0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(5):2610–2617

doi: 10.1210/jc.2004-1221

Oral Testosterone in Oil Plus Dutasteride in Men: A Pharmacokinetic Study

John K. Amory and William J. Bremner

Center for Research in Reproduction and Contraception, Divisions of General Internal Medicine and Endocrinology, Metabolism, and Nutrition, University of Washington Medical School, Seattle, Washington 98195

Testosterone (T) is not administered orally, because it has been reported to be rapidly metabolized by the liver. We hypothesized that sufficient doses of T or T enanthate (TE), administered orally in oil, would result in clinically useful elevations in serum T. We also hypothesized that coadministration of dutasteride (D) with T or TE would minimize increases in serum DHT seen previously with oral administration. Therefore, we conducted a pharmacokinetic study of oral T and TE in oil, with and without concomitant D, in normal men whose T production had been temporarily suppressed by the GnRH antagonist acyline. Thirteen healthy men (mean age, 24 ± 6 yr) were enrolled and assigned to oral T (n = 7) and oral TE (n = 6) groups and were administered 200, 400, or 800 mg of either T or TE in sesame oil in the morning on 3 successive days 24 h after receiving acyline. Blood samples for measurement of serum T and dihydrotestosterone were obtained before T or TE administration and 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 h after administration. Subjects were then administered D for 4 d before repeating the sequence of T or TE doses with D. Serum T was significantly increased in a dose-dependent fashion with the administration of oral T or TE in oil. Coadministration of D with oral T or TE significantly increased the 24-hr average serum T levels compared with administration of T or TE alone [average serum T after 400 mg dose, 8.7 ± 3.0 nmol/l (T) and 8.3 ± 5.7 nmol/l (TE) *vs.* 16.1 ± 5.8 nmol/l (T +D) and 15.0 ± 8.8 nmol/l (TE + D); $P < 0.05$ for T *vs.* T and D]. The administration of oral T or TE in oil combined with D results in unexpected and potentially therapeutic increases in serum T. Additional studies of this combination as a novel form of oral androgen therapy are warranted. (*J Clin Endocrinol Metab* 90: 2610–2617, 2005)

TESTOSTERONE (T) IS crucial for male health. The normal male testes produce 4–8 mg T daily (1, 2). Depending on age, 2.5–10% of men have T levels below the normal range (3). T has effects on a variety of tissues, including brain, liver, muscle, bone and bone marrow, blood vessels, skin, prostate, and penis. Men with T deficiency have symptoms of depression, reduced libido, and low energy and suffer from anemia, osteoporosis, and debilitating muscle weakness. These men require T replacement therapy to improve well-being, maintain bone and muscle mass, and retain healthy sexual function (4–8), yet there is no acceptable form of oral T for therapy in the United States.

Most T regimens in the United States depend on parenteral injections, skin patches, gels, or buccal tablets (9–11), because currently available oral forms of T are aklylated and cause liver toxicity when used long term (11–16). Injections are administered im every 1–3 wk and can be painful (17). Some T patches can cause moderate to severe skin reactions due to the vehicle that facilitates T absorption across the skin (18). The T gels are effective and generally well accepted by patients, but are expensive, and care must be taken to avoid inadvertent exposure to women and children (19).

Oral administration of unmodified T at doses up to 100 mg have little effect on serum T levels in T-deficient men (20, 21); however, 200-mg doses of oral T have been shown to elevate serum T levels to the low normal range for up to 8 h (22, 23). At the time, these serum T levels were thought to be insufficient for clinical use, and research into using unmodified oral T was largely abandoned.

Testosterone undecanoate (TU) is a T ester currently given orally in oil and used clinically in Europe and Canada for the treatment of T deficiency. When administered orally, TU therapy results in therapeutic increases in serum T; however, it also results in elevations in serum dihydrotestosterone (DHT) well above the normal range (24–27). Because DHT is required for cell growth within the prostate, concern has been raised about the potential for long-term harm associated with oral TU therapy from the elevated levels of serum DHT; however, no increased risk of prostate disease has been reported to date.

Because the androgen TU is absorbed well in oil, we believed that other androgens such as T enanthate (TE) and potentially T itself might be well absorbed if also administered orally in oil. Moreover, because the recently available 5α-reductase inhibitor, dutasteride (D), lowers serum DHT levels more than 90% by inhibiting both isozymes of 5α-reductase (28), we hypothesized that oral administration of the combination of higher doses of unmodified T or the T ester, TE, in oil when combined with D would be safe and result in therapeutic serum T levels. In addition, we hypothesized that the concomitant administration of the 5α-reductase inhibitor D with T or TE would further increase serum T levels while minimizing the elevations in serum DHT seen after oral administration of oral androgens such as TU. If effective, we believed that this novel means of T therapy would allow for selective androgen therapy in men with T

First Published Online February 15, 2005

Abbreviations: D, Dutasteride; DHT, dihydrotestosterone; E2, estradiol; T, testosterone; $t_{1/2}$, half-life; TE, testosterone enanthate; TU, testosterone undecanoate.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

deficiency. Therefore, we conducted a pilot study of the oral administration of single doses of T and TE with and without concomitant administration of D to determine the pharmacokinetics and safety of single high doses oral T in oil in healthy men rendered temporarily hypogonadal with the GnRH antagonist acyline.

Materials and Methods

Subjects

Fourteen healthy, normal male volunteers between 18 and 45 yr 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, and routine hematology, blood chemistry, and liver function. Exclusion criteria included regular use of any medication; abnormal serum T, DHT, or estradiol (E2); or previous or current ethanol, illicit drug, or anabolic steroid abuse. A total of 16 men were evaluated for eligibility. Of these, 14 men were potentially eligible and agreed to participate in the study. The two men who did not enroll in the study were excluded for elevated bilirubin (one subject) and use of finasteride (for the treatment of male-pattern baldness). One enrolled subject failed to appear for his acyline injection and was therefore not studied further; thus, 13 men completed the study period. The institutional review board of University of Washington approved all study procedures, and subjects gave written informed consent before screening.

