given twice per day. To determine the effect of food on the absorption of oral TU, the TU dose was given 30 minutes after initiation of a high-fat (approximately 50% fat) meal on day 7 and during the fasting state on day 8, and serial samples for PK were assessed. The third part of the study involved administration of oral T 200 mg twice a day for 28 days to determine the time to reach steady-state PK. Periodically during the 28-day treatment period, a single trough sample was obtained in the morning prior to the AM dose. On day 28, only a morning dose of 200 mg of oral T was given, and serial PK samples were obtained for 36 hours. Serum T, DHT, and, in some study parts, TU, DHTU, and estradiol, were drawn at −30 and 0 minutes before dose and at between 1- and 4-hour intervals for up to 12 to 36 hours after oral TU administration. Safety laboratories were obtained at baseline and on the final day of each study part.

Analytical Methods

Serum total T and DHT were measured by sensitive, specific, and validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) without modification as previously described (Shiraishi et al, 2008). Intraassay and interassay coefficients of variation for T and DHT are less than 5%. The lower limit of quantification for testosterone and DHT is 0.96 nmol/L (2 ng/dL). The reference range for serum T for this study is defined as 10.4 to 34.7 nmol/L (300–1000 ng/dL). The reference range for DHT is 0.47 to 2.7 nmol/L (13.7–77 ng/dL, determined in our laboratory from 113 healthy adult men). Serum TU and DHTU were measured simultaneously by LC-MS/MS using a published method with modifications (Shackleton et al, 1997; Peng et al, 2002). Deuterium-labeled TU and DHTU (synthesized by CDN Isotopes, Pointe-Claire, Canada) were used as internal standards. Serum samples were treated with acetonitrile to precipitate proteins before extracting twice with ethyl acetate–hexane 3:2 by volume. The organic solvent was pooled, treated with potassium hydroxide solution, washed with acetic acid and distilled water, dried, and then reconstituted with 50% methanol before injection. The TU and DHTU analyses were conducted using a Shimadzu high-performance LC system (Columbia, Maryland) with an Applied Biosystems API-5500 LC-MS/MS (Foster City, California). A Thermo Hypersil GOLD LC-8 DB column (50 ×4.6 mm, 5 μm; Waltham, Massachusetts) was used with a gradient profile at a flow rate of 0.4 mL/min and a mobile phase of MeOH and 98% H_2O (2% MeOH, 0.1% formic acid). TU and DHTU were analyzed using the turbo ion spray source in positive mode. The interassay and intraassay variations for TU and DHTU assays are 5.6% to 10.4%, and 8.9% to 15.4%, respectively, spanning the different concentrations. The lower limits of quantification for TU and DHTU are both 6.6 nmol/L (3 ng/mL). Serum estradiol (E2) concentrations were measured with LC-MS/MS validated in our laboratory as previously described (Rothman et al, 2011). The within-run precision range is 2.78% to 3.58%, and between-run precision is 3.7% to 9.8% for E2. The recovery of samples spiked with E2 was 101.8% for E2. The reference range of E2 for adult men is

27.5 to 112.3 pmol/L (7.5–30.6 pg/mL, determined in our laboratory from 95 healthy adult men). Serum luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were measured by previously reported immunoassays (Swerdloff et al, 2000).

Statistical Analysis

Because this was a proof-of-concept study, the number of participants was not powered for statistical significance and was considered appropriate to achieve the stated objective. PK parameters were derived using noncompartmental methods. The area under the curve (AUC) was calculated using the trapezoidal method. The average concentration during 24 hours (C_{avg}) was calculated as AUC_{0-24} divided by 24 hours. The maximum serum concentration (C_{max}), time to reach C_{max} (T_{max}), and time within the reference T range (T_{norm}) of T and DHT were obtained and/or derived from measured serum concentration levels. The fluctuation index was calculated as $(C_{max} - C_{min})/C_{avg}$, with C_{min} representing minimum serum concentration. All data were presented as mean ± SEM.

