Journal of Andrology, Vol. 27, No. 1, January/February 2006

Oral Testosterone in Oil: Pharmacokinetic Effects of 5α Reduction by Finasteride or Dutasteride and Food Intake in Men

JOHN K. AMORY, STEPHANIE T. PAGE, AND WILLIAM J. BREMNER

From the Center for Research in Reproduction and Contraception, Divisions of General Internal Medicine and Endocrinology, Metabolism and Nutrition, Department of Medicine, University of Washington Medical School, Seattle, Washington.

ABSTRACT: Oral administration of 400 mg of testosterone (T) in oil, when combined with the 5α reductase inhibitor dutasteride (D), elevates serum T in medically castrated men to the normal range. In this study, we sought to determine the impact of 1) finasteride (F) and 2) food intake on the serum T and dihydrotestosterone (DHT) levels observed after the oral administration of T in oil. Therefore, we conducted a pharmacokinetic study of oral T in oil, alone or with D or F, in the fasting and fed states in normal men whose endogenous T production was suppressed by the GnRH antagonist acyline. After acyline administration, 7 healthy men (mean age 31 ± 8 years) were sequentially administered five 400-mg doses of oral T in sesame oil once daily. The first dose of oral T (T-alone) in oil was given while fasting without F or D. The second (fasting) and third (fed) doses were administered after pretreatment with F (T + F). Four days later, the fourth (fasting) and fifth (fed) doses were administered after pretreatment with D (T + D). Blood samples for measurement of serum T and DHT were obtained before T dosing and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after each administration. In the fasting state, 24-hour area-under-the-curve of serum T after oral T administration was significantly greater with coadministration of either D or F compared with T-alone (126 ± 36 nmol-h/L [T-alone] vs 287 ± 98 nmol-h/L [T + F] vs 236 ± 82 nmol-h/L [T + D]; $P < .05$ for T + F and T + D vs T-alone). Administration of the T with food nonsignificantly decreased serum T levels compared with fasting administration. The administration of oral T in oil combined with either F or D results in serum T levels adequate to treat men with testicular failure. Additional studies of the combination of oral T in oil with 5α-reductase inhibitors as a novel form of oral T therapy are warranted.

Key words: Androgen, hypogonadism, metabolism, acyline.
J Androl 2006;27:72–78

Testosterone (T) is necessary for optimal male health; however, around 6%–12% of men have symptoms of androgen deficiency and T levels below the normal range (Araujo et al, 2004). Men with T deficiency can have symptoms of depression, reduced libido and low energy, and may suffer from anemia, osteoporosis and muscle weakness. These men often benefit from T replacement therapy, which has been shown to improve well-being, maintain bone and muscle mass, and improve sexual function (Behre et al, 1997; Katznelson et al, 1996; Wang et al, 1996; Snyder et al, 2000).

There is currently no safe (ie, nonalkylated) form of oral androgen therapy approved for use in the United States. Testosterone undecanoate (TU) is a long-chain testosterone ester that is used clinically in many countries for the treatment of T deficiency and is administered orally in oil. TU has been shown to be absorbed via intestinal lymphatics, bypassing the liver and reaching the systemic circulation via the thoracic duct (Coert et al, 1975; Horst et al, 1976; Shackleford et al, 2003). When dosed 3 times daily, oral TU therapy results in therapeutic increases in serum T; however, it also results in elevations in serum dihydrotestosterone (DHT) that greatly exceed the normal range (Fanchi et al, 1978; Skakkebaek et al, 1981; Gooren 1994; Houwing et al, 2003). Because of the marked increases in serum DHT seen with oral TU, concern exists about the potential for harm to the prostate associated with long-term oral TU therapy, although no increase in prostate disease has been reported to date despite long-term use of oral TU (Gooren, 1994).

Oral administration of unmodified T in a crystalline

Supported by the National Institute of Child Health and Human Development, a division of the National Institute of Health through cooperative agreements U54-HD-12629 and U54 HD42454 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 National Institute of Child Health and Human Development, a division of the National Institute of Health by grant 1K23 HD45386-10A1. A portion of this work was conducted through the Clinical Research Center facility at the University of Washington and supported by NIH grant M01-RR-00037.

