Effects of 28 Days of Oral Dimethandrolone Undecanoate in Healthy Men: A Prototype Male Pill

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Context: Dimethandrolone (DMA) has androgenic and progestational activity. Single oral doses of DMA undecanoate (DMAU) were well tolerated and reversibly suppressed serum LH and testosterone (T) in men.  

Objective: Assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of oral DMAU.  

Design: Double-blind, randomized, placebo-controlled study.  

Setting: Two academic medical centers.  

Participants: Healthy men (18 to 50 years).  

Interventions: One hundred men received DMAU [0, 100, 200, or 400 mg, formulated in castor oil/benzyl benzoate (C) or powder (P)] for 28 days. Subjects underwent 24-hour PK sampling on days 1 and 28 and twice weekly ambulatory visits throughout treatment.  

Main Outcome Measures: Primary outcomes were safety and tolerability parameters (vitals, laboratory data, mood, and sexual function scores) and adverse events. Secondary outcomes were drug PK profiles and PD effects (serum LH, FSH, and sex hormones).  

Results: Eighty-two subjects completed the study and were included in the analysis. There were no serious adverse events. No clinically significant changes developed in safety laboratory parameters. A significant dose effect was seen for weight, hematocrit, high-density lipoprotein cholesterol, corrected QT interval, and sexual desire. Serum 24-hour average concentrations of DMAU and DMA showed dose-related increases (P < 0.001). All six subjects in the P400 group and 12 of 13 subjects in the C400 group achieved marked suppression of LH and FSH (<1.0 IU/L) and serum T (<50 ng/dL).  

Conclusions: Daily oral administration of DMAU for 28 days in healthy men is well tolerated. Doses of ≥200 mg markedly suppress serum T, LH, and FSH. These results support further testing of DMAU as a male contraceptive. (J Clin Endocrinol Metab 104: 423–432, 2019)
In the United States, 45% of pregnancies are unintended and 42% of these unintended pregnancies end in abortion (1) resulting in substantial public expenditure (2). Male contraceptive methods presently available, namely condoms and withdrawal, have high failure rates (3) or require vasectomy, which is difficult to reverse. The majority of men and women surveyed across ethnicities and nationalities respond that they are interested in reversible hormonal male contraceptives (4, 5) and welcome expanded male contraceptive choices.

Hormonal male contraceptive methods in clinical trials have primarily used testosterone (T) gels, injections, or implants, with or without a progestin (6). The addition of a progestin to T increases the proportion of men who suppress their sperm concentration to <1 million/mL (7, 8), a level consistent with >97% contraceptive efficacy (9). Although the results of these studies are promising, men across three continents suggest that many men prefer a pill over an injection (10), results compatible with some survey data (11). Development of an oral male contraceptive is therefore desirable to maximize uptake and impact of new male contraceptive methods.

Dimethandrolone undecanoate (DMAU; 7α,11β-methyl-19-nortestosterone undecanoate) is hydrolyzed in vivo to dimethandroline (DMA). The undecanoate ester increases absorption and slows the clearance of DMAU. DMA does not appear to be aromatized or 5α reduced in vivo (12, 13) and therefore may be a “prostate-sparing” androgen. DMA binds to androgen and progesterone receptors (14). The relative binding affinity of DMA, from in vitro receptor binding studies, is 18% that of progesterone at the progesterone receptor and 400% that of T at the androgen receptor. Therefore, DMA acts as a very potent androgen with some progestational activity (14). These are ideal characteristics for a single-agent male hormonal contraceptive (7, 8). In preclinical studies, oral DMAU reversibly suppressed gonadotropins, spermatogenesis, and fertility in rodents while maintaining androgenic effects (15–17). Therefore, DMAU is under development by the National Institute of Child Health and Human Development as an oral male contraceptive pill.