Results

Participants

Participant demographics are shown in Table 1. The serum baseline T concentrations were 5.2 ± 0.80, 5.9 ± 0.53, and 8.09 ± 1.17 nmol/L in the 1-day, 7-day, and 28-day parts of the study, respectively. The hypogonadal men were obese with a mean body mass index >30 in all three parts of the study. All enrolled participants completed corresponding study parts.

Serum Concentrations and PK Parameters

Across all three parts of the study, oral administration of the study TU SEDDS formulation to hypogonadal men resulted in a peak concentration (T_{max}) between 4 and 5 hours, after which time T concentrations declined in an approximately zero-order pattern and reached baseline after approximately 12 hours unless a second dose was administered. The T concentration pattern observed following the evening dose was similar to the pattern observed following the morning dose.

Single-Day Dose Study

With TU dosed for a single day as 100 mg twice a day, 200 mg given once in the morning, and 200 mg twice a day, there was a dose-dependent relationship, with higher serum T C_{avg} when 200 mg twice a day dosing was compared with 100 mg twice a day dosing for both 12- and 24-hour data (Figure 1 and Supplemental Table 1, available online at www.andrologyjournal.org). By 8 hours, serum T levels declined below the lower limit of the eugonadal range with 100 mg twice a day and 200 mg once daily dosing, and levels were near the lower limit with 200 mg twice a day dosing. T_{norm} during 24 hours ranged from 5.6 ± 0.9 hours with 200 mg daily, 8.6 ± 1.8 hours for 100 mg twice a day dosing, and 13.0 ± 0.9 hours for 200 mg twice a day dosing. A total of 75% of participants achieved C_{avg} in the adult male reference range after 200 mg twice a day dosing for a day; percentages were lower with other dosing schedules.

Seven-Day Repeat Dosing

With TU dosed as T 300 mg twice a day (anticipated maximum dose in phase 3 development), C_{avg} for serum T was 26.5 ± 2.2 nmol/L when 12-hour postdosing data were analyzed; PK results were similar when examining 24-hour data (Figure 2). Approximately 87% of participants achieved C_{avg} within the adult male reference range. Serum T C_{max} (48.9 ± 5.1 nmol/L) was above the upper limit of the physiologic range (34.7 nmol/L [1000 ng/dL]) in 61% of participants. C_{min} (10.6 ± 1.1 nmol/L) was within the reference range of young adult men.

Seven-Day Repeat Dosing Under Fed vs Fasting Conditions

After TU 200 mg twice a day for 7 days, the 12-hour PK values for C_{max}, C_{avg}, and T_{max} for T and DHT were higher (by about 2-fold) following meals compared with fasting (Supplemental Table 2 and Figure 3). The same parameters were also much higher (by 6-fold) for serum TU in the fed state. Postprandial increases in C_{avg} and C_{max} were most pronounced for DHTU, demonstrating 8- to 9-fold increases after meals compared with fasting. A total of 77% of fed participants were able to achieve C_{avg} within the serum T reference range, compared with only 25% of fasted participants. Food intake prolonged T_{max} on average by more than 2 hours and resulted in higher minimum T concentrations. Serum T levels generally returned to baseline levels at 12 hours after TU dosing.

Steady-State Dosing (During 28 Days)

Time to steady-state following administration of oral TU was assessed based on trough concentrations of serum T, DHT, and E2. The mean baseline serum T for this group of men was 9.6 ± 2.8 nmol/L (screening serum T was 8.09 ± 1.2 nmol/L), which was close to the lower limit of the reference range. The average trough (before the next dose of oral TU) serum T remained above the lower limit of the normal range of 10.4 nmol/L. The slope of the regression line through the AM trough concentrations from day 7 to day 28 was not statistically different from 0, indicating that oral TU 200 mg twice a day administered with meals yielded steady-state serum T levels by day 7 (Figure 4). Serum free T and DHT levels both tracked serum total T levels. DHT/T ratios varied around 0.30 during the 28-day period. Serum E2 concentrations showed an increase to achieve steady-state concentration by day 7. Serum E2/T ratios showed minor fluctuations, rising from a mean of 0.0054 ± 0.0005 on day 1, and subsequently ranged from 0.0046 to 0.0079, with most ratios between 0.006 and 0.007 (Figure 4).