Correspondence to: Dr John K. Amory, University of Washington, Box 356429, 1959 NE Pacific St, Seattle, WA 98195 (e-mail: jamory@u.washington.edu).

Received for publication March 17, 2005; accepted for publication August 2, 2005.

DOI: 10.2164/jandrol.05058

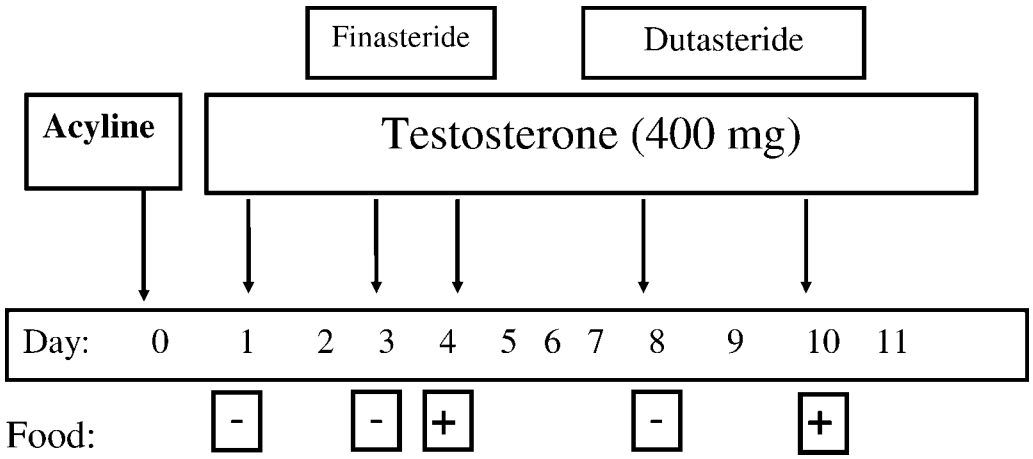

Figure 1. Study design.

form does not result in elevations in serum T levels due to extensive hepatic first-pass metabolism (Foss 1939; Johnsen et al, 1974; Nieschlag et al, 1975; Daggett et al, 1978). However, we have recently reported that, when unmodified testosterone is administered orally in sesame oil, serum T levels within the normal range can be achieved in medically castrated normal men. Furthermore, when the oral T in oil is combined with the 5α reductase inhibitor dutasteride, the resulting serum T levels are roughly doubled, and serum T remains within the normal range for 12 hours (Amory and Bremner, 2005).

As is the case with oral TU, serum DHT levels seen after oral administration of T in sesame oil are markedly elevated. The combination of oral T in oil and dutasteride, however, maintains serum DHT levels within the normal range (Amory and Bremner, 2005). In this work, we sought to determine if finasteride, like dutasteride, would also augment the serum T levels seen after the administration of oral T in oil.

A second issue relating to oral T therapy is the role of food in absorption of an oral dose of T. The absorption of oral TU is dramatically enhanced by concomitant fat intake due to its marked lipophilicity (Frey et al, 1979; Bagchus et al, 2003). Therefore, to determine the impact of food intake and finasteride on the absorption of oral T, we conducted a pharmacokinetic study of oral T in oil. We administered T in oil alone in the fasting state, and with concomitant D or F in the fasting and fed states in normal men whose endogenous T production had been temporarily suppressed by the GnRH antagonist acyline.

Materials and Methods

Subjects

Seven healthy, normal male volunteers between 18 and 45 years of age were recruited through local news media (newspaper and radio) and college campus bulletin boards and enrolled in the study. The inclusion criteria were: no prior medical illnesses; normal physical examination; routine hematology, blood chemistry, and liver function. Exclusion criteria included regular use of any medication, abnormal serum T or DHT, or previous or current ethanol, illicit drug or anabolic steroid abuse. Eight men were evaluated for eligibility. Of these, 7 men agreed to participate in the study. The institutional review board of the University of Washington approved all study procedures, and subjects gave written informed consent before screening.

