

## Nanomilled Oral Testosterone Plus Dutasteride Effectively Normalizes Serum Testosterone in Normal Men With Induced Hypogonadism

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**ABSTRACT:** Oral androgen development has been hampered by the rapid metabolism of orally administered testosterone (T) and low bioavailability. The addition of the 5 $\alpha$ -reductase inhibitor dutasteride (D) to oral T in oil dramatically improves concentrations of serum T. In this study we evaluate the absorption of oral T+D, comparing nanomilled T (NmT+D) vs T dissolved in oil (Capmul; CpT+D), as nanomilling might offer a simpler, more practical means of oral T administration, given the limited solubility of T in oil. Twelve healthy men were administered leuprolide on Day -14 to suppress endogenous T biosynthesis and were pretreated with D to block 5 $\alpha$ -reductase. Once hypogonadal, subjects were sequentially administered 200- and 400-mg doses of CpT+D and NmT+D in the fasted and fed states. Serum T and dihydrotestosterone (DHT) were measured: before dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after each dose. Two weeks after leuprolide administration,

T levels were below the normal range. A 400-mg dose of either formulation of oral T+D increased mean serum T above the lower limit of the normal range for 8–10 hours. Food had a minimal effect on the pharmacokinetic parameters of the NmT+D formulation but decreased the maximum observed concentration after dosing ( $C_{max}$ ) for CpT+D. Serum DHT remained below the normal range throughout the study period with both formulations. No significant changes in liver function tests or other adverse events were observed. A 400-mg dose of either oral T+D formulation normalized serum T for 8–10 hours and suppressed DHT. NmT allows for tablet formulation, and its pharmacokinetics were not affected by food, demonstrating the feasibility of oral nanomilled T as a promising and practical twice-daily therapy for the treatment of male hypogonadism.

Key words: Androgen, 5 $\alpha$ -reductase.

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A total of 6%–12% of men have symptoms of androgen deficiency associated with testosterone (T) levels below the normal range (Araujo et al, 2004). Signs and symptoms of T deficiency are improved with testosterone replacement (Behre et al, 1997; Snyder et al,

2000), which can currently be safely achieved with intramuscular injections, transdermal patches, or gels. Each of these methods of T delivery has drawbacks. Until recently, intramuscular injections were required every 1–3 weeks, and these can be painful (Fossa et al, 1999). In Europe, the testosterone ester, testosterone undecanoate, can be administered intramuscularly every 12 weeks, but this product is not presently available in the United States. Patches can cause skin reactions in more than half of users (Amory and Matsumoto, 1998). T gels are safe and effective (Swerdlow et al, 2000), but care must be taken to avoid inadvertent exposure to women and children (Brachet et al, 2005).

The only orally available testosterone replacement products currently approved for use in the United States are alkylated T derivatives, such as methyltestosterone, which can cause cholestatic jaundice, drug-induced hepatocellular injury, and peliosis hepatitis, and have been associated with the development of liver adenomas (Westaby et al, 1977). Oral testosterone undecanoate is available in many countries and is not associated with the liver injury seen with methyltestosterone. However, the bioavailability of testosterone undecanoate is

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significantly dependent upon the simultaneous ingestion of a fatty meal (Bagchus et al, 2003) and it must be dosed at least 2 times a day. A safe, oral formulation of T with reliable bioavailability might be preferable for some men compared with currently available options.

Oral administration of crystalline T does not greatly increase serum T levels due to extensive hepatic first-pass metabolism and low bioavailability (Foss, 1939; Johnsen et al, 1974; Nieschlag et al, 1975; Daggett et al, 1978). However, we recently demonstrated that the addition of a  $5\alpha$ -reductase inhibitor to orally administered T in an oil emulsion profoundly improved the absorption of T compared with oral T alone (Amory and Bremner, 2005; Amory et al, 2006). In these studies, serum T levels within the normal range were achieved for 10 hours in normal men with reversible, medically induced hypogonadism when a single dose of T was administered orally in oil together with a  $5\alpha$ -reductase inhibitor. Unfortunately, the solubility of T in oil is partially temperature dependent, making it difficult to encapsulate the dose in an acceptable volume at room temperature without precipitation. Nanomilling, a process of formulating compounds into nanometer-sized particles using high-shear media milling, has been shown to improve the bioavailability of some lipophilic compounds (Merisko-Liversidge et al, 2003).