Twelve-hour mean C_{max}, mean C_{min}, and C_{avg} for serum T and DHT on day 28 (Table 2; Figure 5) were very similar to serum T and DHT levels in the fed state following 7 days of treatment (Supplemental Table 2). More than 86% of participants had C_{avg} (17.9 ± 2.0 nmol/L) within the physiologic range for T during 12 hours. C_{max} was within the physiologic range for T in 53.3% of participants. C_{min} averaged 23.5% of $C_{max.}$ There were no participants with C_{max} higher than 62.5 nmol/L (1800 ng/dL). The fluctuation index indicated that the peak to trough fluctuation was 156% of C_{avg}. The elimination half-life of T could only be evaluated in about half of the participants, and its median value was 18.4 hours (mean, 29 hours). The average DHT/T ratio was 0.245, although values during the dosing interval ranged from a mean maximum ratio of 0.380 to a mean minimum ratio of

0.131. DHT/T was lowest when serum T levels were highest (3–6 hours after dosing) and highest when serum T concentrations were lowest (beginning and at the end of the 12-hour period). E2 concentrations also showed systematic variation during the dosing interval and tracked T levels (Figure 5). The mean C_{max}, mean C_{min}, and C_{avg} values for E2 were 110.3, 56.6, and 80.3 pmol/L, respectively. On day 28, serum E2/T ratio decreased from a trough level of 0.0078 to about 0.0040 when serum T peaked between 3 and 6 hours. Serum E2/T then increased gradually to reach levels slightly above the tough level at 12 hours.

Mean decreases in luteinizing hormone and follicle-stimulating hormone from baseline to day 28 were 3.6 mIU/mL and 3.3 mIU/mL, representing mean percent decreases of 77.5% and 60.1%, respectively. Sex hormone–binding globulin was 22.2 ± 2.4 nmol/L at baseline and 13.3 ± 1.76 nmol/L after 28 days (representing a 38.4% decrease that was significantly lower; $P < .0001$). This decrease did not appear to affect free T (baseline, 0.24 ± 0.016 nmol/L; after 28 days, 0.30 ± 0.067 nmol/L; $P = .22$) or total T (baseline, 9.6 ± 0.73 nmol/L; after 28 days, 10.0 ± 2.05 nmol/L; $P = .41$).

Safety Measurement/Adverse Events

Fifteen possibly or probably drug-related adverse events (AE) were reported across the various parts of the study. Of these, the most common were heartburn (n = 3), decrease in penile erection (n = 2), and headache (n = 2). Each of the remaining adverse events occurred in 1 participant: elevation in liver enzymes (baseline serum aspartate aminotransferase [AST] was 30 U/L and alanine aminotransferase [ALT] was 22 U/L; at a single time point during treatment AST rose to 92 U/L and ALT to 112 U/L; by the end of study AST had decreased to 31 and ALT 43 U/L), hypertension (baseline blood pressure 144/92 on 2 antihypertensive agents and 157/96 at the end of study, at which time a third agent was added), intermittent self-reported prostate enlargement (with baseline and end-of-study digital rectal examination normal), mood changes, feeling hot, skin rash, and loss of appetite. No clinically significant changes in vital signs, physical examination, or clinical laboratory variables were found. No indications of liver function abnormalities except the aforementioned transient elevation in hepatic aminotransferases were observed.

In the 28-day steady-state study part, mean ± SEM serum high-density lipoprotein cholesterol decreased from 36.1 ± 7.1 to 29.2 ± 6.5 mg/dL (a mean decrease of 6.9 mg/dL, or 19.1%) from baseline to final visit. An observed mean ± SEM increase in hematocrit from .432 ± .019 L/L to .468 ± .029 L/L (increase of .036 ± .021 L/L) and in hemoglobin from 15.0 ± 0.7 to 15.8 ± 1.0 (increase of 0.75 ± 0.70 mg/dL) at final visit was not considered clinically significant and reflects the known action of androgens on red blood cell production (Snyder et al, 1989).

