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Oral Testosterone With and Without Concomitant Inhibition of 5 α -Reductase by Dutasteride in Hypogonadal Men for 28 Days

John K. Amory, Mark A. Bush*, Hui Zhi*, Ralph B. Caricofe*, Alvin M. Matsumoto†, Ronald S. Swerdloff, Christina Wang‡, and Richard V. Clark§

University of Washington (JKA) and Geriatric Research Education and Clinical Center, Veterans Affairs-Puget Sound Health Care System (AMM), Seattle, Washington, GlaxoSmithKline Research and Development (MAB, HZ, RBC, RVC), Research Triangle Park, North Carolina, and Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute (RSS, CW), Torrance, California

Abstract

Purpose—Co-administration of the 5 α -reductase inhibitor dutasteride increases the oral testosterone bioavailability in men with experimentally induced hypogonadism. We examined oral testosterone with and without dutasteride administration in hypogonadal men for 28 days.

Materials and Methods—We randomly assigned 43 hypogonadal men to twice daily oral doses of 150, 250 or 400 mg testosterone with 0.25 mg dutasteride, 400 mg testosterone alone or 0.25 mg dutasteride alone for 28 days in a multicenter study. Subjects underwent pharmacokinetic profiling of serum hormones on days 1 and 28. A total of 32 men completed all study procedures.

Results—Serum testosterone increased in all groups on testosterone compared with that in the dutasteride only group. At the 400 mg dose the combination of testosterone and dutasteride resulted in average testosterone concentrations that were 2.7 and 4.6 times higher than in the testosterone only group on days 1 and 28, respectively ($p < 0.01$). On day 28 average testosterone was 20% to 30% lower in all groups on testosterone and dutasteride, and 50% lower in the testosterone only group compared with day 1. Serum dihydrotestosterone was suppressed in all groups on dutasteride and increased in the testosterone only group.

Conclusions—Oral testosterone administration resulted in a therapeutic serum testosterone concentration in hypogonadal men. Dutasteride improved the oral bio-availability of testosterone while suppressing dihydrotestosterone. Compared with day 1, testosterone was decreased after 28 days of administration. Additional study is warranted of oral testosterone with dutasteride for testosterone deficiency.

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§Address for correspondence/reprint requests: Metabolic Discovery Medicine, Muscle Metabolism DPU, Metabolic Pathways CEDD, GlaxoSmithKline Research and Development, 5 Moore Dr. N2.3212, P. O. Box 13398, Research Triangle Park, North Carolina 27709-3398.

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Keywords

testis; hypogonadism; administration, oral; testosterone; dutasteride

Testosterone, the most important male sex hormone, is crucial for male health. Normal testes produce 4 to 8 mg T daily¹ and T has effects on various tissues, including the brain, liver, muscle, bone and bone marrow, blood vessels, skin, prostate and penis.² Depending on age, about 6% to 18% of men have T below the normal range and symptoms of T deficiency, such as low libido, erectile dysfunction, depression and decreased physical performance.³ These men benefit from T replacement, which improves mood, increases bone and muscle mass, and maintains sexual function.⁴⁻⁶

Current approved T therapies in the United States include injections, patches, gels, buccal tablets and oral alkylated T derivatives, eg methyltestosterone and oxandrolone. Each form of T delivery has drawbacks. Intramuscular injections must be given every 1 to 3 weeks to maintain normal serum T and they can be painful.⁷ Patches can cause skin reactions in more than half of subjects.⁸ T gels are safe and effective⁹ but expensive. Also, there is the risk of inadvertent contact exposure and transfer to women and children,^{10,11} which recently resulted in a black box warning from the United States Food and Drug Administration.

Oral administration of T may be preferable to currently available options based on the potential for convenience, safety and tolerability. Unfortunately the currently available oral T formulations in the United States, which are alkylated at the 17-carbon position, are associated with cholestatic jaundice and peliosis hepatis in some long-term users.^{12,13} As a result, these oral androgens are not considered safe for long-term treatment for hypogonadism.¹⁴ In Europe and other countries oral testosterone undecanoate is approved for use and is not associated with hepatotoxicity. However, it must be ingested with a fatty meal for adequate absorption.