Study design

Participants were randomly assigned to one of two groups: 1) oral T in sesame oil, or 2) oral TE in sesame oil (Delatestryl, BTG Pharmaceuticals, Iselin, NJ) at a concentration of 200 mg/ml. A sample size of seven subjects per group was estimated to have an 80% power with an α of 0.05 to detect a 50% in the change in serum T area under the curve between a given dose of T and T plus D or between TE and TE plus D. The oral T in sesame oil was manufactured by the compounding pharmacy at University of Washington. Briefly, micronized T (U.S.P. grade, Spectrum Quality Projects, Gardena, CA) was suspended at 100 mg/ml in 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 the emulsion into syringes at the desired dose levels (200, 400, and 800 mg) immediately before treatment. The syringe was sent to the Clinical Research Unit, where it was vigorously mixed (by shaking) with milk and administered to the subject. The dose of oral TE in sesame oil was normalized for the T content, so that the subjects in the TE group (molecular weight, 397) were administered 276, 554, and 1108 mg TE, corresponding to 200, 400, and 800 mg T.

The drug exposure period lasted 11 d (Fig. 1). On d 0, subjects received a single injection of the GnRH antagonist acyline (300 μg/kg, sc), which has been shown to suppress T production in normal men for a minimum of 15 d (29). One, 2, and 3 d after acyline administration, subjects drank 200, 400, or 800 mg T or 276, 554, or 1108 mg TE. Subjects self-administered D (0.5 mg, orally, once daily) on d 5–10 after acyline injection, and doses of T and TE were repeated on days 8, 9, and 10. For safety, subjects underwent daily testing of liver function (aspartate aminotransferase, bilirubin, and alkaline phosphatase), kidney function (urea nitrogen and creatinine), and hemopoiesis (hemoglobin and hematocrit).

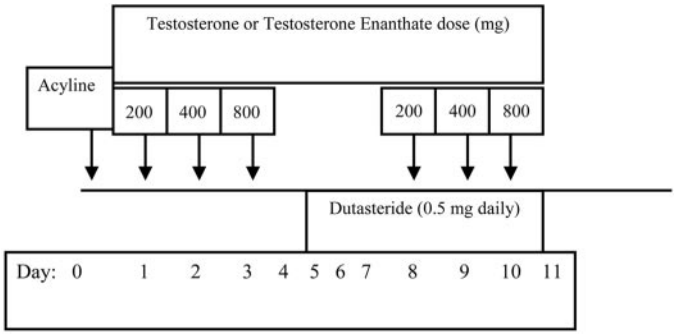

FIG. 1. Study design.

Measurements

After treatment on d 1, 2, 3, 8, 9, and 10, subjects had blood drawn via a heparin-locked iv line at 30 min and 1, 2, 4, 6, 8, 10, 12, and 24 h for measurement of serum T, DHT, E2, and SHBG. Total T was measured by a RIA (Diagnostic Products Corp., Webster, TX) The assay had a sensitivity of 0.35 nmol/liter; interassay variations for low, medium, and high pools of 13.6%, 6.1%, and 6.8%, respectively; and intraassay variations of 10.0%, 5.3%, and 6.6%. The normal range was 8.7–33 nmol/liter. DHT was measured using an RIA kit (Diagnostic Systems Laboratory, Inc., Los Angeles, CA). The sensitivity of this assay was 0.043 nmol/liter, and the intraassay variations for medium and low range pools were 9.9% and 11%, respectively, with interassay coefficients of variations of 19% and 25%. The normal range for serum DHT was 1.0–2.9 nmol/liter. SHBG was measured by RIA (Delphia, Wallac Oy, Turku, Finland). The sensitivity of this assay was 0.2 nmol/liter, and the interassay variations for low, medium, and high pools were 31%, 10.6%, and 6.8%, respectively; the intraassay variations were 3.8%, 1.7%, and 2.2%. The normal range was 3.2–47 nmol/liter. The normal ranges for T, DHT, and SHBG were determined in our laboratory using serum samples obtained from 100 normal men, aged 20–50 yr. Serum E2 was measured in the laboratory of Dr. David Hess (Oregon National Primate Research Center, Portland, OR) with an Elecsys 2010 Platform (Roche, Indianapolis, IN). The sensitivity of this assay was 5.5 pmol/liter, intraassay variations were 3.7%, and 2.8% for medium and high range values, and the interassay coefficient of variation was 4.7%. The normal range for serum E2 in this assay in men was 40–220 pmol/liter.

Statistics

Serum hormone levels at each time point for each dose of T or TE with or without D were compared using a Wilcoxon sign-rank test. Pharmacokinetic parameters between successive doses of T or TE with or without D were compared using a Wilcoxon sign-rank test with a Bonferroni correction for repeated measures (effective $\alpha = 0.01$). The average concentration during the 24-h period after treatment, the maximum concentration after dosing, time to maximum concentration, area under the curve, and elimination phase half-life ($t_{1/2}$) were calculated using a pharmacokinetics program (PK Solutions, Golden, CO). Statistical analyses were performed using STATA (College Park, TX).

Results

Subjects

Fourteen men were enrolled in the study; seven were randomized to the T group, and seven were randomized to the TE group, but one man assigned to the TE group failed to report for his acyline injection. Therefore, seven men completed the T arm, and six completed the TE arm of the study (Table 1). Except for the subject who failed to appear for his acyline injection, all subjects completed the drug exposure

TABLE 1. Baseline characteristics of study subjects by group

	T group (n = 7)	TE group (n = 6)
Age (yr)	24.2 ± 8.7	24.7 ± 6.7
Weight (kg)	77 ± 4.0	89 ± 16
Height (cm)	182 ± 9	186 ± 11
BMI (kg/m^2)	23.3 ± 2.3	25.8 ± 4.2
Total T (nmol/liter)	22.7 ± 8.0	17.0 ± 5.8
DHT (nmol/liter)	1.24 ± 0.46	1.1 ± 0.5
SHBG (nmol/liter)	33.2 ± 9.84	24.0 ± 10.7
Free T (pmol/liter)	435 ± 156	341 ± 92
E2 (pmol/liter)	132 ± 17	121 ± 31

Values are the mean ± SD. BMI, Body mass index (weight in kilograms/[height in meters]^2).

period. There were no serious adverse effects during the study. Nine of the subjects experienced transient mild pruritis at the site of the acyline injection, which resolved in all cases within 1 h of the injection. Eight subjects 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 anger, aggression, or irritability during treatment. There were no adverse gastrointestinal symptoms associated with oral T or oral TE in oil. One subject developed a small area of gynecomastia ($<1 \times 1$ cm) immediately under the nipple during the treatment period, but this resolved during follow-up. There were no changes in serum markers of liver or kidney function or in the hematocrit or hemoglobin during the treatment phase or at follow-up. Furthermore, no significant changes in blood pressure or pulse were observed. T and gonadotropin levels returned to baseline in all subjects during the follow-up period (data not shown). No subjects were lost to follow-up.