Discussion

This phase 2 PK study demonstrated that repeated dosing of TU in an SEDDS formulation in hypogonadal men is well tolerated with dose-proportional PK. When 100 mg of T as TU twice a day was administered to hypogonadal men, only one-third of participants had average serum T levels within the adult male range in the 24 hours after dosing, suggesting that this dose would not be adequate in most hypogonadal men. When oral TU 200 mg was

administered twice per day, mean serum T levels were within the adult reference range in more than 75% of participants, notably without dose adjustment. Repeat dosing of TU 200 mg twice a day during 28 days resulted in trough T levels reaching a steady state after about 7 days, whereupon they remained slightly above the lower limit of the adult reference range, indicating minimal evidence of drug accumulation. Higher trough T levels were not seen because the PK of this oral TU formulation was such that serum T levels 12 hours after dose reached near-baseline levels. This group of participants had appreciably higher average baseline serum T levels than other groups while still meeting study eligibility criteria and were diagnosed with hypogonadism by their physicians. The probable reason that trough T levels following treatment with oral TU for 28 days were not significantly higher than pretreatment baseline levels likely reflects the balance between the ongoing pharmacodynamics of endogenous T suppression by the continuous administration of oral TU and the contribution from exogenous T provided by administered oral TU. By day 28, 87% of men had average serum T levels within the adult male range, and none of the participants had C_{avg} for serum T higher than 52 nmol/L (1500 ng/dL). If the dose of TU was increased to 300 mg twice a day, the average serum T during 12 hours was about 1.5-fold higher than with 200 mg twice a day, demonstrating a dose-proportional increase in serum T levels after TU administration. As expected, the higher dose of oral TU resulted in a higher percentage of participants with supraphysiologic serum T levels. It should be noted that the hypogonadal men who participated in the study were generally overweight and middle aged. Studies involving younger and leaner men with higher baseline serum T and sex hormone–binding globulin levels may yield serum testosterone levels different from those reported in this study.

In contrast to the older oil-based formulation of TU Andriol, the current SEDDS formulation uses a unique combination of lipophilic and hydrophilic surfactants to increase solubility of the lipophilic T ester and promote emulsification in the aqueous environment of the gastrointestinal tract. The elimination half-life of T in response to TU in the SEDDS formulation studied after 28 days of dosing was appreciably longer than has been reported for T alone or for oral TU in other (non-SEDDS) formulations (Sandberg and Slaunwhite, 1956). Although there is a paucity of detailed serum T PK data with repeat dosing of Andriol in the literature, recent large studies showed that trough serum T levels after oral TU in oil were near to or lower than the baseline serum T levels in hypogonadal men (Emmelot-Vonk et al, 2008; Legros et al, 2009). And although serum T levels increased after administration of Andriol at the recommended dose of 80 mg twice a day (equivalent to T 50 mg twice a day; Nieschlag et al, 1975; Jungwirth et al, 2007), a significant percentage of hypogonadal men failed to achieve serum T levels in the eugonadal range (Skakkebaek et al, 1981; Gooren, 1994). The higher serum T concentrations observed with SEDDS formulation of TU used in this study when compared with Andriol could be due to more T administered in the improved formulation of TU in the SEDDS, or the methods used for quantifying serum T. In earlier publications, serum T was measured by immunoassays after chromatography, whereas the LC-MS/MS used in the present study is more accurate and precise (Taieb et al, 2003; Wang et al, 2004a).