Single oral doses of DMAU (up to 800 mg), in healthy men, were safe (18, 19). Coadministration with food greatly increases absorption, resulting in higher serum levels of DMA compared with dosing after fasting. Absorption was marginally better when oral DMAU was formulated in castor oil compared with powder, without additional safety or tolerability concerns. Single doses ≥200 mg of DMAU in castor oil, administered with food, resulted in significant serum gonadotropin and T suppression. Given these promising findings, DMAU, formulated in castor oil or powder, progressed to the next stage of contraceptive development.

We conducted a 28-day repeat-dosing, dose-escalation study of DMAU formulated in castor oil (100, 200, and 400 mg) and in powder (200 and 400 mg). We hypothesized that oral DMAU, given with food, would be well tolerated and result in significant, sustained, dose-dependent suppression of serum gonadotropins and T in healthy men. In addition, because DMA potently activates the androgen receptor, we expected that, despite marked suppression of endogenous T, men would not have significant symptoms of hypogonadism if adequate DMA concentrations were maintained throughout the treatment period.

Materials and Methods

Subjects

This study was conducted at the University of Washington and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed), with equal numbers of subjects enrolled at each site. The institutional review boards for both participating institutions approved the study protocol. Subjects were healthy men 18 to 50 years old. Pertinent inclusion criteria included general good health and normal reproductive function, whereas exclusion criteria included significant medication use or chronic medical conditions (20).

Investigational drug

DMAU was manufactured by Evestra Inc. (San Antonio, TX) or Ash Stevens Inc. (Detroit, MI). Micronization for powder formulation was conducted by Micron Technologies Inc. (Exton, PA). Capsules containing 100 mg DMAU in powder blend or castor oil/benzyl benzoate, and corresponding placebo capsules, were manufactured, tested, and packaged under Good Manufacturing Practice conditions by Stanford Research International (Menlo Park, CA) or QS Pharma (Boothwyn, PA).

Study design and procedures

This was a phase 1b, double-blind, placebo-controlled study. Subjects were randomized to either active drug (n = 15) or placebo (n = 5) in each of five groups: 100, 200, or 400 mg DMAU in 70% castor oil/30% benzyl benzoate (C) or 200 or 400 mg DMAU powder (P) in capsule. Dose escalation occurred in a stepwise manner following safety reviews (20). Following screening, subjects were randomized in a 3:1 manner to active drug or placebo within each stage by Health Decisions, the data and statistical coordinating center for the study. Subjects took the drug daily for 28 consecutive days. Subjects were admitted to the Clinical Research Centers on days 1 and 28. They underwent observed dosing (after eating breakfast containing 25 to 30g fat). Hourly vital sign measurements and serial blood sampling at ~0.5, 0, 1, 2, 4, 6, 8, 12, 18, and 24 hours were obtained for quantification of serum DMA, DMAU, and hormones over 24 hours. ECGs were performed 4 to 6 hours after dosing and before discharge from the Clinical
Research Centers. Subjects returned twice weekly for safety assessments and drug accountability. Mood was assessed using the patient health questionnaire-9 (PHQ-9) questionnaire (21). Sexual function was assessed using a psychosexual daily questionnaire (PDQ) for 7 consecutive days (22). Recovery was assessed at 3 and 6 weeks after the last dose. Subjects exited the study when hormones returned to the normal range (20).

**Laboratory methods**

**Safety laboratories, serum hormones, DMAU, and DMA concentrations**

The respective licensed clinical laboratory at each site quantified the safety laboratory assessments. Serum T and estradiol were measured using liquid chromatography tandem mass spectrometry assays developed and validated at the Endocrine and Metabolic Research Laboratory at LA BioMed. The lower limit of quantification for T is 2 ng/dL (23–25) and 2 pg/mL for estradiol.

Serum LH and FSH levels were measured by an ultrasensitive, highly specific fluoroenzymometric assay from Delta (Wallac Oy, Turku, Finland). The LH assay sensitivity was 0.2 IU/L, with intra-assay and interassay variations of 5.1% and 9.9%, respectively, and cross-reactivity with TSH, FSH, and free α subunit of <1%. The FSH assay sensitivity was 0.2 IU/L, with intra-assay and interassay variations of 5.8% and 8.7% and cross-reactivity with LH and free α subunit of <1% (26, 27).