Oral administration of unmodified T was previously thought to be ineffective due to hepatic metabolism.^{15,16} Nevertheless, we recently reported that when unmodified T is administered at a sufficient dose, serum T within the normal range was achieved in single dose PK studies without adverse effects on liver function.^{17,18} Also, we noted that when oral T is combined with the 5 α -reductase inhibitor D, the resulting serum T is approximately doubled and serum DHT is decreased. Since 5 α -reductase inhibitors decrease DHT, their combination with T therapy may be useful since DHT has a role in the pathophysiology of androgenic alopecia, acne, benign prostatic hyperplasia and possibly prostate cancer.

In this study we determined the PK profiles of oral T alone and combined with the 5 α -reductase inhibitor D in hypogonadal men during 28 days of dosing to assess the feasibility of this approach for treating male hypogonadism.

MATERIALS AND METHODS

Study Design and Measurements

This randomized, open label, parallel group study consisted of a screening period, followed by a continuous 28-day treatment period (fig. 1). Subjects were randomized using a random number sequence to 1 of 5 treatments administered orally BID, including 1) 150 mg T plus 0.25 mg D, 2) 250 mg T plus 0.25 mg D, 3) 400 mg T plus 0.25 mg D, 4) 400 mg T alone or 5) 0.25 mg D alone. The T plus D and D alone groups but not the T only group received a D loading dose of 24.5 mg, followed by 3 consecutive days of 0.25 mg D BID before starting the 28-day treatment phase.

On days 1 and 28 of treatment serum samples were drawn before dosing, and 0.5, 1, 2, 4, 6, 8, 10, 12, 12.5, 13, 14, 16, 18, 20, 22 and 24 hours after the morning dose to assess serum T, DHT and E2. Serum T, DHT and E2 were measured by a validated gas chromatography/tandem mass spectrometry assay at a central laboratory, as described previously.¹⁸ Normal ranges were T 300 to 1,000 ng/dl, DHT 30 to 90 ng/dl and E2 10 to 60 pg/ml. Luteinizing hormone, FSH and SHBG were measured on days 1 and 28 by radioimmunoassay.¹⁹

Subjects

The study recruited hypogonadal males between 18 and 60 years old who required T replacement therapy. All subjects discontinued T replacement therapy for 7 days if they used a T gel, patch, buccal or oral T formulation, or for at least 2 weeks if they used intramuscular T. Study inclusion criteria were body mass index between 21 and 32 kg/m² and the ability to provide written informed consent. Exclusion criteria were D or finasteride use, a positive hepatitis B surface antigen, hepatitis C or HIV antibody test, a history of breast or prostate cancer, sleep apnea, psychiatric illness, polycythemia, serum PSA greater than 2.0 ng/ml or untreated hypertension. The study was approved by the institutional review boards at each clinical site and each subject provided signed informed consent before participation. The trial was registered in advance at clinical-trials.gov as study NCT00398580.

Statistics

Study end points were the hormonal PK parameters. The primary end points were to evaluate Tavg during 24 hours in each treatment group on days 1 and 28, and the percent of subjects in each treatment group in whom Tavg was within the normal range. Secondary end points were the maximum concentration and the time to maximum concentration of T, DHT and E2 on days 1 and 28. Summary PK parameters were calculated in each subject after subtracting baseline T, DHT or E2 on each day using Win-Nonlin®. We analyzed comparisons of PK parameters between days 1 and 28, and between groups using a 2-way repeated measure ANOVA model with interaction. Due to large variances and the large number of multiple comparisons hormonal concentrations at each time point on days 1 and 28 are shown in descriptive fashion. All statistical analysis was done with SAS® with $\alpha < 0.05$ considered significant for all comparisons. No adjustments were made for multiplicity.