We hypothesized that oral nanomilled T (NmT) would be as orally bioavailable as T in oil. Therefore, we conducted a pharmacokinetic study comparing dutasteride (D) coadministered with oral T in oil (Capmul; CpT) vs D coadministered with encapsulated NmT. We administered CpT+D or NmT+D in both fasting and fed states to healthy men whose endogenous T production had been temporarily suppressed by the gonadotropin-releasing hormone (GnRH) agonist, leuprolide. Serum T and dihydrotestosterone (DHT) concentrations were assessed over a 24-hour period after each oral dose.

## Methods

### Subjects

A total of 19 healthy male volunteers ages 18–50 years were screened, and 12 were enrolled in the study. The inclusion criteria were: no prior medical illnesses, normal physical examination, and normal hematology, blood chemistry, and liver function tests. Exclusion criteria included: regular use of any medication, substance abuse (alcohol, illicit drugs, anabolic steroids), or abnormal serum T or DHT. The institutional review board of the University of Washington approved all study procedures. Subjects gave written informed consent before screening.

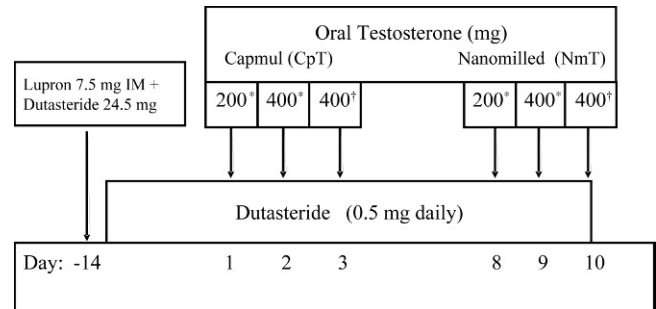


Figure 1. Study design. \* indicates fasting; †, fed.

### Study Drugs

The oral T in the Capmul formulation was prepared by the compounding pharmacy at the University of Washington. Micronized US Pharmacopeia-grade testosterone (Spectrum Quality Products, Gareda, Calif) was added at 100 mg/mL to monodiglycerides of caprylic/capric acid, Capmul (Abitec Corp., Janesville, Wis), that had been liquefied at 55°C. To create a homogenous CpT emulsion, the mixture was thoroughly stirred at 40°C for 15 minutes and then encapsulated in a hard gelatin capsule (Capsugel, Greenwood, SC). The encapsulated Capmul/T formulation is stable for 2–3 hours following preparation, and visible crystallization does not occur when maintained at 40°C. Subjects were administered the warm capsules within 30 minutes of preparation and were not given capsules if crystallization was observed. Nanomilled T (GlaxoSmithKline, Research Triangle Park, NC) was directly encapsulated at room temperature in the hard gelatin capsule. Dutasteride was provided by GlaxoSmithKline. Leuprolide (Lupron) was purchased from TAP Pharmaceuticals (Lake Forest, Ill).

### Study Design

The study design is outlined in Figure 1. Fourteen days prior to dosing (Day –14), subjects received an injection of the GnRH agonist leuprolide (7.5 mg intramuscularly), which suppresses T production in men by 95%, reaching hypogonadal levels by 2 weeks after injection (Mazzei et al, 1990; Perez-Marreno et al, 2002). At this same visit, subjects received a single 24.5-mg loading dose of D to rapidly attain steady-state concentrations (approximately 40 ng/mL) necessitated by the long half-life and large volume of distribution of D. Subjects then self-administered 0.5 mg D daily for the duration of the study (25 days, Day –14 through Day 11). On study days 1, 2, 3, 8, 9, and 10, subjects had blood drawn before dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after administration of oral T+D for measurement of serum T and DHT (CpT on days 1–3 and NmT on days 8–10; Figure 1). On days 1, 2, 8, and 9, the oral T was dosed while fasting, whereas on days 3 and 10, the T was administered with a 750-kcal meal, including at least 250 kcal (~30 g) of fat. Serum liver enzymes, creatinine, and blood counts were obtained at each clinic visit and daily during oral T dosing. Based upon pharmacokinetic data from prior studies of oral T administered in oil (Amory and Bremner, 2005; Amory et al, 2006), a sample size of 12