Serum DMAU and DMA concentrations were measured by liquid chromatography tandem mass spectrometry using a method developed and validated at LA BioMed. The lower limits of quantification for serum DMA and DMAU were 0.5 ng/mL and 1 ng/mL, respectively (18, 19).

**Semen analysis**

Subjects were asked to refrain from ejaculation for 48 hours prior to semen collection. The analysis was performed at individual study sites following the fifth edition of the World Health Organization Laboratory Manual for the Examination of Human Semen (28).

**Adverse events and medication adherence**

Adverse events were collected at each visit and analyzed using the MedDRA subject system. Subjects were provided a log to record breakfast eaten and drug consumed (time and amount), which was reviewed at each visit.

**Outcomes and statistical analyses**

All analyses were performed using SAS (version 9.4; Cary, NC). All subjects receiving placebo across the stages were considered as the all-treated population, defined as all treated subjects who used at least 90% of study medication and had taken their study drug within 1 day of the reported study visit.

Nonparametric Kruskal-Wallis analysis of variance was done to compare the changes in the six groups (placebo, C100, C200, P200, P400, and C400). Wherever \( P < 0.05 \) was noted, further pairwise comparisons were performed using the Mann-Whitney \( U \) test using \( P < 0.01 \) as significant, adjusting for multiple comparisons. Additionally, within-group changes were assessed by the Wilcoxon signed-rank test comparing data from days 1 and 28, with \( P < 0.05 \) considered significant. Suppression of serum LH and FSH was also calculated as percentage of subjects receiving active drug who both gonadotropins were suppressed to <1.0 IU/L.

**Results**

**Research participants**

Two hundred and two research participants were screened, 100 were randomized and received study medication, and 83 completed the study. The study was designed to complete 20 subjects in each dose group; however, castor oil capsule leakage limited full enrollment in the C400 group and powder capsule availability limited it in the P400 group. Among all treated subjects, compliance was 96%, as assessed by drug accountability logs and pill counts. Eighty-two subjects constituted the efficacy-evaluable population. At baseline, there were no differences in subject characteristics across the six treatment groups (Table 1). An online repository (20) summarizes the subject enrollment, disposition, discontinuation, and reasons for discontinuation by treatment group.
### Safety and tolerability

There were no serious adverse events. Adverse events deemed related to drug treatment are presented in an online repository (20). The most common adverse event overall was headache, reported by 13 subjects [5 of 27 (19%) placebo, 8 of 73 (11%) drug]. Nine subjects [1 of 27 (4%) placebo, 8 of 73 (11%) drug] reported decreased libido, and it was significantly more common in the 400-mg groups [6 of 24 subjects (25%)]. Similarly, 3 of 24 (13%) subjects in the 400-mg groups reported erectile dysfunction but none in other groups. Eight men reported acne [3 of 27 (11%) placebo, 5 of 73 (7%) drug; including 4 of 24 (17%) in the 400-mg groups]. In all cases but two, these events were rated “mild.” One instance of decreased libido and one of acne were deemed moderate. Other adverse events reported by >5% of subjects included nasal pharyngitis, upper respiratory tract infection, oropharyngeal pain, and fatigue, none of which were deemed related to drug treatment. All adverse events resolved by study conclusion.

Consistent with the participant-reported decreased libido, mixed-model analysis confirmed a significant effect of DMAU dose on sexual desire (on question 1 of the PDQ; Table 2). However, notably, there were no statistically significant changes in sexual activity (PDQ question 4) or erectile function satisfaction (PDQ question 6). There was also no significant change in mood (total PHQ-9 score) in any treatment group (P = 0.19).

Vital signs (blood pressure, pulse, respirations) were not significantly different in the active treatment groups compared with placebo. Although remaining in the normal range, QTc was lower in all treatment groups.