RESULTS

Subjects

Of the 43 men enrolled in the study 2 withdrew consent before dosing and 6 were dosed incorrectly at a single study site. Of the remaining 35 subjects 5 to 8 were assigned to a given treatment group (table 1). Ten men had primary hypogonadism (FSH greater than 15 IU/l) due to Klinefelter's syndrome and 23 had secondary hypogonadism due to various congenital and acquired causes. Three men failed to complete the study, 2 were discontinued due to missed visits early in the protocol and 1 withdrew voluntarily. Of these withdrawn subjects only the latter completed day 1. Thus, 33 men were included in day 1 analysis and 32 were included in day 28 per protocol analysis. No subjects were lost to followup.

Serum Hormones

Concentrations—Serum T was markedly increased into and above the normal reference range of 300 to 1,000 ng/dl by oral T administration on day 1 and after 28 days of treatment in all groups on T (fig. 2, A and B). Mean serum T was supraphysiological throughout the 24-hour period on days 1 and 28 in the 400 mg T plus D group and below the lower limit of the normal range in the D alone group. Serum DHT was transiently increased above the normal range after dosing in the 400 mg T alone group for 3 to 6 hours but suppressed in all groups on D (fig. 2, C and D). Serum E2 was normal throughout the 24-hour period on days 1 and 28 in all treatment groups (fig. 2, E and F).

Pharmacokinetics—Tavg was increased in all groups receiving T (fig. 3, A). Tavg in the 400 mg T plus D group was significantly greater than in all other groups ($p < 0.05$). Tavg in this group was 2.7 times higher than in the 400 mg T alone group on day 1 and 4.6 times higher on day 28 (each $p < 0.01$). Compared with day 1 Tavg was 48% lower on day 28 in the T only group ($p < 0.001$). In the T plus D groups Tavg on day 28 was nonsignificantly decreased by 20% to 30% compared with day 1. The incidence of subjects with Tavg in the normal range on day 28 was 33%, 75%, 63%, 50% and 12% in the 150, 250 and 400 mg T plus D, 400 mg T alone and D alone groups, respectively.

Table 2 shows maximum T by group. Maximum T in the 400 mg T plus D group was significantly greater than in all other groups on days 1 and 28. No subject in the 150 or 250 mg T plus D, or the D alone group had a maximum T of greater than 2,500 ng/dl. In contrast, 63% of subjects in the 400 mg T plus D group and 16% in the T alone group had a maximum T of greater than 2,500 ng/dl after 28 days of treatment. Time to maximum concentration was between 1 and 2 hours after dosing in each 400 mg T group but between 6 and 8 hours in the lower dose groups (table 2).

Mean DHT was significantly greater in the T alone group compared with that in all groups on D, in which mean DHT was well below the normal range (fig. 3, B). Mean maximum DHT in all groups on D was below the lower limit of the normal range but significantly increased in the T alone group (table 2). E2 PK profiles were similar in all groups regardless of treatment (table 2).

Hormone Pharmacodynamics

Eight of 9 men with primary hypogonadism who were treated for 28 days and received T plus D or T alone experienced 25% to 50% decreased serum luteinizing hormone and FSH compared with baseline (as a group $p < 0.05$). The exception was a subject who received the lowest dose of T plus D (150 mg). Between days 1 and 28 serum SHBG was significantly decreased by 50% in the 2 groups on 400 mg T, including 13.3 to 7.48 nmol/l on days 1 to 28 in the 400 mg T plus D group and 17.0 to 7.9 nmol/l on days 1 to 28 in the 400 mg T alone group (vs baseline each $p < 0.01$).

Safety and Adverse Events

There were 2 serious adverse events during the study. The first event occurred in a man on 150 mg T plus D who was hospitalized with onset of congestive heart failure attributable to self-discontinuation of medications during the study without medical authorization. He responded well to diuresis. The other man, who was on 400 mg T plus D, was hospitalized for new onset atrial fibrillation attributable to excess thyroid hormone replacement, which was held until thyroid hormones decreased to the normal range. In neither subject was the serious adverse event considered drug related by the site primary investigator. Each man continued on study drug and completed the study without further problems. There were 16 nonserious adverse events without evidence of clustering to a specific treatment, of which the most common were headache, dizziness, upper respiratory infection, vomiting, back pain and frequent urination in 2 men each. There were no significant changes in hemoglobin and blood counts, serum chemistry, or markers of liver inflammation or PSA (data not shown).