subjects was estimated to have an 84% power to detect a difference greater than 40% in the serum testosterone area under the curve ( $AUC_{0-24}$ ) between CpT and NmT at the 400-mg dose at an  $\alpha$  of .05.

### Measurements

Serum total T and DHT were measured by a validated gas chromatography/mass spectroscopy assay (Taylor Technologies, Princeton, NJ). Interassay coefficients of variation for low, mid, and high levels of T and DHT were 5.4%, 4.5%, and 1.2%, and 6.3%, 6.3%, and 3.3%, respectively. Intraassay coefficients of variation for low, mid, and high levels of T and DHT were 3.7%, 4.1%, and 0.8%, and 1.4%, 3.4%, and 5.1%, respectively. Lower limits of detection for T and DHT were 50.0 pg/mL and 10.0 pg/mL, respectively.

### Statistics

$AUC_{0-24}$ , maximum observed concentration after dosing ( $C_{max}$ ), and time to maximum observed concentration ( $T_{max}$ ) were calculated for each subject after subtraction of baseline T or DHT concentration for each day (WinNonlin 4.1; Pharsight, Mountain View, Calif). Following  $\log_e$  transformation,  $AUC_{0-24}$  and  $C_{max}$  of testosterone and DHT were analyzed separately by a mixed-effect model fitting day as a fixed effect and subject as a random effect. No adjustments for multiple comparisons were made. For all comparisons, a  $P < .05$  was considered significant. Version 8.2 of the SAS system (SAS Institute Inc, Cary, NC) was used to analyze the data.

## Results

### Subjects

Twelve healthy men were enrolled in the study (Table 1). Eleven subjects completed all blood draws. One subject missed his CpT 400-mg fasting dose due to an unexpected personal conflict.

### Serum Testosterone

In all subjects, serum T levels were suppressed well below the normal range by day 1, 2 weeks after Lupron administration ( $383 \pm 161$  ng/dL at baseline vs  $170 \pm 18$  ng/dL on Day 0;  $P < .001$ ), and on the morning of each study day (ie, 24 hours after the previous T dose; data not shown).

In the fasting state, the combination of D and either 200 or 400 mg of CpT or NmT rapidly raised serum T above the lower limit of normal for approximately 4 hours (200 mg) and approximately 8 hours (400 mg; Figure 2). In the fasting state, the  $AUC_{0-24}$  after CpT or NmT administration was similar after correction for baseline T levels (Table 2). Dosing of oral CpT+D with food significantly decreased the  $C_{max}$  for serum T compared with fasting administration. However, food did not affect the  $C_{max}$  or  $AUC_{0-24}$  of the NmT

Table 1. Baseline and day 1 (days after leuprolide injection, first dose of oral T administered) characteristics of study subjects ( $N = 12$ ; means  $\pm$  SD)

	Baseline
Age, y	34 $\pm$ 8.0
Weight, kg	93 $\pm$ 19
Height, cm	179 $\pm$ 7
Body mass index, kg/m <sup>2</sup>	29 $\pm$ 6
Total testosterone, ng/dL	
Baseline	383 $\pm$ 161
Day 1	170 $\pm$ 18
Dihydrotestosterone, ng/dL	
Baseline	34.9 $\pm$ 5.8
Day 1	6.5 $\pm$ 6.2

formulations. When the oral T was administered with food,  $AUC_{0-24}$  and  $C_{max}$  were not significantly different between CpT+D and NmT+D. For both formulations, dose-dependent increases in exposure were observed in the fasting state (Table 2).

