A multicentre study investigating subcutaneous etonogestrel implants with injectable testosterone decanoate as a potential long-acting male contraceptive


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BACKGROUND: The combination of etonogestrel implants with injectable testosterone decanoate was investigated as a potential male contraceptive. METHODS: One hundred and thirty subjects were randomly assigned to three treatment groups, all receiving two etonogestrel rods (204 mg etonogestrel) and 400 mg testosterone decanoate either every 4 weeks (group I, n = 42), or every 6 weeks (group II, n = 51) or 600 mg testosterone decanoate every 6 weeks (group III, n = 37) for a treatment period of 48 weeks. RESULTS: One hundred and ten men completed 48 weeks of treatment. Sperm concentrations of <1 × 10^6/ml were achieved in 90% (group I), 82% (group II) and 89% (group III) of subjects by week 24. Suppression was slower in group II, which also demonstrated more frequent escape from gonadotrophin suppression than groups I and III. Peak testosterone concentrations remained in the normal range throughout in all groups. Mean trough testosterone concentrations were initially subphysiological but increased into the normal range during treatment. Mean haemoglobin levels increased in group I, and a non-significant increase in weight and decline in high-density lipoprotein cholesterol was observed in all groups. Fourteen subjects discontinued treatment due to adverse events. CONCLUSIONS: Subcutaneous etonogestrel implants in combination with injectable testosterone decanoate resulted in profound suppression of spermatogenesis that could be maintained for up to 1 year. Efficacy of suppression was less in group II, probably due to inadequate testosterone dosage. This combination has potential as a long-acting male hormonal contraceptive.

Key words: etonogestrel/gestogen/male contraceptive/spermatogenesis/testosterone decanoate

Introduction

The concept of hormonal male contraception is based upon the administration of exogenous steroid to suppress pituitary gonadotrophins, with the subsequent suppression of spermatogenesis (Anderson and Baird, 2002; Nieschlag et al., 2003; Kamischke and Nieschlag, 2004; Wang and Swerdloff, 2004). Earlier approaches involved the administration of androgen alone (World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990, 1996). However, low rates of spermatogenesis were maintained in approximately one third of Caucasians, with the resulting risk of pregnancy. Furthermore, supraphysiological androgen levels resulted in significant side-effects on skin, haematopoiesis and serum lipoproteins (Wu et al., 1996). The administration of a second agent, such as a progestogen, improves the degree of spermatogenic suppression and permits lowering of the dose of testosterone to nearer physiological replacement (Bebb et al., 1996; Handelsman et al., 1996; Meriggiola et al., 1996, 2002). Several progestogens have been investigated, including levonorgestrel (Bebb et al., 1996), cyproterone acetate (Meriggiola et al., 1996, 1998), medroxyprogesterone acetate (Knuth et al., 1989; World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1993; Handelsman et al., 1996; Turner et al., 2003), norethisterone (Kamischke et al., 2001, 2002) and desogestrel (Wu et al., 1999; Anawalt et al., 2000; Kinniburgh et al., 2002). Results with desogestrel have been promising, with near universal suppression of spermatogenesis.

Etonogestrel, the active metabolite of desogestrel, is now licensed as a long-acting implant preparation for use as a female contraceptive (Implanon®). In addition to convenience and
optimum levels of compliance, administration as an implant may confer advantages over an oral preparation, allowing dose-sparing and avoiding liver exposure by bypassing first-pass metabolism, thus minimising adverse metabolic effects. This has indeed been demonstrated in a recent study using two 68 mg etonogestrel implants with depot testosterone (Anderson et al., 2002a). Despite using lower exposure to etonogestrel in comparison with oral desogestrel, similar efficacy in suppression of spermatogenesis was observed with reduced non-reproductive effects (Kinniburgh et al., 2002). In that study, suppression of spermatogenesis was greater with two implants than with one (75 versus 64% azoospermia). We therefore hypothesized that suppression of spermatogenesis may be improved by further increasing this dose by 50%, and two larger implants (each containing 102 mg etonogestrel) were administered in the present study.