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### Table 1. Baseline Characteristics of Subjects by Treatment Group (Median and 25th and 75th Percentiles)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>C100</th>
<th>C200</th>
<th>P200</th>
<th>P400</th>
<th>C400</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>26</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>26 (23, 33)</td>
<td>35 (31, 42)</td>
<td>29 (24, 36)</td>
<td>27 (25, 32)</td>
<td>34 (26, 37)</td>
<td>30 (25, 34)</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83 (73, 94)</td>
<td>90 (80, 103)</td>
<td>80 (75, 93)</td>
<td>81 (77, 88)</td>
<td>88 (67, 89)</td>
<td>76 (68, 84)</td>
<td>0.21</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 (22, 27)</td>
<td>30 (26, 31)</td>
<td>26 (24, 29)</td>
<td>25 (23, 26)</td>
<td>27 (22, 28)</td>
<td>24 (22, 27)</td>
<td>0.12</td>
</tr>
<tr>
<td>Serum T, ng/dL</td>
<td>477 (414, 593)</td>
<td>390 (316, 449)</td>
<td>534 (458, 671)</td>
<td>467 (323, 503)</td>
<td>504 (338, 570)</td>
<td>492 (447, 591)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum FSH, IU/L</td>
<td>2.5 (1.7, 4.3)</td>
<td>4.4 (2.4, 4.7)</td>
<td>2 (1.3, 3.1)</td>
<td>2.6 (1.6, 4.1)</td>
<td>2 (1.5, 3.2)</td>
<td>2.7 (2.6, 3.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum LH, IU/L</td>
<td>3 (2.5, 4)</td>
<td>3.6 (3, 4.5)</td>
<td>3.1 (2.2, 4.1)</td>
<td>3.5 (3, 4.8)</td>
<td>3.6 (2.2, 4)</td>
<td>2.6 (1.9, 3)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Only efficacy evaluable population data are included here.

Abbreviation: BMI, body mass index.

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### Table 2. Change in Safety Parameters From D 1 to D 28 by Treatment Group (Median and 25th and 75th Percentiles)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Value</th>
<th>Placebo</th>
<th>C100</th>
<th>C200</th>
<th>P200</th>
<th>P400</th>
<th>C400</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>27</td>
<td>16</td>
<td>18</td>
<td>19</td>
<td>9</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.7 (40, 43)</td>
<td>−1 (−1.8, 0)</td>
<td>1.1 (0, 3)</td>
<td>0 (−0.5, 2)</td>
<td>2 (1.23)</td>
<td>0.4 (−2, 1)</td>
<td>2 (1, 3)</td>
<td>0.007* 0.56</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>17 (13, 24)</td>
<td>−1 (−4, 2)</td>
<td>−4 (−5, 4)</td>
<td>−1 (−3, 4)</td>
<td>1 (−12, 3)</td>
<td>5 (−11.9)</td>
<td>6 (3, 7)</td>
<td>0.15    0.13</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>3 (2.5, 4)</td>
<td>3.6 (3, 4.5)</td>
<td>3.1 (2.2, 4.1)</td>
<td>3.5 (3, 4.8)</td>
<td>3.6 (2.2, 4)</td>
<td>2.6 (1.9, 3)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td>31 (22, 48)</td>
<td>22 (19, 27)</td>
<td>27 (24, 37)</td>
<td>26 (20, 33)</td>
<td>39 (19, 43)</td>
<td>28 (20, 33)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Sperm concentration, million/mL</td>
<td>71 (52, 124)</td>
<td>64 (45, 88)</td>
<td>43 (26, 88)</td>
<td>79 (52, 126)</td>
<td>80 (71, 90)</td>
<td>55 (35, 122)</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

Baseline value is median and 25th and 75th percentile data across all groups on d 1. Note: Data shown is all-treated population. PDQ q1 assessed sexual desire, q4 assessed sexual activity, and q6 assessed erectile function satisfaction.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*P < 0.01 for dose effect on mixed-model analysis. R² value is from mixed-model analysis.