### Serum DHT Levels

Serum DHT levels were suppressed to well below the normal range by day 1 of the study, following the loading of D (Table 1; Figure 3). In the fasting state, the combination of D with either 200 or 400 mg of CpT or NmT raised serum DHT slightly above the predose value by 1 hour; however, DHT levels remained well below the normal range throughout the treatment period (Table 3). Food intake did not affect the DHT levels for either oral T formulation compared with the fasting doses.

### Safety and Tolerability

There were no clinically significant or serious adverse events during the study. Three subjects complained of mild hot flashes and decreased libido after completion of the last dose of oral T due to low T levels attributable to leuprolide administration. These subjects received a 200-mg injection of T enanthate with symptom resolution. There were no significant changes in serum liver or kidney function tests or vital signs during the study (data not shown).

## Discussion

This study is the first reported use of nanomilling to improve the bioavailability of oral T. We have previously shown that the addition of a 5 $\alpha$ -reductase inhibitor to oral T profoundly increases the absorption of oral T administered in oil (Amory and Bremner, 2005; Amory et al, 2006), presumably by inhibiting 5 $\alpha$ -reductase in the gastrointestinal tract, although the precise mechanism is not known. However, T in oil has

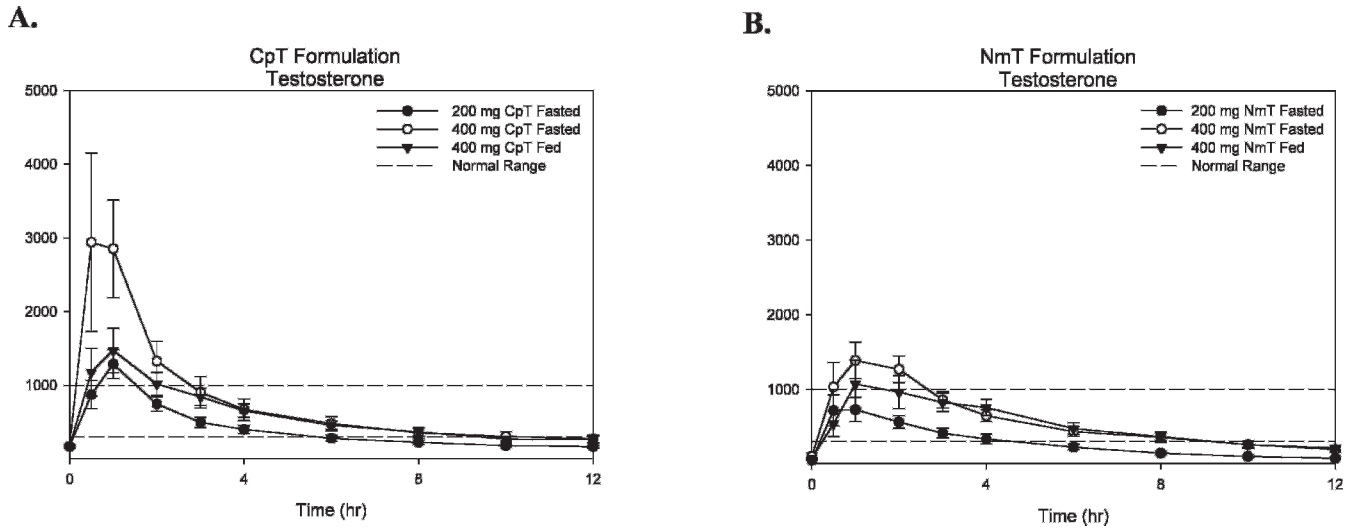


Figure 2. Serum testosterone concentrations after oral administration of testosterone (T) with dutasteride (D) to men with medically induced reversible hypogonadism. Serum T after (A) CpT or (B) NmT. Dotted lines represent the upper and lower limits of the normal range for serum T in men. Data are means ± SEM.