The lack of availability of a convenient long-acting injectable testosterone preparation has been a major obstacle to the development of hormonal male contraception. Previous studies with testosterone enanthate relied on weekly injection intervals. Not only may this be unacceptable to volunteers, but supraphysiological testosterone peaks were observed as well. Testosterone decanoate (TD) is one of the testosterone esters contained in Sustanon®, which has been used for several years in the treatment of hypogonadism. Preliminary data demonstrated that 400 mg administered every 4 weeks with etonogestrel implants resulted in good spermatogenic suppression (Anderson et al., 2002b). We therefore further explored the optimal dose of this androgen in three administration regimens: 400 mg every 4 weeks (group I), 400 mg every 6 weeks (group II) and 600 mg every 6 weeks (group III).

This combination of TD with etonogestrel implants was investigated in a Phase IIb multicentre trial. The primary objective was to assess its effects on the suppression of spermatogenesis in the three treatment groups. Secondary objectives included evaluation of the suppression of gonadotrophins, the pharmacokinetics of the TD regimes, and safety monitoring.

Subject and methods

Subjects
One hundred and thirty subjects were recruited from six centres in Europe and the USA. The inclusion criteria included age ≥18 and ≤45 years; mentally and physically healthy; BMI ≥18 and ≤32 kg/m²; normal semen analysis on two occasions (examination within 60 min, based on WHO criteria (World Health Organization, 1999) for sperm concentration and WHO criteria or local reference ranges for sperm motility and morphology); normal hormone (FSH, LH and testosterone) concentrations based on local reference ranges; and willingness to provide written informed consent. Men in a sexual relationship at study inclusion had to be willing to use a reliable form of contraception. Each subject gave informed written consent. Ethical approval was received from each centre’s local Ethical Review Committee.

Medication
Etonogestrel implants were 6 cm long and each contained 102 mg etonogestrel (Organon, Oss, The Netherlands). They were inserted under local anaesthetic under the skin of the medial aspect of the non-dominant upper arm and removed following the 48-week treatment period. Testosterone decanoate (3-oxo-androst-4-en-17β-yl decanoate, TD) at a concentration of 200 mg/ml was administered by deep intramuscular injection on the day of etonogestrel implant insertion. Subjects re-attended every 4 or 6 weeks (±3 days) thereafter, depending on the treatment group, for subsequent injections.

Study design
The study was an open-label randomized multicentre trial investigating the suppressive effects of etonogestrel subcutaneous implants with injectable TD on spermatogenesis. The study also aimed to investigate the suppressive effect of these regimes on gonadotrophins as well as the safety and pharmacokinetics of this regime. Subjects were randomized into three treatment groups. All groups received two etonogestrel implants. Group I received 400 mg TD every 4 weeks, group II 400 mg TD every 6 weeks and group III 600 mg TD every 6 weeks.

Subjects were reviewed every 4 weeks in the first 24 weeks of the treatment phase and during recovery. During weeks 24–48, subjects attended every 4 or 6 weeks depending on the treatment group. At each visit, subjects submitted a semen sample and safety assessments were performed, checking routine laboratory parameters, including prostate-specific antigen, inspection of the implant site, and recording of adverse events and any concomitant medications. Physical examination was performed every 12 weeks (with andrological examination assessing testes, and prostate assessment by digital examination or transrectal ultrasonography at weeks 24, 48 and final assessment). During the treatment phase, venepuncture was performed for hormone measurements at weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, 24, 36 and 48 in the 4-week group and at weeks 1, 2, 4, 6, 12, 13, 14, 16, 18, 24, 36 and 48 in the 6-week group. At most of these time points, trough levels were measured because blood sampling occurred prior to the TD injection. Peak testosterone levels were measured at weeks 1 and 2 (after the first injection) and at weeks 13 and 14 after the third (4 weeks group) and second (6 weeks group) injections. Etonogestrel concentrations were assessed at weeks 1, 2, 4, 8, 12, 24, 36 and 48. During the follow-up phase, subjects attended every 4 weeks until week 16, when they underwent final assessment if sperm concentration was greater than 20 × 10⁶/ml or they continued until week 24. Any subject not recovered at week 24 entered an extended phase of follow-up of indefinite duration.

Semen analysis
Semen samples were submitted after 2–7 days of abstinence and assessed for semen volume, sperm concentration, morphology and motility by WHO criteria. Motility was assessed within 60 min of ejaculation. Azoospermia was confirmed by centrifugation of the entire ejaculate according to WHO criteria. Motility and morphology were not assessed during treatment because, as a result of profound suppression, there were insufficient sperm to enable accurate assessment.