In the present study, 200 mg of an SEDDS formulation of oral TU given twice daily resulted in 2.1- to 2.4-fold higher C_{avg} and mean C_{max} serum T levels in the fed state vs fasting. The

food effect on oral TU PK had been reported with Andriol 80 mg coadministered with a "normal diet" containing 19 to 23 g of lipids (Bagchus et al, 2003; Schnabel et al, 2007) in postmenopausal women that resulted in serum T concentrations more than 10-fold higher than fasting. We showed that after oral dosing of TU, serum TU and DHTU rose to high levels, with maximal serum concentration achieved at about 4 hours for TU and an hour later for DHTU. Average serum TU and DHTU concentrations were 6.2- and 8.8-fold higher, respectively, in the fed state compared with fasting. The previously observed changes in TU and DHTU concentrations after food with Andriol (Houwing et al, 2003) in women were not proportional to the present study. Additional studies involving different levels of dietary fat are needed to more fully characterize the food effect on TU absorption when administered in an SEDDS formulation. Once this information is more clearly elucidated, specific guidelines for meal content and the importance of administration with meals can be developed.

At baseline, the serum DHT concentrations were approximately one-tenth of the serum T concentration. As expected, serum DHT levels rose above the reference range and remained at similar levels with continuous TU administration. Similar to serum T, serum DHT concentrations were much lower when the TU was administered while fasting. After 28 days of oral TU administration, the serum DHT/T ratio was about 0.3. These results were similar to serum DHT levels previously reported after Andriol administration in women (Houwing et al, 2003) and in men (Gooren, 1994). The higher serum DHT levels may be a result of intestinal 5-alpha reductase activity (Shackleford et al, 2003). The significance of the increase in serum DHT levels is not known. Furthermore, a 10-year study of a small group of hypogonadal men suggested that TU is a safe oral androgen (Gooren, 1994) and was well tolerated in larger, short-term studies (Emmelot-Vonk et al, 2008; Legros et al, 2009). Administration of T is not associated with increases in intraprostatic T and DHT levels (Marks et al, 2006). Long-term administration of DHT gel on the skin resulting in DHT/T ratios many-fold higher than after oral TU administration was not associated with increased prostate growth or indices of prostate disease (Idan et al, 2010). These recent data suggest that circulating levels of androgens (ie, T and DHT) do not appear to have any measurable effect on intraprostatic androgen concentrations, nor do they have a significant effect on prostate growth or activation of genes associated with prostate cancer (Page et al, 2011).

Serum E2 generally tracked serum T levels. During 28 days of oral TU administration, trough E2 levels were increased from baseline but remained within the reference range. Trough serum E2/T ratios showed small fluctuations around the baseline level. During the 12-hour PK sampling on day 28, serum E2 increased with serum T levels, and serum E2/T ratios were lowest when serum T levels peaked between 3 and 6 hours. There is no clinical evidence that increased serum E2 remaining within the adult male range has any adverse clinical effects.

There were few adverse events associated with short-term oral TU administration. As expected, because of the pharmacologic action of androgens and consistent with other forms of T replacement, there was a 19.1% decrease in serum high-density lipoprotein cholesterol levels. The magnitude of decrease in HDL cholesterol observed in this study was less than reported for some other T-replacement methods (ie, parenteral T enanthate [36% decrease]

and subcutaneous T implant [33% decrease]; Jockenhovel et al, 1999) but more than reported for transdermal T gels (10% decrease; Wang et al, 2004b). The long-term clinical significance of decreased HDL levels following T treatment remains unknown given the complex actions of T on overall cardiovascular health and the association between low T and increased cardiovascular disease risk (Liu et al, 2003; Wu and von Eckardstein, 2003; Laughlin et al, 2008). The study duration was too short to assess longer-term effects of reduced HDL cholesterol. However, it is noteworthy that the modest decrease of HDL cholesterol observed in response to intramuscular injections of TU in the first 30 months of treatment reverted to baseline and increased (by 28%) in hypogonadal men treated for more than 4 years (Minnemann et al, 2007). A similar normalization of HDL was observed after 12-month use of a T-gel product (Wang et al, 2004b). Lastly, the decreased gonadotropin levels reflect the known pharmacologic actions of androgen therapy (ie, negative feedback on hypothalamic-pituitary axis).