Study Drug

The oral T in sesame oil was prepared by the compounding pharmacy at the University of Washington. Micronized T (U.S.P. grade, Spectrum Quality Projects, Gardena, Calif) was added at 100 mg/mL to sesame oil (N.F. grade, Spectrum Quality Projects) and mixed thoroughly on a magnetic stir plate to create a homogenous T/sesame oil emulsion. The compounding pharmacist then drew up 4 cm^3 (400 mg) of the emulsion into syringes immediately before dosing. The syringe was then sent to the Clinical Research Unit, where it was administered to the subject.

Study Design

The study design is summarized in Figure 1. The drug-exposure period lasted 11 days. On day 0, subjects received a single injection of the GnRH antagonist acyline (300 μg/kg SQ), which has been shown to suppress T production in normal men for a minimum of 15 days (Herbst et al, 2004). Blood was drawn before 0800 hours for serum T and DHT daily during the drug-exposure period. In addition, 1, 3, 4, 8, and 10 days after acyline administration, subjects drank 400 mg of T in oil. On days 1, 3, 4, 8, and 10, subjects had blood drawn via a heparin-locked IV line at baseline, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after administration of oral T in oil for measurement of serum T and DHT. On days 1, 3, and 8, subjects ingested the T while fasting and did not eat any food until 90 minutes after dosing. On days 4 and 10, subjects ingested the T with a meal of at least 750 kcal, which included at least 250 kcal (approximately 30 g of fat). Subjects self-administered the finasteride or dutasteride. On day 2, subjects took 5 mg of finasteride twice (morning and

evening) and then took 5 mg daily for day 3 and day 4 (total dose, 20 mg). On day 7, subjects took 0.5 mg dutasteride twice (morning and evening) and then took 0.5 mg daily on days 8–10 (total dose, 2.5 mg). We were unable to study the pharmacokinetics of oral testosterone with food but without concomitant 5α reductase inhibition as the amount of blood drawn from subjects on a sixth day of draws would have exceeded the maximum allowable for the 2-week study period. For safety, subjects underwent daily testing of liver function (aspartate aminotransferase, bilirubin, alkaline phosphatase), kidney function (urea nitrogen, creatinine), and hematopoiesis (hemoglobin and hematocrit). Four weeks after the completion of the drug-exposure period, subjects were examined and underwent a blood draw for serum hormones to ensure they had returned to normal. A sample size of 7 subjects was estimated to have an 80% power with an α of .05 to detect a 30% change in serum testosterone area under the curve between T and T + D or T + F.

Measurements

Serum total T was measured by a radioimmunoassay (Diagnostic Products Corporation, Webster, Tex) The assay had a sensitivity of 0.35 nmol/L and interassay variations for low, mid, and high pools of 13.6%, 6.1%, 6.8%, and intra-assay variation of 10.0%, 5.3%, 6.6%. The normal range was 8.7–33 nmol/L. DHT was measured using an radioimmunoassay (Diagnostic Systems Laboratory, Los Angeles, Calif). The sensitivity of this assay was 0.043 nmol/L and the intra-assay variation for mid- and low-range pools was 9.9% and 11%, with interassay coefficients of variations of 19% and 25%. The normal range for serum DHT was 1.0–3.1 nmol/L. The normal ranges for T and DHT were determined in our laboratory using serum samples obtained from 100 normal men aged 20–50 years.

Statistics

Average concentration during the 24-hour period after dosing, maximum concentration after dosing (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), and elimination phase half-life ($T_{1/2}$) were calculated for each subject using a computer program (PK solutions, Golden, Co). Pharmacokinetic parameters and serum hormone levels at each time point for each of the 3 fasting days of T administration, and for the comparison of fasting vs fed days, were compared using the Wilcoxon sign rank test with a Bonferroni correction for multiple comparisons (effective α, .017). Statistical analyses were performed using STATA (College Park, Tex). For all comparisons, an α of .05 was considered significant.