All parameters are measured as change from d 1 to d 28 (difference) except QTC, which is the absolute value on d 28.
compared with placebo, and the mixed-model showed a dose effect (Table 2). HDL-C decreased and weight and hematocrit increased in a statistically significant manner with treatment compared with placebo, with a significant dose effect (Table 2). Changes in liver enzymes and PSA were not statistically significant. There was no difference in the incidence of adverse events between the two formulations C vs P. The mixed-model analysis showed no effect of formulation on changes in safety assessments.

PK of DMAU and DMA

Following oral administration of DMAU with food, peak serum concentrations of DMAU and DMA were achieved 4 to 6 hours later for both formulations [Fig. 1(a) and 1(c); (20)]. By 24 hours, serum DMAU and DMA concentrations were near the lower limit of quantification for most subjects. Despite daily dosing for 28 days, there were no statistically significant differences in the PK parameters on day 1 compared with day 28 for either formulation [Fig. 1(b) and 1(d)]. Average serum concentrations of the prodrug, DMAU, were about 20-fold higher than DMA.

Serum concentrations of DMAU and DMA increased in a dose-dependent manner with oral administration of both formulations; however, this reached statistical significance only when the C400 group was compared with the lower dose groups. DMAU and DMA serum Cmax, Cavg, and AUC were numerically higher in the C group compared with the P group at each individual dose, although these differences were not statistically significant (20).

Pharmacodynamic effects on serum gonadotropins, T, and estradiol

Daily DMAU administration resulted in marked suppression of serum LH and FSH [Fig. 2(a) and 2(b); Table 3]. All subjects in the P400 group and 12 of 13 subjects (92%) in the C400 group achieved suppression of LH and FSH (to <1 IU/L). Gonadotropin suppression was less complete in the C200 and P200 groups, with 9 of 14 (64%) and 9 of 13 (69%) men suppressing to <1 IU/L for both LH and FSH, and least effective in the C100 (54%) group. Serum LH and FSH were significantly lower on day 28 compared with day 1 in all active treatment groups (P < 0.001 for Cavg and AUC) except for the C100 group.

T suppression was achieved by day 7 of treatment and sustained throughout the 28-day treatment period [Fig. 2(c)]. Serum T concentrations (Cavg) were markedly suppressed (median <24 ng/dL) in all treatment groups (P < 0.001; Table 3). Average serum T concentrations were lower, the range was narrower, and a higher percentage of subjects achieved suppression to castrate levels (<50 ng/dL) in both the 400-mg groups compared with the lower-dose groups (Table 3). In parallel with the suppression of serum T, serum free T levels were also suppressed to below the reference range in all the treatment groups [Fig. 2(d)]. Average serum estradiol was suppressed by day 7 of treatment across treatment groups (P < 0.001) and to <5 pg/mL in the 400-mg group [Fig. 2(e)]. Serum SHBG levels were suppressed in all dose groups to the lower limit of the reference range [Fig. 2(f)]. Despite the observed suppression of T, LH, and FSH, sperm concentration was not significantly decreased after 28 days of treatment (20).

Discussion

Male hormonal contraception relies on the sustained suppression of gonadotropins and endogenous T (29) by the administration of exogenous androgens. In this phase 1b study, we demonstrate that daily oral DMAU, at doses of 100 to 400 mg, is well tolerated by men when taken for 28 consecutive days. Daily oral DMAU rapidly and potently suppressed gonadotropin secretion and endogenous T production after 7 to 10 days of administration. These properties are critical for an effective male hormonal contraceptive and consistent with binding of DMA to both androgen and progesterone receptors (15–17) in the hypothalamus and pituitary to suppress GnRH, LH, and FSH secretion. Previous studies of oral steroid delivery for the purposes of male contraception have required two separate agents and/or multiple daily doses (30, 31); thus, DMAU, a single agent, represents a significant step forward in male hormonal contraceptive development.