In summary, our detailed PK study shows 200 mg of T twice a day as TU is likely to result in an average serum T concentration within the eugonadal range in most hypogonadal men. This supports the continued clinical development of the new oral TU formulation. The present study did not involve dose titration, which can be implemented in future studies and clinical practice to tailor an effective and individualized oral TU regimen for hypogonadal men. Notably, oral TU was well tolerated, and hepatic toxicity was not observed. Evaluation in a larger sample size and for a longer duration is necessary to further demonstrate the safety and efficacy of this novel TU formulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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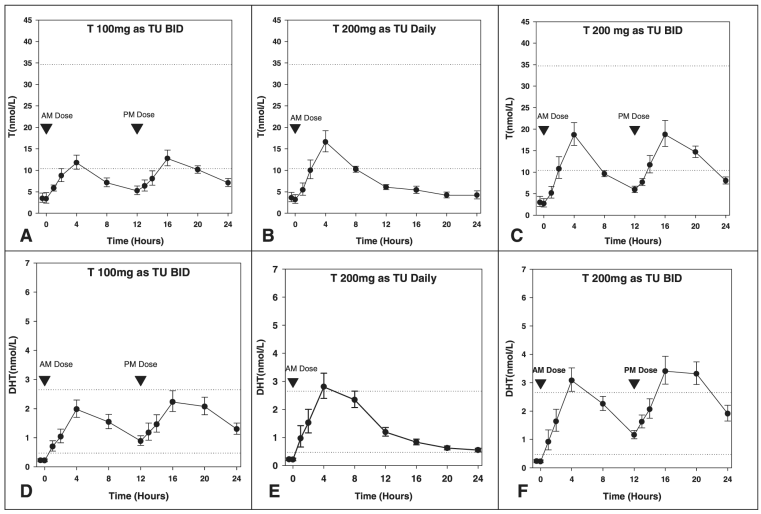

Figure 1.

Serum testosterone (T) **(A, B, C)** and dihydrotestosterone (DHT) **(D, E, F)** concentrations after a single-day oral dose of T 100 mg twice a day (BID) **(A, D)**, 200 mg once **(B, E)**, and 200 mg twice a day **(C, F)** as oral testosterone undecanoate (TU; geometric mean ± SEM).

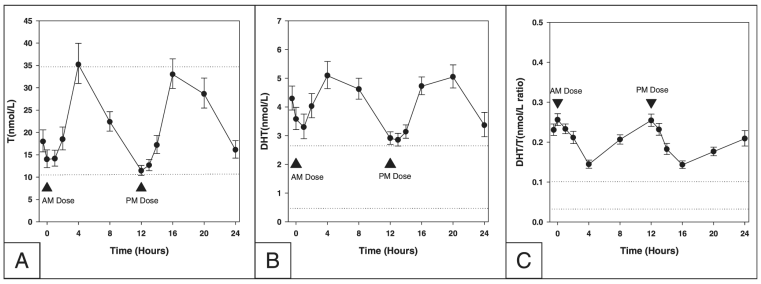

Figure 2.

Serum testosterone (T) **(A)**, dihydrotestosterone (DHT) **(B)**, and DHT/T **(C)** on day 7 after T 300 mg as oral testosterone undecanoate administered twice a day for 7 days (geometric mean ± SEM).

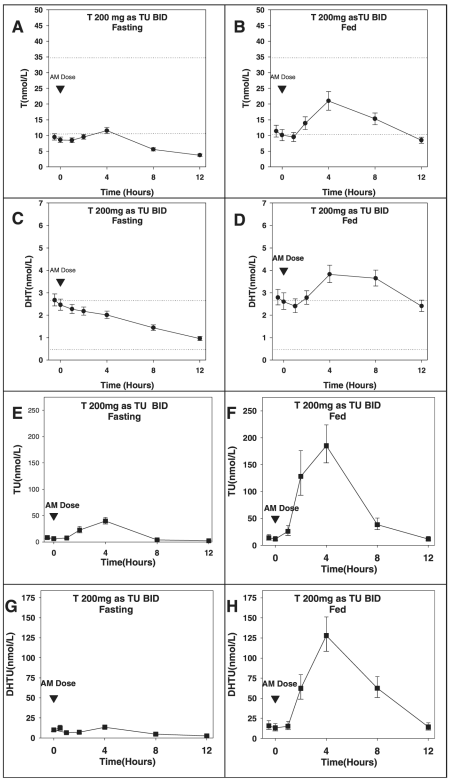

Figure 3.