Serum T

All subjects were suppressed to castrate levels of T by 24 h after acyline administration (d 0 T, 20.0 ± 7.4; d 1 T, 2.3 ± 0.5 nmol/liter; $P < 0.0001$). There was no difference in serum T levels 24 h after acyline between groups [2.3 ± 0.7 (T) *vs.* 2.3 ± 0.8 (TE); $P = 0.9$]. In addition, mean serum T levels before

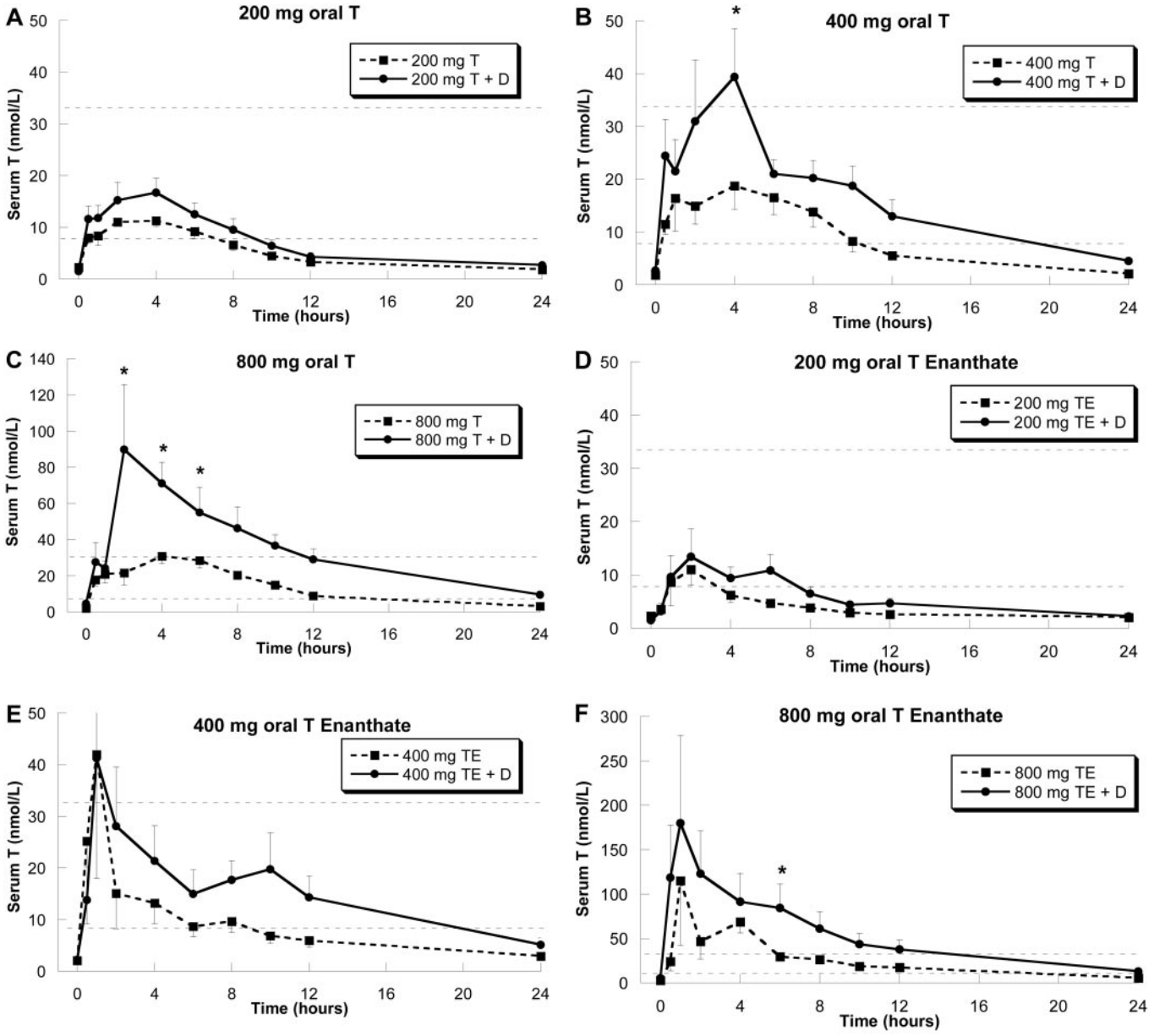

FIG. 2. Serum T concentrations (mean ± SEM) after oral administration of 200, 400, and 800 mg T in oil (A–C) and TE in oil (D–F) with and without D for 24 h in normal men treated with the GnRH antagonist acyline to temporarily suspend T production. Note the larger y-axis for the 800-mg dose. The *dotted lines* represent the upper and lower limits of the normal range for serum T. *, $P < 0.05$ compared with T alone.