The PD effects of DMA on serum T concentrations and gonadotropin secretion showed a dose effect, with the most profound suppression noted in the 400-mg dose groups. Using established LH and FSH assays (23–25), all but one subject within the 400-mg dose groups suppressed both gonadotropins to <1.0 IU/L, a threshold level that has been shown to be associated with sperm suppression to <1 million/mL in longer studies of prototype male hormonal contraceptives (32). Despite profound T suppression, most men did not complain of symptoms of acute androgen deficiency such as hot flashes, suggesting that the androgenic effects of DMA at the doses studied may approximate those of endogenous T. The participants who did complain of decreased libido or erectile dysfunction were concentrated among the 400-mg groups. Consistent with this finding, prospective tracking using the PDQ demonstrated a dose-dependent decrease in sexual desire, although this was not true for decreases in sexual activity and satisfaction with erectile
Figure 1. Pharmacokinetic parameters of DMAU and DMA by treatment group. (a) Serum DMAU concentrations over 24 h on d 1 and 28, trough DMAU concentrations measured twice-weekly during treatment and at recovery visits. (b) Average serum DMAU concentrations (C Average) and maximum serum DMAU concentrations (C Max) on d 1 and 28. (c) Serum DMA concentrations during 24-h stays on d 1 and 28 along with trough DMA concentrations twice weekly during treatment and at recovery visits. (d) Average Serum DMA concentrations and maximum serum DMA concentrations on d 1 and 28. Striped bars represent powder formulation in (b). In (b), serum DMAU concentrations are shown in logarithmic scale to fit full range of values. All values are means ± SEM.
Figure 2. Serum sex hormone concentrations by treatment group. (a) Serum LH concentrations during 24-h stays on d 1 and 28, at twice-weekly visits during treatment, and during recovery. (b) Serum FSH concentrations during 24-h stays on d 1 and 28 along with FSH concentrations at twice-weekly visits during treatment and during recovery. (c) Serum total T concentrations during 24-h stays on d 1 and 28 along with T concentrations at twice-weekly visits during treatment and during recovery. (d) Calculated free T concentrations during 24-h stays on d 1 and 28 along with calculated free T concentrations at twice-weekly visits during treatment and during recovery. (e) Serum estradiol (E2) concentrations on d 1 and 28 along with estradiol concentrations at twice-weekly visits during treatment and during recovery. (f) Serum SHBG concentrations on d 1 and 28 along with SHBG concentrations at twice-weekly visits during treatment and during recovery. Dashed gray lines represent normal reference range for each hormone. LLOQ, lower limit of quantification for the assay. All values are means ± SEM.
study, the conversion from prodrug to active compound was comparable between formulations. Lastly, the fat content of the food consumed prior to dosing in this study was half that of the single-dose study (25 to 30 g vs 56 to 67 g) and more consistent with a “normal” Western diet. Despite this difference, we observed comparable concentrations of DMA and significant pharmacodynamic effects, suggesting this lower fat content is sufficient to ensure effective absorption of the prodrug DMAU. These observations are consistent with studies of oral T undecanoate in hypogonadal men (34).

We demonstrate that 28 days of treatment with DMAU in the doses tested is well tolerated. In contrast to potential effects on libido, other significant changes associated with DMAU are likely attributable to its androgenic action. Overall, subjects did experience weight gain with treatment. The maximal increase in weight was <5% of baseline body weight, the metabolic consequences of which are not clear in this otherwise healthy population. Furthermore, we did not explore whether weight changes were due to gains in lean or fat mass, which will be important in future, longer-term studies given the androgenic effects of DMAU on body composition in animals (15). Because DMAU is not aromatized, it is possible that the relative estrogen deficiency, that men administered the higher doses experience, results in increases in fat mass, while at the same time, the androgenicity of DMAU might increase lean mass. Both of these will lead to increased weight. In longer studies, we plan to investigate DMAU on body composition. Small increases in hematocrit were noted in the treatment groups; however, most of the participants still had values well within the normal range, and the increase noted was not clinically meaningful. Subjects receiving oral DMAU experienced a drop in serum HDL-C concentrations of approximately 6 to 15 mg/dL, which is anticipated because of the first-pass effect through the liver. Oral DMAU may decrease HDL-C via androgen-induced increases in lipoprotein lipase activity, resulting in catabolism of HDL-C and reduced serum concentrations (35, 36). In addition, nonaromatizable androgens, such as DMA, are more likely to lower HDL-C than

function. These results suggest a need for further dose refinement for optimal tolerability of DMAU. Of note, the PHQ-9 did not demonstrate any significant change in mood parameters.