Results

Subjects

Seven men were enrolled in the study; their baseline characteristics are listed in Table 1. All subjects completed all blood draws during the 2-week drug-exposure period. There were no significant adverse effects during the study. Six of the subjects experienced transient mild pruritis at the site of the acyline injection, which resolved in all cases within 1 hour of the injection. One subject complained of mild, transient hot-flash symptoms toward the end of the study period, presumably due to low T levels; however, no subject complained of feelings of aggression or irritability during treatment. There were no adverse gastrointestinal symptoms associated with the oral T in oil. There were no changes seen in serum markers of liver or kidney function or in hematocrit, platelets, or white blood cell count during the treatment phase or at follow-up. Furthermore, no significant changes in blood pressure or pulse were observed. Testosterone and gonadotropin levels returned to baseline in all subjects during the follow-up period (data not shown). No subjects were lost to follow-up.

Table 1. *Baseline characteristics of study subjects (N = 7; means ± SD)**

Age (y)	30.8 ± 8.5
Weight (kg)	95 ± 15
Height (cm)	185 ± 9
BMI (kg/m^2)	27.8 ± 4.2
Total testosterone (nmol/L)	15.8 ± 6.7
Dihydrotestosterone (nmol/L)	1.37 ± 0.87

* BMI indicates body mass index.

Serum Testosterone

In all subjects, serum T levels were suppressed to castrate levels by 24 hours after acyline administration (day zero: T 15.8 ± 6.8 nmol/L vs 1.6 ± 0.9 nmol/L [day 1]; $P < .0001$). In addition, mean serum T levels before each dose of T (ie, 24 hours after the previous dose) were not significantly different from those seen 24 hours after acyline administration in all cases.

In the fasting state, the combination of oral T in oil and either D or F increased the resulting serum T concentrations compared with T in oil alone (Figure 2A). This difference achieved statistical significance 1 and 6 hours after dosing on the day subjects received T + F and 6 hours after dosing on the day subjects received T + D. There were no significant differences between the elevations in serum T levels seen after oral dosing of T in oil between the T + F and T + D treatment days ($P > .05$ for all comparisons). The area under the curve of serum T increased significantly with either F or D compared with T in oil alone ($P < .05$ for both comparisons; Table 2). The maximum concentration of serum T after oral dosing of T in oil with T + F was significantly greater than the maximum with T-alone (50 ± 28 nmol/L [T + F] vs 19.7 ± 9.1 [T-alone]; $P = .02$) with the maximum concentration of T exceeding the normal range in 5 of 7 subjects with T + F. Time of maximum concentration of serum T after oral dosing of T in oil was nonsignificantly earlier on the T + F and T + D days compared with T-alone. Last, the calculated terminal half-life of serum T

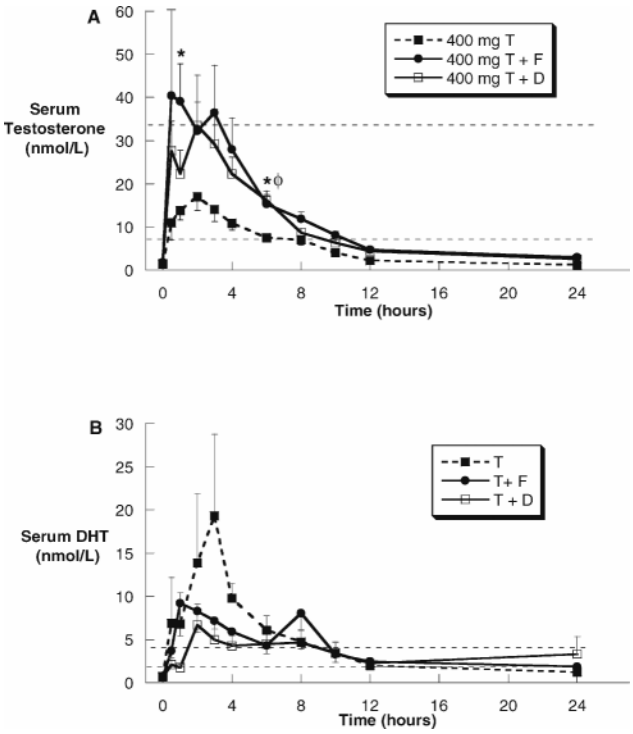

Figure 2. Serum testosterone **(A)** and DHT **(B)** concentrations (means ± SEM) after oral administration of 400 mg of testosterone in oil alone or with finasteride (F) or dutasteride (D) to fasting normal men treated with a GnRH antagonist. The dotted lines represent the upper and lower limits of the normal range for serum T and DHT. * $P < .05$ compared with T alone (T + F); ϕ $P < .05$ compared with T-alone (T + D).