significant solubility constraints, requiring larger volume administration and/or heating to avoid precipitation within a capsule. Here we expand our previous observations and demonstrate that the administration of encapsulated NmT when combined with dutasteride increases serum T to above the lower limit of the normal range for 8–10 hours in healthy volunteers with reversible, medically induced hypogonadism. Oral CpT+D and NmT+D resulted in a similar AUC<sub>0–24</sub> and C<sub>max</sub> at both doses. However, in contrast to NmT+D, the pharmacokinetics of the 400-mg dose of CpT+D were significantly affected by food. Indeed, the higher C<sub>max</sub> associated with CpT+D given while fasting resulted in peak T levels significantly above the upper limit of the normal range (Figure 2). The supraphysiologic serum T levels were approximately 40%–45% lower with NmT+D than with the CpT+D formulation when taken fasting. Although the data are presented

after adjustment for baseline T levels at each point, more extensive, larger studies will be necessary to further characterize the possible effects of concomitant food administration with each formulation.

The time the mean T levels were in the normal range with either formulation at the 400-mg dose suggests that a twice-daily dosing frequency would provide adequate testosterone exposure for men with testosterone deficiency. Given the similarities in the pharmacokinetics of the CpT and NmT formulations and the greater simplicity of dosing T in the smaller volume made possible with nanomilling, the nanomilled preparation appears to be the most practical for further development. There were no apparent toxicities or side effects associated with either form of oral T delivery in this short study. It is possible, however, that changes in lipids, erythrocytosis, or body composition might be observed in a longer trial of these testosterone formu-

Table 2. Testosterone pharmacokinetics after the administration of oral testosterone in oil (CpT) or nanomilled oral testosterone (NmT) to healthy men pretreated with the GnRH agonist Lupron and dutasteride<sup>a</sup>

Dose, mg	State	Testosterone			
		Capmul		Nanomilled	
		AUC <sub>(0–24h)</sub> , ng/h/dL	C <sub>max</sub> , ng/dL	AUC <sub>(0–24h)</sub> , ng/h/dL	C <sub>max</sub> , ng/dL
200	Fasted	2740 (50.4)	1212 (47.8)	2501 (63.7)	705 <sup>b</sup> (76.1)
400	Fasted	5281 <sup>b</sup> (143.2)	2267 <sup>b</sup> (119.3)	6202 <sup>c</sup> (59.1)	1522 <sup>c</sup> (66.8)
400	Fed	4745 (65.8)	1202 <sup>d</sup> (86.7)	5365 (61.9)	1098 (79.9)

Abbreviations: C<sub>max</sub> indicates maximum concentration after dosing; AUC, area under the curve.

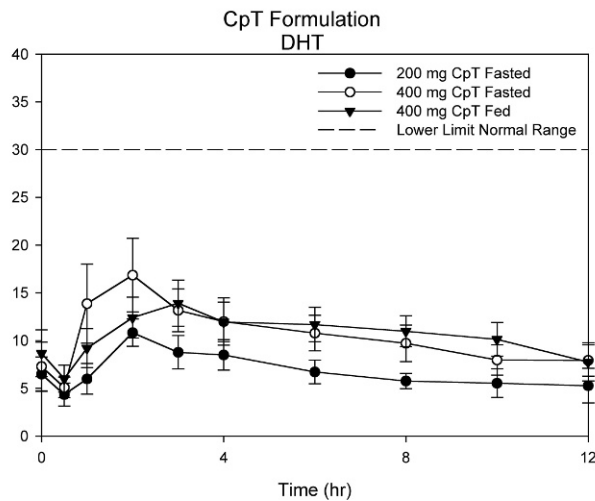
<sup>a</sup> All data are geometric means, with coefficients of variation in parentheses.

<sup>b</sup> P < .05 vs 200 mg CpT.

<sup>c</sup> P < .05 vs 200 mg NmT.

<sup>d</sup> P < .05 vs 400 mg CpT fasted after correction for baseline values.

A.



B.