Serum testosterone (T) **(A, B)**, dihydrotestosterone (DHT) **(C, D)**, testosterone undecanoate (TU) **(E, F)**, and dihydrotestosterone undecanoate (DHTU) **(G, H)** concentrations on day 7 after T 200 mg twice a day (BID) as oral TU for 6 consecutive days (geometric mean ± SEM). A single dose of TU was administered on day 7 after food (right panels) and on day 8 in the fasting state (left panels).

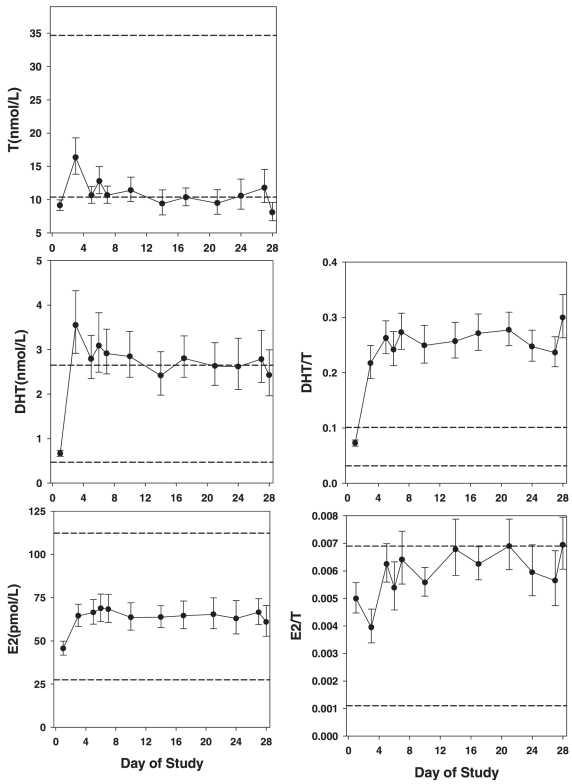

Figure 4.

Serum testosterone (T), dihydrotestosterone (DHT), DHT/T, estradiol (E2), and E2/T trough concentrations (geometric mean ± SEM) during and after T 200 mg twice a day as oral testosterone undecanoate for 28 days.

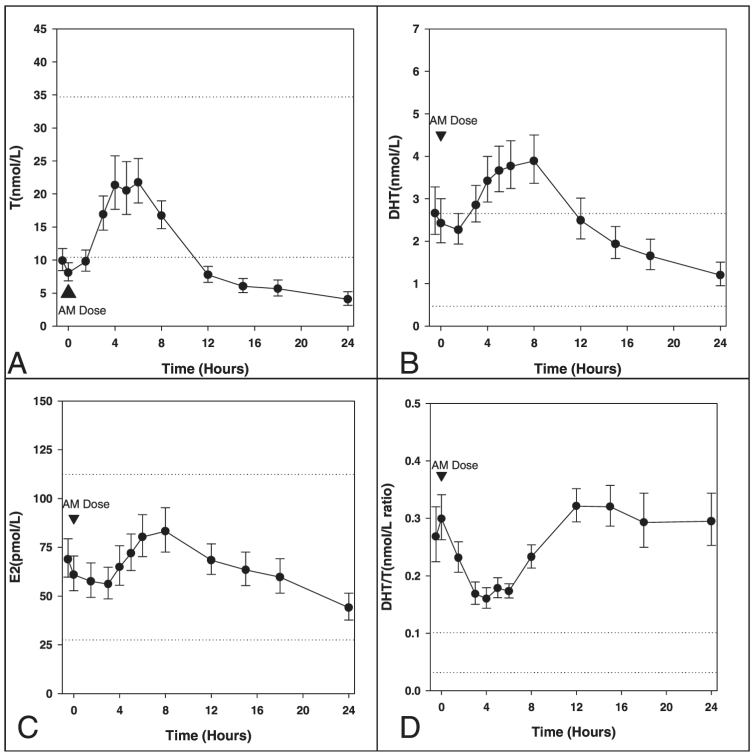

Figure 5.