after dosing was between 6 and 10 hours regardless of treatment.

Serum DHT levels

Serum DHT decreased significantly 24 hours after acyline administration (day 0 DHT: 1.6 ± 0.6 nmol/L vs 0.6 ± 0.2 nmol/L [day 1]; $P < .05$). In addition, mean serum DHT levels before each dose of T (ie, 24 hours after the previous dose) were not significantly different from those seen 24 hours after acyline administration.

In the fasting state, the combination of oral T in oil and either D or F nonsignificantly decreased the resulting serum DHT concentrations compared with T in oil alone (Figure 2B). Moreover, there were no significant differences between the levels of serum DHT levels seen after oral dosing of T in oil with either F or D ($P > .05$ for all comparisons). The AUC of serum DHT decreased nonsignificantly compared with oral T in oil when combined with either F or D compared with T in oil alone ($P > .05$ for both comparisons; Table 3). There was a trend toward a decrease in the maximum concentration of serum DHT with T + D compared with the T-alone (8.7 ± 5.5 nmol/L [T + D] vs 15.7 ± 7.6 [T-alone]; $P = .06$). Time of maximum concentration of serum DHT and calculated terminal half-life of serum DHT after dosing was similar with all treatments.

Effect of Food Intake

Mean serum T was significantly decreased at 1 hour in the T + F fed vs T + F fasting group (Figure 3A). In addition, mean serum T at every other time point with either T + F or T + D was decreased in a nonsignificant fashion when oral T in oil was administered with food compared with administration while subjects were fasting (Figure 3A and B). There was a trend toward decreases in maximum concentration of T with feeding for both T + F and T + D, and a trend toward an increase in the time to maximum concentration of T when the T was administered with food (Table 2).

The AUC of serum DHT was significantly reduced with T + D with food compared with T-alone (Table 3). Compared with T-alone, significant reductions in maximum concentration of serum DHT were seen with T + F and T + D and food. There was no appreciable effect of concomitant food intake on time to maximum concentration of serum DHT or DHT half-life.

Discussion

In this work, we have shown that acute administration of the 5α reductase inhibitor finasteride is as effective at

Table 2. *Testosterone pharmacokinetics after the administration of 400 mg of oral testosterone in oil to normal men pretreated with the GnRH antagonist acyline**

	Food Status	C_{max} (nmol/L)	T_{max} (h)	AUC (nmol-h./L)	$T_{½}$ (h)
Testosterone alone	Fasting	19.7 ± 9.1	2.4 ± 2.5	126 ± 36	6.8 ± 0.6
Testosterone + finasteride	Fasting	50.4 ± 28†	1.2 ± 0.9	287 ± 98†	7.7 ± 3.4
Testosterone + finasteride	With food	30 ± 9.7†,‡	3.0 ± 2.1‡	202 ± 72†,§	8.2 ± 2.7
Testosterone + dutasteride	Fasting	43 ± 29	1.3 ± 1.0	236 ± 82†	7.0 ± 3.3
Testosterone + dutasteride	With food	27 ± 13‡	2.4 ± 1.1§	221 ± 108†	9.8 ± 6.3

* All data are means ± SD. C_{max} indicates maximum concentration after dosing; T_{max}, time of maximum concentration; AUC, area under the curve; and $T_{½}$, terminal half-life.

† $P < .05$ compared with testosterone alone.

‡ $P < .1$ compared with fasting.

§ $P < .05$ compared with fasting.