We did not observe a significant decrease in sperm concentrations despite marked suppression of T and gonadotropin production with DMAU administration. However, this was not unexpected given the length of treatment of 28 days, the 72 days required for the completion of spermatogenesis in men, and that maximal suppression of T production was not observed until day 7 of treatment. Interestingly, 4 of 59 men in the treatment groups did achieve sperm concentrations of <5 million/mL at 28 days, whereas none did in the placebo group. The effectiveness of DMAU in suppression of spermatogenesis is currently being studied in a longer-term study. In studies of injectable androgen plus progesterin combinations (33), sperm concentrations begin to fall after 4 weeks of treatment, but require at least 6 to 8 weeks to demonstrate marked suppression of spermatogenesis to levels compatible with contraceptive efficacy.

The pharmacokinetic profiles of DMAU and DMA noted in this study were similar to the results obtained in our previous single dose-escalation study (18, 19). In this study, peak serum concentrations of DMAU and DMA were reached 4 hours following dosing, and trough levels occurred around the 24-hour mark, suggesting once-daily dosing might be effective. There was a trend toward a dose-responsive increase in serum drug concentrations when comparing the different dose groups; however, given small sample sizes, these differences were not statistically significant. Contrary to our single-dose study (19), in this study, the castor oil formulation at each dose had slightly better pharmacokinetic parameters (Cmax, Cavg, and AUC) when compared with the powder formulation, but these differences were not statistically significant. Our previous study demonstrated greater conversion from DMAU to DMA with the castor oil formulation compared with the powder (19); but, in this study, the conversion from prodrug to active compound

Table 3. Serum Hormone Concentrations (Median and 25th and 75th Percentiles) by Group on D 28 of Treatment

<table>
<thead>
<tr>
<th>Parameter (Cavg)</th>
<th>Placebo (n = 23)</th>
<th>C100 (n = 13)</th>
<th>C200 (n = 14)</th>
<th>P200 (n = 13)</th>
<th>P400 (n = 6)</th>
<th>C400 (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum LH, IU/L</td>
<td>3.3(2.8, 4.9)</td>
<td>0.8 (0.5, 3.7)</td>
<td>0.6 (0.2, 2.3)</td>
<td>0.5 (0.2, 1.0)</td>
<td>0.2 (0.2, 0.2)</td>
<td>0.2 (0.2, 0.2)</td>
</tr>
<tr>
<td>Serum FSH, IU/L</td>
<td>2.5(1.7, 4.1)</td>
<td>1.0 (0.6, 5.1)</td>
<td>0.4 (0.2, 1.1)</td>
<td>0.5 (0.2, 1.0)</td>
<td>0.2 (0.2, 0.2)</td>
<td>0.2 (0.2, 0.2)</td>
</tr>
<tr>
<td>Serum T, ng/dL</td>
<td>474(421, 549)</td>
<td>15.7 (8, 187.5)</td>
<td>24.3 (11.9, 70.2)</td>
<td>12.6 (7.5, 29.9)</td>
<td>7.0 (4.5, 9.9)</td>
<td>8.3 (5.2, 14.2)</td>
</tr>
<tr>
<td>Subjects with T &lt;50 ng/dL, n(%)</td>
<td>0 (0)</td>
<td>6 (46.2)</td>
<td>9 (64.3)</td>
<td>10 (76.9)</td>
<td>6 (100)</td>
<td>12 (92.3)</td>
</tr>
</tbody>
</table>