TABLE 2. T pharmacokinetics after administration of a single dose of oral T and oral TE in oil with and without D to normal men previously administered a GnRH antagonist

Testosterone (n = 7)	T Only			T + D		
	200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax (nmol/liter)	12.3 ± 4.1	26.1 ± 15.1	40.4 ± 10.1[a]	22.2 ± 8.4[b]	50.3 ± 30.9[a,b]	122.1 ± 82
Tmax (h)	2.8 ± 1.9	3.9 ± 2.6	3.1 ± 2.0	3.1 ± 2.0	3.8 ± 3.1	3.4 ± 1.5
AUC (nmol-h/liter)	124 ± 28	208 ± 74[a]	328 ± 72[a]	176 ± 46[c]	393 ± 140[a,c]	846 ± 363[a,c]
$t_{1/2}$ (h)	10.4 ± 2.9	10.7 ± 6.0	8.1 ± 5.0	9.9 ± 3.8	9.0 ± 2.8	7.8 ± 3.2
TE (n = 6)	TE only			TE + D		
	200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax (nmol/liter)	14.6 ± 8.5	51.8 ± 59	160.8 ± 149	20.2 ± 9.4	74 ± 55[a]	229 ± 228
Tmax (h)	3.2 ± 2.6	4.1 ± 4.0	2.7 ± 1.5	4.1 ± 4.2	4.3 ± 3.8	3.3 ± 2.4
AUC (nmol-h/liter)	90 ± 27	200 ± 140	612 ± 249[d]	141 ± 41	450 ± 196[a]	1327 ± 1021
$t_{1/2}$ (h)	10 ± 2.4	10 ± 3.2	8.4 ± 3.2	9.4 ± 3.2	9.2 ± 2.9	8.4 ± 2.4

Values are the mean ± SD. AUC, Area under the curve; Cmax, maximum concentration after dosing; Tmax, time of maximum concentration.
[a] $P < 0.05$ *vs.* immediately lower dose.
[b] $P < 0.05$ *vs.* T and TE only.
[c] $P < 0.01$ *vs.* T only.

each dose of T were not significantly different from those 24 h after acyline administration.

With the administration of both oral T and oral TE in oil, serum T was significantly increased in a dose-dependent fashion (Fig. 2; $P < 0.01$ for trend). In addition, the maximum concentrations of T, average concentrations of serum T, and area under the curve of serum T increased significantly in a dose-dependent fashion (Table 2 and Fig. 3A), with the maximum concentration of T after oil dosing exceeding the normal range for the 800-mg dose of T and the 400- and 800-mg doses of oral TE in oil. The time of maximum concentration was between 2.5 and 4.5 h in all cases, and the calculated terminal $t_{1/2}$ of oral T and TE in oil was between 7.5 and 11 h.

Coadministration of D with oral T or TE in oil significantly increased the resulting serum T levels compared with administration of T or TE alone (Fig. 2; $P < 0.01$ for trend). The maximum concentration of T after oral treatment with the combination of T or TE and D exceeded the normal range for both the 400- and 800-mg doses of T and TE in oil. Similar to the administration of T or TE only, the time to maximum concentration remained between 2.5 and 4.5 h, and the calculated terminal $t_{1/2}$ was between 8 and 10 h. The T area under the curve for the combination of T and D was significantly increased at all doses compared with that for T alone [200 mg, 124 ± 28 nmol-h/liter (T alone) *vs.* 176 ± 45 nmol-h/liter (T + D); 400 mg, 208 ± 74 nmol-h/liter (T alone) *vs.* 393 nmol-h/liter (T plus D); 800 mg, 328 ± 82 nmol-h/liter (T alone) *vs.* 846 ± 363 nmol-h/liter (T plus D); $P < 0.01$ for all comparisons].

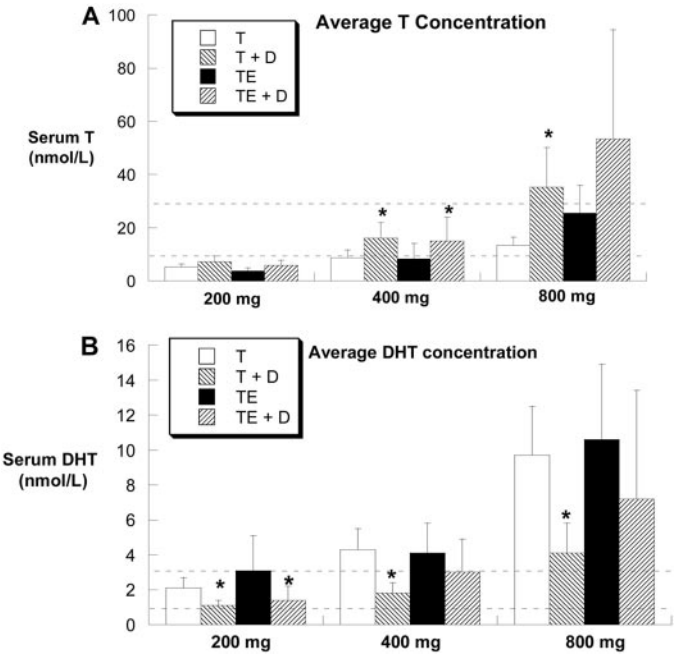

FIG. 3. Average serum T (A) and DHT (B) concentrations (mean ± SD) over the 24-h interval after oral treatment. The *dotted lines* represent the upper and lower limits of the normal range for serum T. *, $P < 0.05$ compared with T alone.

Serum DHT levels

Serum DHT decreased significantly 24 h after acyline administration (d 0 DHT, 1.6 ± 0.6 nmol/liter; d 1 DHT, 0.6 ± 0.2 nmol/liter; $P < 0.05$). There was no difference in serum DHT levels 24 h after acyline administration between groups (T, 0.5 ± 0.2; TE, 0.6 ± 0.2; $P = 0.63$).

The administration of both oral T and oral TE in oil significantly increased serum DHT in a dose-dependent fashion (Fig. 4). In addition, the maximum concentration of DHT and the area under the curve increased significantly (Table 3), with the maximum concentration of DHT after oral treatment exceeding the normal range for all doses of T and TE in oil. The time of maximum concentration was between 3.9 and 6 h in all cases, and the calculated terminal $t_{1/2}$ of oral T and TE in oil was between 7.5 and 11 h.