Table 3. *DHT pharmacokinetics after the administration 400 mg of oral testosterone in oil to normal men pretreated with the GnRH antagonist acyline**

	Food Status	C_{max} (nmol/L)	T_{max} (h)	AUC (nmol-h/L)	$T_{½}$ (h)
Testosterone alone	Fasting	15.7 ± 7.6	2.7 ± 1.1	84 ± 35	7.3 ± 1.1
Testosterone + finasteride	Fasting	15.8 ± 11.1	3.1 ± 2.7	70 ± 50	6.7 ± 2.0
Testosterone + finasteride	With food	7.9 ± 3.3†,‡	3.4 ± 2.0	63 ± 32	7.1 ± 1.1
Testosterone + dutasteride	Fasting	8.7 ± 5.5	4.2 ± 3.1	67 ± 51	8.9 ± 3.1
Testosterone + dutasteride	With food	5.4 ± 3.9†	3.3 ± 2.1	41 ± 23†	10.8 ± 3.9

* All data are means ± SD. C_{max} indicates maximum concentration after dosing; T_{max}, time of maximum concentration; AUC, area under the curve; and $T_{½}$, terminal half-life.
† $P < .05$ compared with testosterone alone.
‡ $P < .05$ compared with fasting.

increasing serum T levels after the administration of an oral dose of T in oil as dutasteride. As in our prior work with oral T in oil, combining the oral T with a 5α reductase inhibitor roughly doubles the resulting serum concentrations of T. Therefore, one can infer that approximately ½ of a dose of oral testosterone is 5α reduced in vivo to DHT. This conversion could occur in either the intestinal lining or the liver, which have both been shown to express 5α reductase (Thigpen et al, 1993). Whether dutasteride, which inhibits both type 1 and 2 5α reductase (Rittmaster, 1997) and results in greater suppression of serum DHT than finasteride (Clark et al, 2004), may be more effective with long-term administration or oral T in oil remains to be determined.

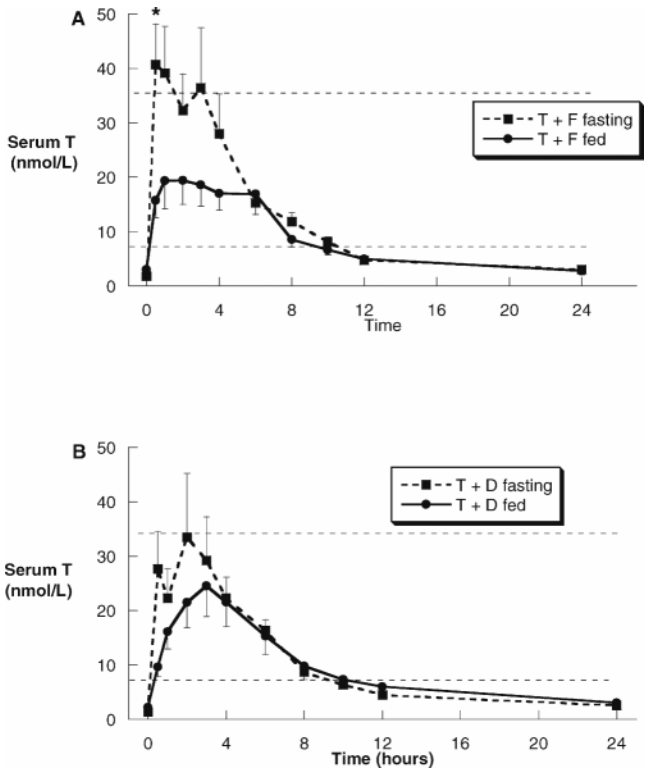

Figure 3. Serum testosterone concentrations (means ± SEM) after oral administration of 400 mg of testosterone in oil with finasteride **(A)** or dutasteride **(B)** in the fasting or fed state to normal men treated with a GnRH antagonist. The dotted lines represent the upper and lower limits of the normal range for serum T. * $P < .05$ compared with T alone.