DISCUSSION

We report that oral T co-administered with D can safely and effectively achieve therapeutic T levels in hypogonadal men during 28 days with BID dosing. We also report that co-administering the 5 α -reductase inhibitor D, which was previously shown to improve serum T in single dose PK studies,^{17,18} continues to have this effect after 28 days. The combination of D with the highest dose of oral T studied resulted in T_{avg} above the upper limit of normal. Thus, future studies will focus on formulations with modified release characteristics for dose optimization to maintain T_{avg} in the normal range and maximum T below a reasonable level.

A drawback to our study was the relatively few men per group, the number who did not complete the study, and the lack of homogeneity in age and baseline T. Nevertheless, the goal of 75% of subjects with T_{avg} in the normal range was achieved in the 250 mg T plus D group, in which maximum T was also less than 2,500 ng/dl. Also, oral T decreased SHBG during treatment, which contributed to the decrease in total T observed at the end of the study period.

A challenge to the development of oral T therapy has been the observation that oral T administration tends to induce its own metabolism by the liver, leading to a decrease in the resulting serum T with time.^{20,21} We observed a significant decrease in serum T with continued dosing of oral T during the 28-day treatment period, which was minimized by

concomitant D administration. The effect of 5 α -reductase inhibition could be due to the inhibition of T metabolism or to decreased induction of CYP3A4 by lower DHT concentrations. To our knowledge whether additional increases in metabolism would continue with longer treatment is unknown but for some medications this effect stabilizes with time. For example, rifampin initially induces its own metabolism, causing a 40% decrease in serum rifampin after 14 days of dosing but after this initial period serum rifampin stabilizes.²² Whether serum T after oral dosing would follow a similar pattern will be the subject of future studies.

Oral T administration in this study did not cause liver inflammation and most adverse events were minor. However, adverse changes in lipids, prostate health or erythrocytosis may be observed in a longer trial since these events are associated with other forms of androgen delivery.²³

As expected, serum DHT was suppressed well below the normal range throughout the study in the groups on D. A combination of oral T and D could be appealing to patients and clinicians since it provides the benefits of T therapy, such as increased bone mineral density and strength, without stimulating prostate growth.^{24,25} Also, DHT inhibition by 5 α -reductase inhibitors may decrease the risk of prostate cancer^{26,27} by lowering DHT in the prostate.²⁸ Lastly, increasing serum T without increasing DHT could minimize the risks of androgenic alopecia and acne without impacting the advantageous effects of T on bone density, serum cholesterol and sexual function since 5 α -reductase inhibitors do not appear to affect these end points.²⁹

CONCLUSIONS

Our study shows that oral T administered alone or combined with D results in potentially therapeutic serum T concentrations in hypogonadal men during 28 days. Longer term studies are warranted to optimize the dose and determine the safety and efficacy of this approach to androgen replacement therapy.

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APPENDIX

Study Sites and Principal Investigators

Drs. John Amory, University of Washington School of Medicine, Seattle, Washington; Ronald Swerdloff, Harbor-UCLA Medical Center, Torrance, California; Alvin Matsumoto, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; Thomas Weber,

Duke University Medical Center, Durham, North Carolina; Adrian Dobs, Johns Hopkins University School of Medicine, Baltimore, Maryland; Stephen Winters, University of Louisville, Louisville, Kentucky; and Dennis Ruff, Healthcare Discoveries, San Antonio, Texas.

Abbreviations and Acronyms

BID	twice daily
D	dutasteride
DHT	5 α -dihydrotestosterone
E2	estradiol
FSH	follicle-stimulating hormone
PK	pharmacokinetics
PSA	prostate specific antigen
SHBG	sex hormone binding globulin
T	testosterone
Tavg	average testosterone

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Figure 1.
Study schematic

Figure 2.