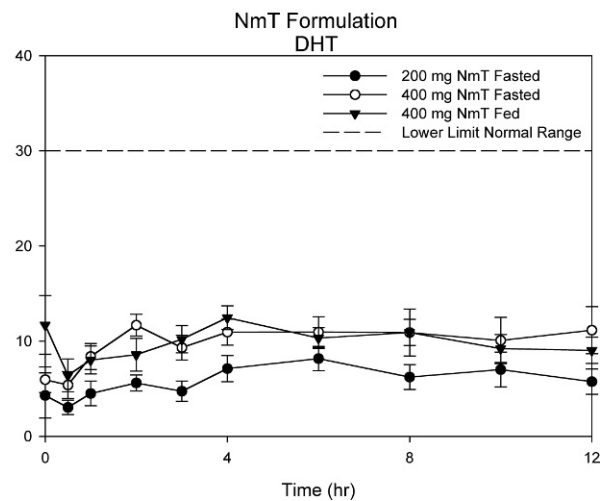


Figure 3. Serum DHT concentrations after oral administration of T with D to men with medically induced reversible hypogonadism. Serum DHT after (A) CpT or (B) NmT. Dotted line represents the lower limit of the normal range for serum DHT in men. Data are means  $\pm$  SEM.

lations, since such changes have been associated with other forms of androgen delivery (Srinivas-Shankar and Wu, 2006). Moreover, it is possible the twice-daily administration could exacerbate such effects, given the potential for swings in testosterone levels throughout the day with such a dosing schedule. These evaluations will be the subject of future, longer-term studies. As expected with the  $5\alpha$ -reductase inhibition by D, serum DHT levels were suppressed well below the normal range throughout the study.

In addition to providing an alternative route of administration for T therapy, it is possible that the combination of oral T+D could have advantages over T treatment alone. Previous work suggests that the combination of T plus a  $5\alpha$ -reductase inhibitor provides the anabolic benefits of T therapy without stimulating prostate growth in older men (Amory et al, 2004; Page et al, 2005). In addition, recent results suggest that  $5\alpha$ -reductase inhibitors may reduce the risk of prostate

cancer, presumably by lowering DHT concentrations (Thompson et al, 2003). In theory, the ability to selectively increase serum T without increasing serum, and perhaps tissue, DHT could minimize the risk of some androgen-dependent diseases, such as benign prostatic hypertrophy and androgenic alopecia, a hypothesis only addressable with long-term studies.

In the current study, we have demonstrated that oral testosterone, either nanomilled or in Capmul, when combined with dutasteride results in normalization of serum T levels in healthy men with medically induced, reversible hypogonadism. This work demonstrates the feasibility of an effective, twice-daily oral testosterone dosing regimen for the treatment of male hypogonadism. The combination of oral testosterone plus dutasteride is an exciting prospect for future investigations. Longer-term studies to determine the safety and efficacy of this approach to androgen replacement therapy are warranted.

Table 3. Dihydrotestosterone pharmacokinetics after the administration of oral testosterone in oil (CpT) or nanomilled oral testosterone (NmT) to healthy men pretreated with the GnRH agonist Lupron and dutasteride<sup>a</sup>

Dose, mg	State	Dihydrotestosterone			
		Capmul		Nanomilled	
		AUC <sub>(0-24h)</sub> , ng/h/dL	C <sub>max</sub> , ng/dL	AUC <sub>(0-24h)</sub> , ng/h/dL	C <sub>max</sub> , ng/dL
200	Fasted	118 (93.4)	13 (55.8)	110 (103.8)	11 (59.3)
400	Fasted	177 <sup>b</sup> (97.4)	17 <sup>b</sup> (69.2)	212 <sup>c</sup> (75.3)	16 <sup>c</sup> (53.4)
400	Fed	184 (67.9)	16 (44.8)	193 (60.9)	15 (48.2)

Abbreviations: C<sub>max</sub> indicates maximum concentration after dosing; AUC, area under the curve.

<sup>a</sup> All data are geometric means, with coefficients of variation in parentheses.

<sup>b</sup>  $P < .05$  vs 200 mg CpT.

<sup>c</sup>  $P < .05$  vs 200 mg NmT.

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