Coadministration of D with oral T or TE in oil significantly decreased both maximum and average serum DHT levels compared with the administration of T or TE alone (Fig. 3B and Table 3). The maximum concentration of DHT after oral treatment with the combination of T and D exceeded the normal range at the 800-mg dose of T and at the 400- and 800-mg doses of TE in oil. The time to maximum concentration was between 2.5 and 7.5 h, and the calculated terminal $t_{1/2}$ was between 8 and 10 h. The DHT area under the curve

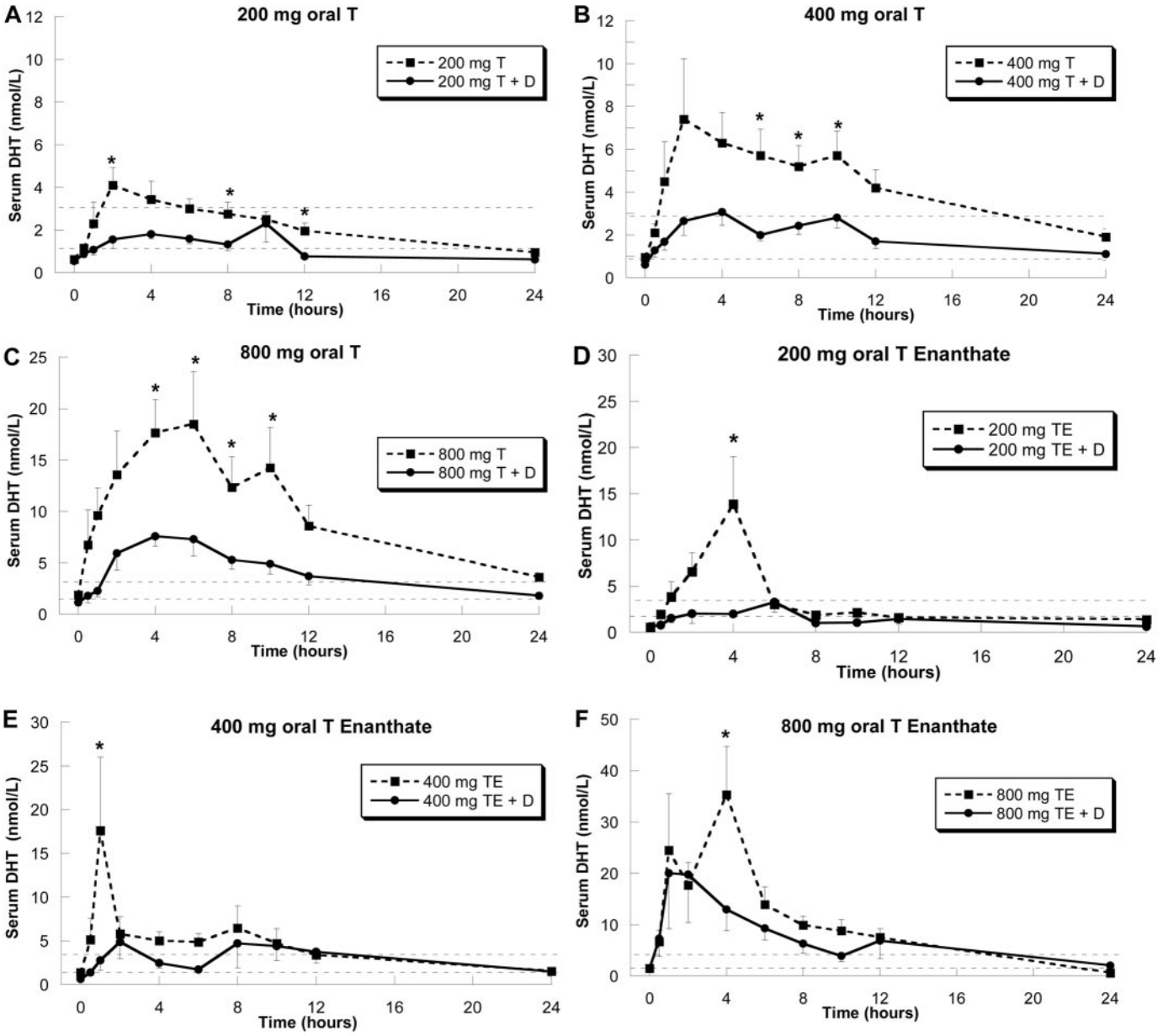

FIG. 4. Serum DHT concentrations (mean ± SEM) after oral administration of 200, 400, and 800 mg T in oil (A–C) and TE in oil (D–F) with and without D for 24 h in normal men treated with the GnRH antagonist acyline to temporarily suspend T production. Note the larger y-axis for the 800-mg dose. The *dotted lines* represent the upper and lower limits of the normal range for serum DHT. *, $P < 0.05$ compared with T plus D.

for the combination of T and D was significantly decreased compared with the area under the curve for T alone at all doses.

Serum E2 and SHBG

Mean serum E2 levels were not significantly different between the treatment groups on d 0 [134 ± 21 (T) *vs.* 116 ± 30 (TE) pmol/liter] or 24 h after acyline administration [94 ± 14 (T) *vs.* 87 ± 12 (TE) pmol/liter]. With oral administration of T or TE, serum E2 levels increased nonsignificantly compared with baseline levels with the 800-mg dose in both the T and TE groups (Fig. 5), but all E2 levels remained within the normal range. There were no significant differences in serum E2 between either T or TE alone compared with T or TE with D coadministration. Serum SHBG did not change significantly after administration of acyline or oral administration of T or TE in oil either with or without concomitant D administration (Fig. 6).

Discussion

In this study we have demonstrated that single doses of T or TE when administered orally in oil can result in serum T levels that would be useful for the treatment of T deficiency. Secondly, we have demonstrated that addition of the 5α-reductase inhibitor D to oral T in oil 1) significantly increases the serum T levels achieved after a given dose of T, and 2)

TABLE 3. DHT pharmacokinetics after administration of a single dose of oral T and oral TE in oil with and without D to normal men previously administered a GnRH antagonist