Serum testosterone (T) **(A)**, dihydrotestosterone (DHT) **(B)**, estradiol (E2) **(C)**, and DHT/T **(D)** concentrations (geometric mean ± SEM) after the last dose of oral T 200 mg twice a day as oral testosterone undecanoate administered for 28 days.

Table 1

Baseline participant demographics and characteristics (mean ± SEM)

	Single-Day PK Study Part (n = 12)	7-Day PK Study Part[a]	28-Day Steady-State PK Study Part (n = 15)
Age, y	53.3 ± 3.6	48.6 ± 1.9	46.7 ± 10.87
Race, n			
African American	3	2	1
White	4	21	14
Hispanic	5	6	0
Hypogonadism etiology, n			
Primary	2	16	0
Secondary	6	13	N/A[b]
Unknown	4	0	N/A[b]
Height, cm	178.8 ± 2.8	177 ± 1.9	180.8 ± 2.96
Weight, kg	112.3 ± 6.7	96.3 ± 3.26	102.3 ± 7.3
BMI, kg/m^2	35.2 ± 2.2	30.3 ± 0.64	31.0 ± 3.35
Serum T, nmol/L	5.2 ± 0.80	5.9 ± 0.53	8.09 ± 1.17
Serum DHT, nmol/L	0.32 ± 0.04	0.62 ± 0.14	0.72 ± 0.08

Abbreviations: BMI, body mass index; DHT, dihydrotestosterone; N/A, not available; PK, pharmacokinetics; T, testosterone; TU, testosterone undecanoate.

[a] n = 29 for TU 300 mg twice a day, and n = 26 fed and n = 24 fasting for TU 200 mg twice a day.

[b] Etiology of hypogonadism not available, although no participant had hypergonadotropic hypogonadism.

Table 2

Twelve-hour pharmacokinetics of serum testosterone (T), dihydrotestosterone (DHT), and estradiol (E2) with oral testosterone undecanoate 200 mg twice a day administered for 28 days (mean ± SEM)

0–12 h	T	DHT	E2
AUC, nmol/L per h	215.0 ± 24.3	45.2 ± 6.5	963.0 ± 125.5[a]
C_{avg}, nmol/L	17.9 ± 2.0	3.8 ± 0.5	80.3 ± 10.5[b]
C_{max}, nmol/L	34.5 ± 3.9	5.2 ± 0.7	110.3 ± 14.3[b]
T_{max}, h	4.9 ± 0.5	5.9 ± 0.7	6.7 ± 0.8
C_{min}, nmol/L	6.9 ± 1.0	2.2 ± 0.4	56.6 ± 8.7[b]
T_{min}, h	6.1 ± 1.5	6.0 ± 1.4	3.6 ± 1.0
T_{norm}, h	7.7 ± 0.7	4.8 ± 1.2	9.1 ± 1.2
No. of participants with C_{avg} in reference range (%)[c]	13 (86.7)	6 (40.0)	12 (80)

Abbreviations: AUC, area under the curve; C_{avg}, mean serum T levels; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; T_{max}, time to reach C_{max}; T_{min}, time to reach C_{min}; and T_{norm}, time within reference T range.

[a] Serum E2 AUC reported as pmol/L per h.

[b] Serum E2 concentration reported as pmol/L per h.

[c] Serum T reference range, 10.4–34.7 nmol/L; serum DHT reference range, 0.47–2.65 nmol/L; and serum E2 reference range, 27.5–112.3 pmol/L.