Assays
Blood samples were separated by centrifugation and serum was stored at −20°C prior to shipping to a central laboratory (Organon) for assay. Serum gonadotrophins and sex hormone-binding globulin (SHBG) were determined by highly sensitive immunofluorometric assays (Delfia; Perkin Elmer). For FSH and LH respectively, assay sensitivities were 0.25 IU/l and 0.52 IU/l and intra- and inter-assay coefficients of variation (CVs) 1.9−7.6% and 2.6−4.9%. The lower limit of quantification for SHBG was 6.25 nmol/l, with intra, and inter-assay CVs of 3.2−5.0%. Testosterone was determined by capillary gas chromatography–mass spectrophotometry with an assay sensitivity of 0.35 nmol/l.
and intra- and inter-assay CVs of 4.5–21.9%. Etonogestrel was measured by in-house radioimmunoassay (Organon) with a lower limit of quantification of 30.0 pg/ml. Samples were analysed locally for routinely haematological and biochemical values, including prostate-specific antigen, cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol at 12 weekly intervals.

**Behavioural assessment**

Sexual function and mood were investigated before treatment, at weeks 12, 24, 36 and 48 of treatment, week 4 of follow-up and at final assessment. Sexual function was assessed by means of the Derogatis Interview for Sexual Functioning—Self Report (DISF-SR) (Derogatis, 1997). Questions on mood were assessed with an unvalidated questionnaire, and included questions on irritability, depression, fatigue and aggression. Moreover, some questions on local tolerance of the injections were asked.

**Statistical analysis**

Statistical analysis was performed by Organon. The efficacy results of the intention-to-treat group are presented. Frequencies of subjects with suppression of sperm concentration to a specified level and a certain time point were compared by means of Fisher’s exact test with Bonferroni correction. Survival analyses were performed and, because of departure from the proportional hazards assumption, log-rank tests were used for comparison. Mean values of sperm and hormone concentrations, biochemistry, haematology and physical parameters were analysed by repeated measures analysis of variance and paired t-tests using Tukey’s multiple comparison procedure. P-values presented for hormones, biochemistry, haematology and physical parameters were not corrected for multiple testing. However, multiplicity was taken into account by regarding a result statistically significant if $P < 0.0001$ (which would correspond to Bonferroni corrected $P$-values below 0.05). Values were expressed as the arithmetical mean ± SEM. Hormone concentrations below the detection level were allocated the value of half of the lower limit of detection.

**Results**

**Subjects**

Pretreatment values for the subjects in each group are shown in Table I. There were no significant differences in age, BMI, sperm density and LH, FSH and testosterone concentrations between the three treatment groups.

One hundred and thirty subjects were randomized to the three groups, as follows: group I ($n = 42$), II ($n = 46$) and III ($n = 42$). Five subjects in group III were treated erroneously with 400 mg TD instead of 600 mg TD and therefore were analysed in group II, resulting in 42, 51 and 37 subjects in the respective groups. In total, 119 subjects completed 24 weeks of treatment and 110 subjects completed the treatment period (84.6%); 33 subjects in group I (78.6%), 43 subjects in group II (84.3%) and 34 subjects in group III (91.9%). Overall, compliance with study medication was good, with 100% compliance with TD injections in group II and almost 99% compliance in the other two treatment groups.

**Sperm concentrations**

All men demonstrated a profound suppression of spermatogenesis (Figure 1a, Table II). By week 24, azoospermia was achieved in 28 (71.8%), 25 (55.6%) and 24 (68.6%) subjects in groups I, II and III respectively (Figure 1b). The extents of suppression in groups I and III at week 24 were similar and appeared greater than the suppression demonstrated by group II, although there was no statistically significant difference between suppression at weeks 16 or 24. At week 24, sperm concentrations had fallen to $< 1 \times 10^6$ in 89.7% (group I), 82.2% (group II) and 88.6% (group III) of subjects (Figure 1c). Four subjects in group I, five in group II and three in group III maintained sperm concentrations of $> 3 \times 10^5$ at week 24; all but four of these proceeded to concentrations close to azoospermia by week 48. Sperm concentrations further decreased in all groups after week 24, with azoospermia achieved in 81% (group I), 78% (group II) and 85% (group III) of subjects by the end of the treatment period. Once subjects were azoospermic, this was maintained at all subsequent visits in 56% (20/36 subjects, group I), 72% (26/36 subjects, group II) and 80% (24/30 subjects, group III) of subjects. Using the threshold of $< 1 \times 10^6$, faster suppression of spermatogenesis was observed in groups I and III, the median number of days to reach this threshold being 59 (group I), 84 (group II) and 61 (group III) respectively. However, suppression to azoospermia occurred in a similar time for all three groups, the median number of days to reach this being 114 (group I), 118 (group II) and 113 (group III).