T (n = 7)	T Only			T + D		
	200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax (nmol/liter)	5.6 ± 2.0	12.0 ± 3.9[a]	30.0 ± 7.0[a]	2.2 ± 0.7[b]	4.2 ± 1.6[a,b]	10.3 ± 3.5[a,b]
Tmax (h)	4.7 ± 3.4	5.0 ± 3.8	3.9 ± 3.5	5.1 ± 3.0	6.0 ± 3.3	4.6 ± 2.2
AUC (nmol-h/liter)	51 ± 15	106 ± 29[a]	239 ± 71[a]	25 ± 8.5[c]	45 ± 15[a,b]	99 ± 40[a,b]
$t_{1/2}$ (h)	10 ± 2.3	9.3 ± 2.0	7.5 ± 3.6	9.9 ± 3.8	10.6 ± 2.3	9.9 ± 2.2
TE (n = 6)	**TE only**			**TE + D**		
	200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax (nmol/liter)	15.3 ± 12	21.0 ± 19	48.8 ± 22.6[a]	4.0 ± 2.4[c]	8.0 ± 6.5[a]	25.3 ± 24[c]
Tmax (h)	3.2 ± 1.3	4.2 ± 3.5	2.5 ± 1.6	5.5 ± 3.7	7.2 ± 4.0	2.7 ± 2.0
AUC (nmol-h/liter)	75 ± 48	100 ± 42	253 ± 101	35 ± 18[c]	72 ± 45	173 ± 148
$t_{1/2}$ (h)	10 ± 2.2	9.1 ± 3.5	8.6 ± 2.9	8.6 ± 3.5	8.4 ± 3.4	9.0 ± 3.3

Values are the mean ± SD. AUC, Area under the curve; Cavg, average concentration during 24-h period after dosing; Cmax, maximum concentration after dosing; Tmax, time of maximum concentration.

[a] $P < 0.05$ *vs.* immediately lower dose.

[b] $P < 0.01$ *vs.* T only.

[c] $P < 0.05$ *vs.* T and TE only.

attenuates the supraphysiological elevations in serum DHT seen with the administration of oral T or T esters (*e.g.* TU) without concomitant 5α-reductase inhibition.

These data contradict the prevailing wisdom in the field, which states that the oral route for T delivery is impractical due to near-complete hepatic first-pass metabolism of orally administered T (11). Although it is true that the bioavailability of orally administered T is very low, probably around 1% (30, 31), our work demonstrates that if sufficient T is administered orally in oil, potentially therapeutic levels of serum T can be achieved after oral dosing. It is likely that liver metabolism of orally dosed T is extensive, because oral T administered to men with cirrhosis results in serum T levels that are markedly elevated compared with normal controls (32, 33). Whether long-term administration of oral T in oil would induce increased hepatic metabolism of oral T and therefore reduce T bioavailability will be the subject of future research.

Previous studies of the oral administration of T may have found reduced levels of serum T in part due to 5α-reductase activity in the intestine and liver (34). In this study using T or TE, and in the work of others with TU (24–27), serum levels of DHT after oral administration are markedly elevated, implying that a large fraction of the orally adminis-

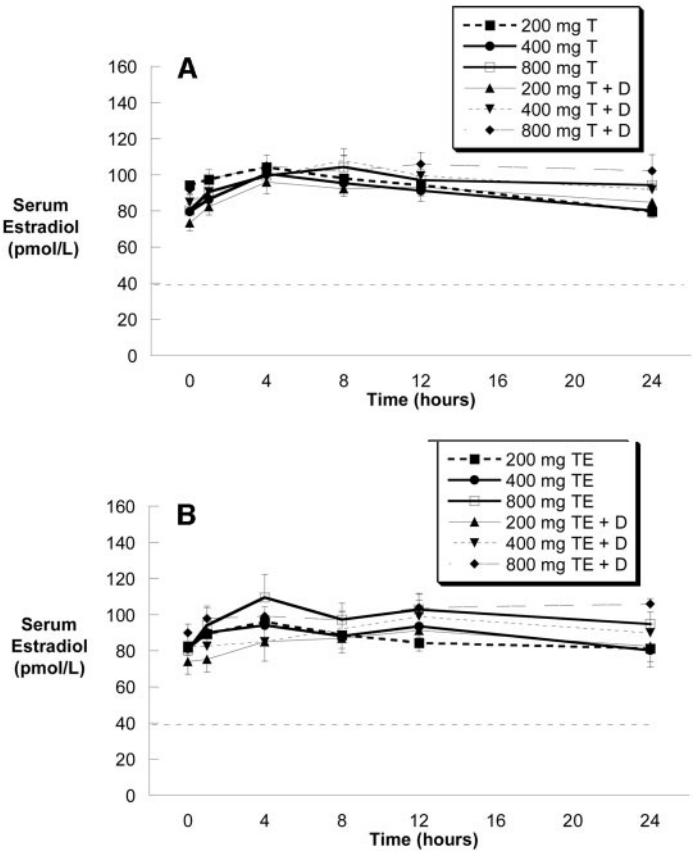

FIG. 5. Serum E2 (mean ± SEM) after oral administration of 200, 400, and 800 mg T (A) and TE (B) in oil with and without D for 24 h in normal men treated with the GnRH antagonist acyline to temporarily suspend T production. The *dotted line* represents the lower limit of the normal range.

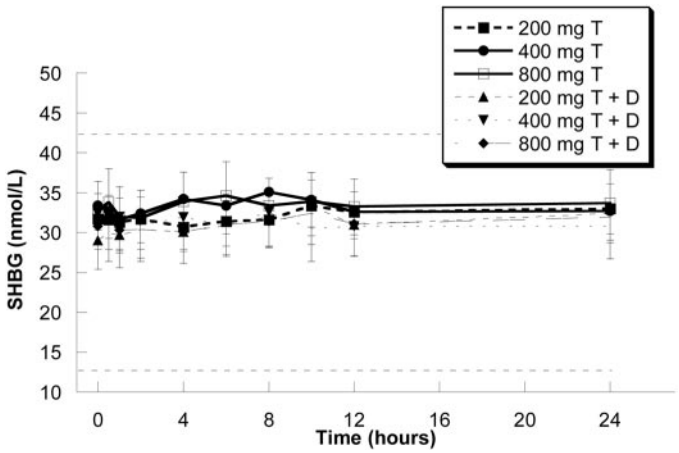

FIG. 6. Serum SHBG concentrations (mean ± SEM) after oral administration of 200, 400, and 800 mg T and TE in oil with and without D for 24 h in normal men treated with the GnRH antagonist acyline to temporarily suspend T production. The *dotted lines* represent the upper and lower limits of the normal range.

tered T dose may be metabolized in the liver and intestines to DHT. Surprisingly, in this study, the coadministration of a 5α-reductase inhibitor roughly doubles the average T concentration and the area under the curve for the serum T while reducing the elevations of serum DHT by approximately half. These marked elevations in serum T with concomitant 5α-reductase inhibition are probably due to inhibition of the 5α-reductase enzyme in intestine and liver, which appears to account for approximately one half of the metabolism of T after an oral dose. Importantly, the combination of elevated serum T without marked elevations in serum DHT may allow for selective oral androgen therapy, which may be useful in decreasing the risk for DHT-dependent disease, such as benign prostate hyperplasia and prostate cancer.