Mean $\pm$ SEM serum T (A and B), DHT (C and D) and E2 (E and F) on days 1 and 28 in hypogonadal men treated with oral nanomilled T with or without D. Dotted lines indicate upper and lower limits of reference range in men. Black squares represent 150 mg T plus D. Hatched squares indicate 250 mg T plus D. Circles indicate 400 mg T plus D. Triangles indicate D only. Inverted triangles indicate 400 mg T only.

Figure 3.

Average serum T (A) and DHT (B) on days 1 and 28 in hypogonadal men treated with nanomilled T with or without D orally BID for 28 days. Values are shown as geometric mean with 95% CI. Dotted lines represent upper and lower limits of reference range in men. Asterisk indicates $p < 0.05$ vs 400 mg T plus D. [H9278] indicates $p < 0.05$ vs day 1. ψ indicates $p < 0.05$ vs T only.

Table 1
Subject baseline characteristics by treatment

BID Treatment (mg)	No. Pts	Mean $\pm$ SD Age	Mean $\pm$ SD BMI (kg/m²)	Mean $\pm$ SD T (ng/dl)
150 T + 0.25 D	6	58.4 $\pm$ 6.1	29.0 $\pm$ 3.2	191 $\pm$ 119
250 T + 0.25 D	5	44.6 $\pm$ 20.3	30.7 $\pm$ 3.8	139 $\pm$ 95
400 T + 0.25 D	8	53.0 $\pm$ 20.1	30.5 $\pm$ 7.4	180 $\pm$ 130
400 T	7	61.1 $\pm$ 7.6	31.2 $\pm$ 3.6	221 $\pm$ 75
0.25 D	7	50.4 $\pm$ 13.8	27.6 $\pm$ 5.0	179 $\pm$ 111
Overall	33	53.9 $\pm$ 14.8	29.7 $\pm$ 4.9	184 $\pm$ 63

Table 2
Serum hormone PK

Variable (day)	150 mg T + 0.25 mg D BID	250 mg T + 0.25 mg D BID	400 mg T + 0.25 mg D BID	400 mg T BID	0.25 mg D BID
<i>Testosterone</i>					
Mean ± SEM % CV max (ng/dl):					
1	1,044 ± 47 [*]	1,427 ± 65 [*]	4,720 ± 52	1,762 ± 27 [*]	176 ± 114 ^{*,‡}
28	1,112 ± 83 [*]	887 ± 79 [*]	3,782 ± 82	1,104 ± 105 ^{*,†}	201 ± 114 ^{*,‡}
Median hrs to max (range):					
1	2.0 (1.0–15.9)	1.0 (0.5–14.0)	1.0 (0.5–14.0)	1.0 (0.5–13.0)	24.0 (8.0–24.1)
28	6.5 (0.4–18.0)	8.5 (1.0–14.0)	1.5 (1.0–14.0)	1.3 (0.5–13.0)	22.0 (0.0–24.0)
<i>Dihydrotestosterone</i>					
Mean ± SEM % CV max (ng/dl):					
1	7.6 ± 52 ^{*,‡}	5.9 ± 57 ^{*,‡}	28 ± 67	227 ± 66 [*]	1.3 ± 30 ^{*,‡}
28	8.0 ± 96 ^{*,‡}	7.4 ± 88 ^{*,‡}	28 ± 83	145 ± 129 [*]	1.2 ± 25 ^{*,‡}
Mean ± SEM % CV max (pg/ml):					
1	33 ± 69	28 ± 55	29 ± 49	29 ± 36	18 ± 80
28	32 ± 78	28 ± 82	39 ± 47 [†]	25 ± 59	17 ± 102 [*]
Mean ± SEM % CV (ng/dl):					
1	23 ± 82	20 ± 51	19 ± 50	20 ± 40	13 ± 82
28	24 ± 85	21 ± 86	28 ± 44	17 ± 53	13 ± 88 [*]

^{*} p < 0.05 vs 400 mg T plus D.

[†] p < 0.05 vs day 1.

[‡] p < 0.05 vs 400 mg T only.