The bioavailability of orally administered T has been previously reported to be around 3.5%, due to extensive hepatic metabolism, whereas the bioavailability of oral TU is approximately 6.8% (Tauber et al, 1986). The superior bioavailability of oral TU is likely due to the fact that around 80% of an oral dose of TU is absorbed via the lymphatics (Shackleford et al, 2003), a process that is markedly enhanced by the simultaneous intake of fatty foods (Frey et al, 1979; Bagchus et al, 2003). If oral administration of unesterified T in oil were similarly absorbed via the lymphatics, one might expect food intake to also improve T absorption; however, in our study, the opposite occurred. We observed decreases in maximum concentration of serum T, AUC of T, and a delay to maximum concentration when the oral T in oil was given with food as compared with fasting administration. Because the F and D were dosed before the oral T and food, there is little chance that the food decreased the effect of the F or D. Therefore, it is tempting to speculate that, in contrast with oral TU, oral T in oil is not completely absorbed via the lymphatics. Exactly how oral T in oil is absorbed will require additional study.

Comparison of the results obtained in this study with our original study of oral T in oil (Amory and Bremner, 2005) demonstrates slightly lower serum T values and a shorter duration of serum T in the normal range after dosing a 400-mg dose or oral T in oil by about 25%. While this could represent chance or regression to the mean, another possible explanation for these differences is that, in this study, the period of 5α reductase pretreatment for all but 1 of the treatment days was only 24–48 hours as compared with 72–120 hours of dutasteride pretreatment in the original study. Indeed, the greatest reductions in serum DHT levels were seen on treatment day 10, the only study day in which a 72-hour period of dutasteride pretreatment was employed. This finding emphasizes the importance of adequate 5α reduction in attaining therapeutic levels of serum T (without supraphysiologic elevations of serum DHT) after the administration

of oral T in oil and implies that longer-term studies of these combinations will be required to more accurately determine the full impact of 5α reduction on the augmentation of serum T levels after oral administration.

Direct comparison between finasteride and dutasteride in this study is not possible for several reasons. First, although the half-life of finasteride is only 12 hours, and there was a 96-hour interval between the last dose of finasteride on day 4, and the dose of oral testosterone on study day 8, there may have been residual 5α reductase inhibition from the finasteride during the second week of the study. This is possible as the biological activity of finasteride (as assessed by significant DHT suppression) may be seen for up to 5–7 days after doses of 10–40 mg (Vermuelen et al, 1989). Moreover, because of the long half-life of dutasteride and its relative potency for type 2 vs the type 1 enzyme (Clark et al, 2004), it is likely, at the dose and duration of dutasteride used in this study, that the dutasteride was mainly inhibiting the type 2 enzyme. If the type 1 5α reductase significantly contributes to the metabolism of oral testosterone, dutasteride may prove to be a superior drug to finasteride with long-term administration. Testing this hypothesis will require comparison of the 2 drugs over longer periods of time.

Importantly, there was no evidence of either liver or kidney toxicity associated with the doses of oral T administered in this study; however, longer term study of these doses of T combined with a 5α reductase inhibitor will be required to determine the safety of this approach to T therapy. In theory, the ability to selectively increase serum T without increasing serum DHT may be attractive in minimizing the risk for DHT-dependent disease, such as prostate hypertrophy, acne, and alopecia associated with T therapy.

In conclusion, we have demonstrated that single doses of T administered orally in oil combined with either finasteride or dutasteride can result in elevated serum levels of T in normal men with experimentally induced hypogonadism. Such serum T levels would presumably be therapeutically effective in treating testicular failure. In addition, we have demonstrated that, in contrast with oral TU, concomitant food intake tends to decrease the serum T levels observed after administration of oral T in oil. Combinations of oral T in oil and 5α reductase inhibitors may allow for an oral, selective form of androgen therapy. Additional studies of the long-term safety, pharmacokinetics, and pharmacodynamics of these combinations are warranted to determine if they will be a clinically useful alternative method to treat T deficiency.

Acknowledgments

The authors would like to acknowledge Ms Amanda Wiseman for assistance with study implementation, Mr Richard Hoffman for the preparation of the testosterone suspension, and Ms Dorothy McGuinness for performing the hormone assays.

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