It is also important to note that previous studies of oral T administration demonstrating poor oral bioavailability of T have used T in powder form at doses of 100 and 200 mg (21–23). We have tested oral T in powder form in doses as high as 400 mg without achieving therapeutic serum T levels (data not shown), implying that the administration of T in oil is crucial for the achievement of the therapeutic serum T levels seen in this study. It has been previously shown that the absorption of oral TU is markedly affected by concomitant intake of fatty foods (27, 30). This is probably due to the fact that much of the orally administered TU is absorbed via the lymphatics (35). In an animal model of TU absorption, more than 80% of the bioavailable T is thought to be absorbed via the lymphatics (36). Whether food intake will affect the absorption of oral T in oil is unknown and probably depends on how much of the dose is absorbed via lymphatics *vs.* via the portal circulation. Because T was administered in oil in this study, some of the dose may have been absorbed via the lymphatics. This might explain in part the unexpectedly long serum half-life of T seen with oral compared with iv administration of T, which has been reported to have a half-life of less than 1 h (31, 37). Another possibility is that there is some degree of enterohepatic circulation of the orally administered T, prolonging the apparent half-life in serum. Because of this uncertainty, the impact of food intake on the absorption and serum levels of T after the administration of oral high dose T will be the subject of future study.

It is important to note that there was no evidence of either liver or kidney toxicity associated with the doses of oral T administered in this study; however, additional long-term study of these doses combined with a 5α-reductase inhibitor will be required to determine the safety of this approach to T therapy. Although one subject did report transient gynecomastia, this subject's serum E2 level remained within the normal range. Additionally, no subject complained of impotence, decreased libido, or sexual dysfunction during the treatment period. These side effects have been reported when D is administered alone for benign prostate hyperplasia (38); however, in theory, they would be less likely when D is administered in combination with T. Additionally, the implication of long-term 5α-reductase inhibition will need examination given the increase in high grade prostate cancer (despite an overall decrease in prostate cancer incidence) seen with chronic finasteride administration in the prostate cancer prevention trial (39).

There were slight, nonsignificant increases in serum E2 seen after oral dosing of T and TE in oil. This implies that although orally administered T can undergo aromatization to E2, it does not do so at high levels, suggesting that there is probably little aromatase activity in the intestine and liver in man. This finding is reassuring in showing that orally administered T is likely to allow for the important functions of estrogen in man, such as maintenance of bone density (40), but not lead to an increased risk of estrogen-related side effects such as gynecomastia.

From a practical standpoint, a regimen using oral T in oil in the formulation used in this study may need to be administered twice daily; however, additional refinements of this approach, such as the use of slow-release capsules, may allow for more controlled release of T in the intestine and could lead to a formulation that could be administered orally once daily, a major improvement over current T replacement options.

In conclusion, we have demonstrated that single doses of T or TE, when administered orally in oil, can result in markedly elevated serum levels of T in normal men with induced hypogonadism; such levels would presumably be therapeutically effective in treating testicular failure. In addition, we have demonstrated that addition of the 5α-reductase inhibitor D to oral T in oil significantly increases the serum T levels observed with a given dose of T and attenuates the supraphysiological elevations in serum DHT seen with the administration of oral T alone. Combinations of oral T 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 this combination are warranted to determine whether it might be a clinically useful and attractive method of treating T deficiency.

Acknowledgments

We acknowledge Ms. Amanda Wiseman for assistance with study implementation, and Ms. Dorothy McGuinness for performing the hormone assays.

Received June 25, 2004. Accepted February 9, 2005.

Address all correspondence and requests for reprints to: Dr. John K. Amory, University of Washington, Box 356429, 1959 NE Pacific Street, Seattle, Washington 98195. E-mail: jamory@u.washington.edu.

This work was supported by the National Institute of Child Health and Human Development, a division of the National Institutes of Health, through Cooperative Agreements U54-HD-12629 and U54-HD-42454 as part of the specialized Cooperative Centers Program in Reproductive Research and the Cooperative Contraceptive Research Centers Program. J.K.A. is supported in part by the National Institute of Child Health and Human Development, a division of the National Institutes of Health (NIH), by Grant 1K23-HD-45386-10A1. A portion of this work was conducted through the Clinical Research Center facility at University of Washington and supported by NIH Grant M01-RR-00037.

References

1. **Kelch RP, Jenner MR, Weinstein R, Kaplan SL, Grumbach MM** 1972 Estradiol and testosterone in the male: secretion by human, simian, and canine testes. J Clin Invest 51:824–830
2. **Weinstein R, Kelch RP, Jenner MR, Kaplan SL, Grumbach MM** 1974 Secretion of androgens and estrogens by the normal and abnormal human testis. J Clin Invest 153:1–6
3. **Plymate SR** 2001 Male hypogonadism. In: Becker KL, ed. Principles and practice of endocrinology and metabolism, 3rd Ed. Philadelphia: Lippincott Williams & Wilkins; 1125–1150
4. **Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal KI, Klibanski A** 1996 Increase in bone density and lean body mass during testosterone ad-