Only efficacy-evaluable population data are included here. For serum T, FSH, and LH, Cavg was calculated for each subject. Then medians and 25th and 75th percentiles were calculated from those values by treatment group.
androgens that can be converted to estradiol (37). However, the clinical implications of such changes in HDL-C relative to cardiovascular risk are uncertain (38). Reassuringly, low-density lipoprotein cholesterol concentrations were unchanged with DMAU. Longer-term studies of DMAU and its impact on lipids, including on measures of HDL function, are warranted. QTc decreased in participants on drug compared with placebo but still remained well above the threshold considered “short.” This is a known androgenic effect that has been shown in studies of T replacement (39). The clinical implications, if any, of such a small magnitude decrease in QTc are unclear. For all of these changes (in weight, hematocrit, HDL-C, and QTc), a dose effect was noted in our analysis. This is important as drug development of DMAU proceeds further, as we can fine-tune a dose at which we can optimize the pharmacodynamic effects of the drug while minimizing the side effect profile.

The reported adverse events were not higher in the active drug population compared with placebo, with the exception of decreased libido (eight drug vs one placebo). Notably, six of the eight subjects who reported decreased libido received the 400-mg dose, and this was also corroborated by a dose effect on sexual desire on the PDQ. Reassuringly, we did not observe any significant change in sexual activity, erection, or mood using the PDQ and PHQ-9; thus, the clinical significance of these complaints is unclear. Decreases in libido could reflect greater progestogenic rather than androgenic effects of DMAU centrally. In addition, recent studies have highlighted the importance of estradiol in maintaining sexual desire and function (40); thus, the suppression of estradiol in consequence of reduced T production may also impact libido. Larger, placebo-controlled, longer-term studies are required to more clearly define the frequency and magnitude of any potential effects on sexual health associated with DMAU. Such studies will also be necessary to assess other potential physiologic changes, such as effects on bone, energy, and mood, that may arise from changes in endogenous androgen and estrogen production resulting from DMAU administration. In subsequent longer studies of DMAU, we intend to monitor bone turnover markers, bone mineral density, and body composition closely to delineate any changes that might result from alterations to the balance of T and estradiol levels.

In conclusion, daily oral administration of DMAU for 28 days in healthy men is well tolerated. Doses of ≥200 mg suppress serum T, LH, and FSH, properties consistent with an effective male contraceptive without significant changes in sexual function or signs of liver toxicity. Further studies of oral DMAU are warranted to determine whether longer-term daily administration will suppress sperm production to levels consistent with effective male contraception.

Acknowledgments

We thank all the study participants, study coordinators/nurses Kathryn Torrez Duncan (University of Washington) and Xiaodan Han, Elizabeth Ruiz, and Lauryn Maes (Los Angeles Biomedical Research Institute and Harbor UCLA Medical Center) for their work conducting this study, Abbey Townsend, Sarah Godfrey, Jerry Kinard, and Tricia Brady from Health Decisions for assistance with monitoring, Clint Dart from Health Decisions for input in data analysis, and Drs. Alicia Christy and Mark Payson from the National Institutes of Health for medical monitoring of the study.

Financial Support: This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the Robert McMillen Professorship in Lipid Research (to S.T.P.), the National Institute of Diabetes, Digestive, and Kidney Disease through the Diabetes, Obesity, and Metabolism Training Program (T32 DK 007247; to A.T.), and the National Heart, Lung, and Blood Institute (K24 HL138632; to P.Y.L.).

Clinical Trial Information: ClinicalTrials.gov no. NCT01382069 (registered 27 June 2011).

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Disclosure Summary: R.S. is a consultant for Clarus and Antares and receives grant support from Clarus. C.W. receives grant support from Clarus, Antares, and TesoRx. J.K.A. and S.T.P. are consultants for Clarus. E.H. is an employee of Health Decisions. D.L.B. is a Principal Investigator on a cooperative research and development agreement with HRA Pharma. The remaining authors have nothing to disclose.

References