Overall, 102 (81%) men recovered within 24 weeks of follow-up. At that time, 77% (group I), 82% (group II) and 83% (group III) of subjects had reached normal sperm concentration by WHO criteria ($> 20 \times 10^6$) in at least one sample. All of the remaining subjects except three recovered spermatogenesis within 52 weeks. Two of them recovered within 69 weeks and one subject discontinued follow-up before a semen sample of $20 \times 10^6$ ml was obtained because his partner was pregnant (last sperm concentration was 18.3 $\times 10^6$ ml at 69 weeks of follow-up). Recovery was faster in group II (400 mg/6 weeks) than in groups I and III (at week 24; $P = 0.01$), with a median time to recovery of approximately 130 days in all treatment groups (Figure 2).

**Reproductive hormones**

Profound suppression of both LH and FSH was observed in all three treatment groups (Figure 3a and b). Gonadotrophin concentrations were suppressed to the level of detection by week 4 in the majority of subjects and remained suppressed throughout the treatment period. Suppression was, however, less consistent in the 400 mg/6 weeks group (group II), with more frequent fluctuation or ‘escape’ being observed. Recovery of both LH

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**Table I.** Pretreatment values of subjects in the three treatment groups

<table>
<thead>
<tr>
<th>Pretreatment value</th>
<th>Group I ($n = 41$)</th>
<th>Group II ($n = 51$)</th>
<th>Group II ($n = 37$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.8 ± 0.9</td>
<td>31 ± 0.8</td>
<td>31.5 ± 1.1</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 0.4</td>
<td>24.7 ± 0.4</td>
<td>25.0 ± 0.5</td>
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<tr>
<td>LH (IU/l)</td>
<td>3.6 ± 0.3</td>
<td>3.6 ± 0.2</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>3.4 ± 0.3</td>
<td>3.2 ± 0.2</td>
<td>3.6 ± 0.3</td>
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<tr>
<td>Testosterone (nmol/l)</td>
<td>19.2 ± 1.3</td>
<td>18.7 ± 0.7</td>
<td>20.5 ± 1.3</td>
</tr>
<tr>
<td>Sperm density ($\times 10^6$/ml)</td>
<td>72.6 ± 6.6</td>
<td>90.6 ± 7.9</td>
<td>75.2 ± 7.7</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
Figure 1. (a) Sperm concentrations during etonogestrel/TD treatment and recovery. Note the log scale on the ordinate. Data are mean ± SEM. Group I, 400 mg TD/4 weeks; group II, 400 mg TD/6 weeks; group III, 600 mg TD/6 weeks. (b) Achievement of azoospermia and (c) sperm concentration of $<1 \times 10^6$/ml during treatment. Panels b and c show cumulative event rates assessed during treatment by Kaplan–Meier estimation. Treatment groups are indicated in the legends.
and FSH was faster in group II than in groups I and III ($P < 0.05$ at 4 weeks of follow-up), with no significant difference in recovery between groups I and III. There were no statistically significant differences between groups at the end of follow-up or when comparing final visit with pretreatment gonadotrophin concentrations.

**Testosterone**

Fluctuations in testosterone concentrations were observed, in keeping with the scheduling of TD injections (Figure 4). Mean peak testosterone concentrations remained within the physiological range (9.85–35.57 nmol/l) for all groups throughout the treatment period. Mean trough testosterone concentrations gradually increased over the time-course of the study, and were initially subphysiological in all three treatment groups (Figure 4). In group II, mean trough testosterone concentrations remained below the physiological range until between week 24 and 36, whereas in groups I and III mean trough testosterone concentrations were in the normal range between week 12 and 16.

**Other hormones**

Peak mean etonogestrel concentrations were measured 1 week after insertion of the implants and demonstrated similar concentrations in all three treatment groups, of approximately 800–900 pg/ml. Thereafter, there was a gradual decline to approximately 300 pg/ml after 48 weeks of treatment.