ministration in men with acquired hypogonadism. J Clin Endocrinol Metab 81:4358–4365
5. **Behre HM, Kliesch S, Leifke R, Link RM, Nieschlag E** 1997 Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 82:2386–2390
6. **Bhasin S, Bremner WJ** 1997 Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab 1982:3–8
7. **Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L Callegari C, Swerdloff RS** 1996 Testosterone replacement therapy improves mood in hypogonadal men-a clinical research center study. J Clin Endocrinol Metab 81:3578–3583
8. **Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL** 2000 Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 85:2670–2677
9. **Bagatell CJ, Bremner WJ** 1996 Androgens in men-uses and abuses. N Eng J Med 334:707–714
10. **Matsumoto AM** 2001 Clinical use and abuse of androgens and antiandrogens. In: Becker KL, ed. Principles and practice of endocrinology and metabolism, 3rd Ed. Philadelphia: Lippincott Williams & Wilkins; 1181–1199
11. **Snyder P** 2001 Androgens. In: Hardman JG, Lumbard LE, eds. Goodman and Gilman's the pharmacological basis of therapeutics, 4th Ed. New York: McGraw-Hill; 1635–1648
12. **Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM** 1977 Liver damage from long-term methyltestosterone. Lancet 2:262–263
13. **Turani H, Levi J, Zevin D, Kessler E** 1983 Hepatic lesions in patients on anabolic androgenic therapy. Isr J Med Sci 19:332–337
14. **Lowdell CP, Murray-Lyon IM** 1985 Reversal of liver damage due to long term methyltestosterone and safety of non-17-α alkylated androgens. Br Med J 291:637–645
15. **Cabasso A** 1994 Peliosis hepatis in a young adult bodybuilder. Med Sci Sports Exerc 26:2–4
16. **Pavlatos AM, Fultz O, Monberg MJ, Vootkur A** 2001 Review of oxymetholone: a 17α-alkylated anabolic-androgenic steroid. Clin Ther 23:789–801
17. **Fossa SD, Opjordsmoen S, Haug E** 1999 Androgen replacement and quality of life in patients treated for bilateral testicular cancer. Eur J Cancer 35:1220–1225
18. **Amory JK, Matsumoto AM** 1998 The therapeutic potential of testosterone patches. Exp Opin Invest Drugs 7:1977–1985
19. **Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N** 2000 Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab 85:4500–4507
20. **Foss GL** 1939 Clinical administration of androgens. Lancet 1:502–504
21. **Nieschlag E, Mauss J, Coert A, Kicovic P** 1975 Plasma androgen levels in men after oral administration of testosterone and testosterone undecanoate. Acta Endocrinol (Copenh) 79:366–374
22. **Johnsen SG, Bennett EP, Jensen VG** 1974 Therapeutic effectiveness of oral testosterone. Lancet 2:1473–1475
23. **Daggett PR, Wheeler MJ, Nabarro JDN** 1978 Oral testosterone, a reappraisal. Horm Res 9:121–129
24. **Skakkebaek NE, Bancroft J, Davidson DW, Warner P** 1981 Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double-blind controlled study. Clin Endocrinol (Oxf) 14:49–61
25. **Gooren LJG** 1994 A ten-year safety study of the oral androgen testosterone undecanoate. J Androl 15:212–215
26. **Houwing NS, Maris F, Schnabel PG, Bagchus WM** 2003 Pharmacokinetic study in women of three different doses of a new formulation of oral testosterone undecanoate, Andriol Testocaps. Pharmacotherapy 23:1257–1265
27. **Bagchus WM, Hust R, Maris F, Schnabel PG, Houwing NS** 2003 Important effect of food on the bioavailability of oral testosterone undecanoate. Pharmacotherapy 23:319–325
28. **Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G** 2002 Efficacy and safety of a dual inhibitor of 5α-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 60:434–441
29. **Herbst KL, Coviello AD, Page S, Amory JK, Anawalt BD, Bremner WJ** 2004 A single dose of the potent gonadotropin-releasing hormone antagonist acyline suppresses gonadotropins and testosterone for 2 weeks in healthy young men. J Clin Endocrinol Metab 89:5959–5965
30. **Frey H, Aakvaag A, Saanum D, Falch J** 1979 Bioavailability of oral testosterone in males. Eur J Clin Pharmacol 16:345–349
31. **Tauber U, Schroder K, Dusterberg B, Matthes H** 1986 Absolute bioavailability of testosterone after oral administration of testosterone undecanoate and testosterone. Eur J Drug Metab Pharmacokinet 11:145–149
32. **Gluud C, Bennett P, Dietrichson O, Johnsen SG, Ranek L, Swendsen LB, Juhl E** 1981 Short-term parenteral and peroral testosterone administration in men with alcoholic cirrhosis. Scand J Gastroenterol 16:749–755
33. **Gluud C, Bahnsen M, Bennett P, Dietrichson O, Henriksen JH, Johnsen SG, Svendsen LB, Brodthagen UA, Juhl E** 1983 Oral testosterone load related to liver function in men with alcoholic cirrhosis. Scand J Gastroenterol 18:391–396
34. **Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW** 1993 Tissue distribution and ontogeny of steroid 5α reductase isozymes expression. J Clin Invest 92:903–910
35. **Horst HJ, Holtje WJ, Dennis M, Coert A, Geelen J, Voigt KD** 1976 Lymphatic absorption and metabolism of orally administered testosterone undecanoate in man. Klin Wschr 54:875–879
36. **Shackleford DM, Faassen WA, Houwing N, Lass H, Edwards GA, Porter CJ, Charman WN** 2003 Contribution of lymphatically transported testosterone undecanoate to the systemic exposure of testosterone after oral administration of two andriol formulations in conscious lymph duct-cannulated dogs. J Pharmcol Exp Ther 306:925–933
37. **Southren AK, Gordon GG, Tochimoto S, Pinzon G, Lane DR, Stypulkowski W** 1967 Mean plasma concentration, metabolic clearance and basal testosterone production rates of testosterone in normal young men and women using a constant infusion procedure: effect of time of day and plasma concentration on the metabolic clearance rate of testosterone. J Clin Endocrinol 27:686–694
38. **Andriole GL, Kirby R** 2003 Safety and tolerability of the dual 5-α-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. Eur Urol 44:82–88
39. **Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ Coltman Jr CA** 2003 The influence of finasteride on the development of prostate cancer. N Engl J Med 349:215–224
40. **Khosla S, Melton LJ, Riggs BL** 2001 Estrogens and bone health in men. Calcif Tissue Int 69:189–192

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.