**Biochemistry and haematology**

Serum SHBG concentrations decreased by approximately 30% within 8 weeks of treatment in all three treatment groups, remaining so until the end of treatment and returning to baseline.
concentrations thereafter. There was a non-significant decline in total cholesterol (approximately 4%) and HDL cholesterol (approximately 15%) in all groups returning to baseline levels following treatment (Table III). Mean haemoglobin concentrations increased in all groups (group I, 5%; group II, 2%; group III, 4%) during treatment, reaching statistical significance when compared with baseline in group I at 48 weeks ($P < 0.0001$), and returning to baseline levels at the final follow-up visit. A small increase in mean haematocrit was also observed in groups I (4%) and III (1%) during treatment; values returned to baseline thereafter, although this was statistically not significant. No relevant changes in other parameters were observed (Table III).

**Physical examination and behaviour**

Testicular volume decreased by approximately 25% in all groups during treatment, returning to pretreatment volumes during the recovery phase (Table IV). There was no significant change in prostate volume, prostate-specific antigen or blood pressure throughout the study period. There was a slight increase in weight (5% in group I, 3.5% in group II and 5% in group III) that did not reach statistical significance. There was no significant change in overall mood scores across treatment groups throughout the study. There were no changes in the overall scores from the Derogatis Interview for Sexual Function throughout treatment or follow-up. Similarly, there were no differences in mean subscores for different DISF-SR functions.

**Discontinuations and side-effects**

Overall, 20 subjects discontinued the study in the respective groups as follows: nine in group I, eight in group II and three in group III. The most frequent reason for discontinuation was an adverse event (14 subjects, 10.8%), other reasons being non-compliance with the protocol or moving to another area. In group III, only one subject discontinued due to an adverse event, which was impotence. One other subject discontinued in group II due to impotence. Other adverse events that led to discontinuation were: aggressive reaction (with or without nervousness or emotional lability) (3); implant complication (2); depression (2); emotional lability (2); arthralgia (1); laryngitis (1); and myocarditis (1).

Four of the seven subjects with emotional events discontinued prior to week 24 of treatment.

Among the possible side-effects that did not lead to discontinuation, the most frequently reported were acne and increased sweating, mood changes, weight increase, and mild reactions related to implant insertion or removal. Most of the latter events concerned mild itching, pain, swelling or excess fibrous tissue, which complicated removal.

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**Figure 3.** (a) Serum LH and (b) FSH concentrations during etonogestrel/TD treatment and recovery. Data are mean $\pm$ SEM. Treatment period is indicated by a double bar. Group I, 400 mg/4 weeks; group II, 400 mg/6 weeks; group III, 600 mg/6 weeks.

**Figure 4.** Serum testosterone concentrations (nmol/l) during etonogestrel/TD treatment and recovery. Data are mean $\pm$ SEM. Treatment period is indicated by double bars and normal ranges by broken lines. Group I, 400 mg/4 weeks; group II, 400 mg/6 weeks; group III (600 mg/6 weeks).
### Table III. Haematological and biochemical parameters during treatment and final visit of the follow-up phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group I (400 mg/4 weeks)</th>
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<th>Group II (400 mg/6 weeks)</th>
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<th>Group III (600 mg/6 weeks)</th>
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<td>Haematocrit</td>
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<td>Cholesterol (mmol/l)</td>
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<td>HDL cholesterol (mmol/l)</td>
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<td>14.9 ± 1.2</td>
<td>17.3 ± 1.3</td>
<td>13.8 ± 1.0</td>
<td>14.5 ± 0.9</td>
<td>13.9 ± 0.8</td>
<td>15.9 ± 1.1</td>
<td>13.8 ± 0.9</td>
<td>15.9 ± 1.3</td>
<td>15.5 ± 1.4</td>
<td>15.8 ± 1.3</td>
<td>15.2 ± 1.4</td>
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<td></td>
</tr>
</tbody>
</table>

Data are mean ± SEM for AST group. *Statistically significant (P < 0.0001) compared with baseline. There were no statistically significant differences between the three groups at any treatment point.

GGT = γ-glutamyl transpeptidase.

### Table IV. Clinical parameters at baseline during treatment and final visits in the follow-up phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group I (400 mg/4 weeks)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Group II (400 mg/6 weeks)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Group III (600 mg/6 weeks)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week</td>
<td>0</td>
<td>24</td>
<td>48</td>
<td>Final</td>
<td>0</td>
<td>24</td>
<td>48</td>
<td>Final</td>
<td>0</td>
<td>24</td>
<td>48</td>
<td>Final</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.0 ± 1.6</td>
<td>81.7 ± 1.5</td>
<td>82.9 ± 1.7</td>
<td>80.0 ± 1.4</td>
<td>79.4 ± 1.7</td>
<td>81.9 ± 1.8</td>
<td>82.0 ± 1.9</td>
<td>81.5 ± 1.6</td>
<td>79.3 ± 1.7</td>
<td>83.3 ± 1.7</td>
<td>83.2 ± 1.9</td>
<td>81.4 ± 1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>18.6 ± 1.0</td>
<td>19.6 ± 1.0</td>
<td>19.6 ± 1.3</td>
<td>18.2 ± 1.0</td>
<td>17.7 ± 1.0</td>
<td>18.6 ± 1.2</td>
<td>17.9 ± 0.7</td>
<td>17.1 ± 0.9</td>
<td>19.2 ± 1.1</td>
<td>19.6 ± 1.0</td>
<td>18.6 ± 1.1</td>
<td>17.3 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prostate-specific</td>
<td>0.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.0</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antigen (ng/ml)</td>
<td>Mean testicular</td>
<td>22.6 ± 0.7</td>
<td>17.0 ± 0.8</td>
<td>16.4 ± 0.9</td>
<td>22.4 ± 0.9</td>
<td>24.9 ± 0.7</td>
<td>18.7 ± 0.8</td>
<td>17.8 ± 0.8</td>
<td>24.3 ± 0.8</td>
<td>24.8 ± 0.7</td>
<td>17.4 ± 0.9</td>
<td>16.2 ± 0.9</td>
<td>23.0 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>volume (ml)</td>
<td>Overall DISF score</td>
<td>103.2 ± 2.4</td>
<td>103.0 ± 3.0</td>
<td>102.3 ± 3.4</td>
<td>97.8 ± 2.7</td>
<td>101.7 ± 2.2</td>
<td>102.3 ± 2.8</td>
<td>100.8 ± 2.7</td>
<td>96.3 ± 3.1</td>
<td>103.5 ± 2.5</td>
<td>107.3 ± 3.0</td>
<td>107.9 ± 3.3</td>
<td>103.3 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SEM for the AST group. *Statistically significant from baseline (P < 0.0001). DISF = Derogatis Interview for Sexual Functioning—Self-Report.
Discussion

The combination of etonogestrel implants and injectable TD resulted in profound suppression of spermatogenesis, comparable to other approaches using a combination of androgen and progestogen for male hormonal contraception (Anderson and Baird, 2002; Nieschlag et al., 2003). In this study, comparatively large numbers of subjects were studied for a longer treatment period of 48 weeks, which has been investigated in only a few studies to date (Gu et al., 2003; Turner et al., 2003; Brady et al., 2004). Overall, azoospermia was achieved by 24 weeks in 55–72% of subjects, increasing to 78–85% of subjects by week 48. In the only contraceptive efficacy study to date using an androgen–progestogen combination, no pregnancies were reported with 426 months of contraceptive exposure in 51 men using the suppression threshold of $1 \times 10^5 \text{ml}$ (Turner et al., 2003). Using the combination of etonogestrel implants with TD, this degree of suppression was achieved in approximately 90% of subjects by week 24, demonstrating that it may have potential as an efficacious contraceptive method.

While all men demonstrated suppression of spermatogenesis, there were differences in the rate and degree of suppression between treatment groups. At week 24, suppression to azoospermia was lower in group II (56%) than in groups I (72%) and III (69%) although this difference was less by the end of the treatment period. There was also a lesser suppression of gonadotrophins in group II, with a greater fluctuation than in the other 2 groups. This may be attributed to the less frequent administration of testosterone in that group. Indeed, trough testosterone concentrations in group II remained sub-physiological until weeks 24–36, and the improved spermatogenic suppression in the latter half of the study may have been related to the higher trough testosterone levels. Comparable differences in the degree of spermatogenic suppression in response to different TD dose regimens has recently been demonstrated using oral etonogestrel with TD (Hay et al., 2005), although overall rates of suppression were slightly higher. This suggests that modifications to the dose of either the testosterone or progestogen component may improve the rate and degree of suppression.

Although the testosterone dosages used in the current study maintain peak testosterone concentrations within the physiological range, trough concentrations showed a continuing slight increase during the length of the treatment period. While it therefore appears that yet longer studies are required to fully investigate the pharmacokinetics of this preparation, the present data clearly indicate that TD has advantages over previously available testosterone preparations. Similarly, testosterone undecanoate has improved pharmacokinetics compared with testosterone enanthate (Chen et al., 1991; Li et al., 1994). In studies with a repeated injection schedule of testosterone undecanoate (Nieschlag et al., 1999; Zhang et al., 1999; Gu et al., 2003, 2004), cumulative effects were also observed. Previous studies in which peak testosterone levels were not assessed (Zhang et al., 1999) may have underestimated the total exposure to testosterone. The slow improvement of testosterone preparations has been a significant barrier to the development of hormonal male contraception, and it appears that these newer preparations offer considerable advantages. The other long-acting testosterone preparation, subcutaneous pellets (Handelsman et al., 1990), also has high efficacy in the context of male contraception, the zero-order release allowing dose-sparing (Handelsman et al., 1992; McLachlan et al., 2000). No studies have compared these preparations directly, but the considerable improvements in testosterone delivery exemplified by this TD preparation now make detailed investigation of the testosterone regimen of importance.

A proportion (21/130, 16%) of men in all three groups entered a period of prolonged follow-up with delayed recovery in spermatogenesis. This has also been observed in previous studies with gestogen–androgen combinations (Brenner et al., 1977). Such prolonged recovery has not been observed in previous studies using a similar dose of desogestrel (Wu et al., 1999; Anawalt et al., 2000; Kinniburgh et al., 2002). However, with the exception of the extension phase in the study by Kinniburgh et al., these studies were of a duration of 24 weeks and not 48, and it cannot be ascertained that their follow-up was complete beyond the usual period of 16–24 weeks. Although the effects of progestogens on the hypothalamus and pituitary in men are unclear, there is evidence to support a possible direct effect of progestogens on the testis. A non-classical progesterone receptor has been identified in spermatozoa (El-Hefwany et al., 2000) and in rat Leydig cells (Rossato et al., 1999) and progesterone has been demonstrated to down-regulate LH receptor expression and function in vitro (El-Hefwany and Huhtaniemi, 1998). Desogestrel may also have a direct effect on Leydig cell steroidogenesis (Satyaswaroop and Gurpide, 1978), further decreasing intratesticular testosterone concentrations and having an inhibitory effect on spermatogenesis. However, as etonogestrel has a half-life of 23.8 hours (Bergink et al., 1990), it is not likely that such mechanisms alone may account for the prolonged recovery of spermatogenesis. Recovery data in previous studies of testosterone esters alone are incomplete. In the WHO study using testosterone enanthate alone (World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1996), although the mean time to recover to normal levels was 16 weeks, 20% of subjects were lost to follow-up. Similarly, more recently in a large efficacy study in China administering testosterone undecanoate alone, the recovery period was 12 months and no information was given on the follow-up of the subjects who discontinued from the study (Gu et al., 2003). The mechanisms of heterogeneity in the response to hormonal regimes discussed above has been a subject of considerable debate (Handelsman et al., 1995; Anderson et al., 1996; Yu and Handelsman, 2001; von Eckardstein et al., 2002) and it appears that this heterogeneity in response may also be true of recovery.

Similarly to studies using androgen–gestogen combinations (Bebb et al., 1996; Wu et al., 1999; Anawalt et al., 2000), a decline in HDL cholesterol and small increase in body weight was observed in all groups. Although demonstrating comparatively greater selectivity for the progesterone receptor than other synthetic progestogens (Phillips et al., 1990), etonogestrel has some affinity for the androgen receptor and may therefore contribute to these androgenic effects. In previous studies using this combination, weight gain and decline in
HDL cholesterol concentrations were dependent on the doses of both desogestrel and testosterone (Anawart et al., 2000).

In conclusion, this study demonstrates profound suppression of spermatogenesis with the combination of etonogestrel implants and testosterone decanoate. Efficacy in spermatogenic suppression was greater in groups I and III than in group II, which received 400 mg TD every 6 weeks, indicating that this is a submaximal regimen, and this was supported by pharmacokinetic analysis. This combination is a valuable approach and may lead to the development of a safe and effective long-term male hormonal contraceptive.

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References


Hay CJ, Brady BM, Zitzmann M et al. (2005) A multicentre phase IIb study of a novel combination of intramuscular androgen (testosterone decanoate) and oral progestogen (etonogestrel) for male hormonal contraception. J Clin Endocrinol Metab 90,2042–2049.


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