Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone

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BACKGROUND: Suppression of spermatogenesis to azoospermia is required for effective hormonal male contraception, but the degree of suppression varies between ethnic groups. We here report the first study of hormonal suppression of spermatogenesis in two African centres using a regimen of oral progestogen with depot testosterone.

METHODS A total of 31 healthy men (21 black) were recruited in Cape Town and 21 men in Sagamu, Nigeria. Subjects were randomized to take either 150 or 300 \(\mu\)g desogestrel daily p.o. with testosterone pellets. In Cape Town, desogestrel was administered for 24 weeks with 400 mg testosterone re-administered 12 weekly. In Sagamu, desogestrel was administered for 52 weeks with 200 mg testosterone (later increased to 400 mg) re-administered 12-weekly. RESULTS: In Cape Town, 22 men completed at least 20 weeks treatment. Azoospermia was achieved in 8/10 and 8/12 men in the 150 \(\mu\)g and 300 \(\mu\)g desogestrel groups. Four men in Sagamu withdrew. Azoospermia was achieved in all 17 men in the two groups. There were no significant changes in lipoprotein or haemoglobin concentrations in any group. CONCLUSION: These data demonstrate that the combination of oral desogestrel with depot testosterone is an effective regimen for suppression of spermatogenesis in African as in Caucasian and Chinese men, with azoospermia achieved in a total of 83/98 (85%) men.

Key words: depot testosterone/desogestrol/male contraception/spermatogenesis

Introduction

The administration of supraphysiological doses of testosterone (World Health Organization, 1990, 1996) or of more physiological doses in combination with another gonadotrophin-suppressing agent such as a progestogen (Patanelli, 1977; Handelsman et al., 1996; Meriggiola and Bremner, 1997) or GnRH antagonist (Pavlou et al., 1991; Swerdloff et al., 1998; Behre et al., 2001) can reversibly induce sufficient suppression of spermatogenesis to result in effective hormonal contraception for men. The degree of suppression of spermatogenesis achieved is near-complete, i.e. to azoospermia, in the majority of men, but a proportion, typically 20–45%, maintain a significant rate of sperm production (World Health Organization 1993,1995; Nieschlag and Behre, 1998). The risk of pregnancy is closely associated with the degree of suppression of spermatogenesis. Induced oligozoospermia to \(<1 \times 10^6/ml\) resulted in a pregnancy rate of \(~1\ per 100\ women-years\) while higher residual rates of spermatogenesis resulted in higher pregnancy rates than associated with female hormonal contraceptive methods (World Health Organization, 1996). The basis for this heterogeneity in response is not clear, but it is widely recognized that uniformly high suppression of spermatogenesis is required for a hormonal male contraceptive method to achieve acceptability.

The prevalence of induced azoospermia appears to vary by ethnic origin, being higher in Chinese and Asian men than Caucasians (World Health Organization, 1995). Asian men show greater susceptibility to suppression of gonadotrophins by testosterone (Wang et al., 1998) although differential suppression of gonadotrophins does not appear to account for the variation in spermatogenic suppression (Handelsman et al., 1995; Anderson and Wu, 1996). Differences in androgen metabolism have been suggested to underlie the variable response in Caucasian men (Lookingbill et al., 1991; Anderson et al., 1996). Diet has also been demonstrated to affect androgen metabolism in men (Santner et al., 1998). Black men also show differences in androgen concentrations and metabolism and androgen receptor CAG repeat length (Ross et al., 1986, 1992; Pettaway, 1999; Sartor et al., 1999). In addition to variation in the effectiveness of contraceptive
regimens in suppressing spermatogenesis between ethnic groups, there also appear to be differences in the metabolic effects. In Caucasian men, steroid-based male contraceptive regimens generally result in a lowering of high density lipoprotein cholesterol (HDL-C) concentrations, whereas no such effect was seen in Chinese men (Wu et al., 1996).

The effect of prototype hormonal male contraceptive regimens in black men has not been specifically investigated. We have previously reported a high acceptability of hormonal contraception among men of all ethnic groups in Cape Town (Martin et al., 2000a) and that the combination of oral desogestrel with testosterone pellets is a promising approach to a contraceptive method in both Caucasian and Chinese men (Kinniburgh et al., 2002). We here report the results of the investigation of this regimen in two African centres.

Materials and methods

Subjects
The study received ethical approval from the local ethics committees in Cape Town, South Africa and Sagamu, Nigeria. In South Africa, permission to perform the study with unregistered medicine was also obtained from the Medicines Control Council. All men gave written informed consent prior to screening and the study was carried out according to the International Conference on Harmanisation, Good Clinical Practice guidelines.

Of a total of 59 men screened, 31 men aged 19–39 years (mean 27 years) were recruited in Cape Town. 21 men were black, 6 white and 4 coloured. In Sagamu 21 men aged 21–41 years (mean 33 years) were recruited from a total of 45 screened, all black. None had a history of significant medical disease or abnormality on examination and screening haematological and biochemical measures were within local norms. Subjects submitted pre-treatment semen samples on two occasions at least 2 weeks apart which were considered to be normal using WHO methodology (World Health Organization, 1999). All men had sperm concentration >20×10⁹/ml.

Study design and medication
The study was a prospective randomized trial comparing two doses of oral desogestrel in combination with testosterone pellets. The primary end point was the prevalence of suppression of spermatogenesis to the two thresholds of azoospermia and ≤1×10⁹/ml. Subjects were randomized equally in each centre into two treatment groups from a table of random numbers and stratified by dose in groups of 10 to receive either 150 or 300 µg desogestrel (NV Organon, Oss, The Netherlands) p.o. daily for 24 weeks in Cape Town or 48 weeks in Sagamu. In Cape Town this resulted in even distribution of the ethnic groups between the two treatment arms, with 10 black, 3 white and 2 coloured men entering the 150 µg group and 11, 3 and 2 respectively entering the 300 µg group. All men in Cape Town additionally received 400 mg testosterone pellets (2×200 mg, NV Organon) inserted s.c. under local anaesthetic into the anterior abdominal wall on the first day of desogestrel treatment. This was repeated 12 weeks later. The protocol in Sagamu also specified administration of 400 mg testosterone pellets on the day of starting desogestrel treatment and at weeks 12, 24 and 36. However 200 mg was administered instead at the initial visit and at some subsequent visits. This error was detected during the course of the study, and the dose of testosterone increased to 400 mg for subsequent administrations. This resulted in all men receiving the lower, 200 mg dose for at least the first 24 weeks of treatment and for the full 48 weeks in 7 men. The 400 mg dose was administered to 3 men for the second 24 weeks and to 6 men for the final 12 weeks.

Subjects were reviewed and examined 2 weeks after commencing medication and subsequently at 4-week intervals during the treatment phase and the recovery phase of 16 weeks (or until sperm concentration recovered to ≥20×10⁹/ml, if longer) after finishing desogestrel. At each visit subjects were examined and any adverse events experienced or observed were recorded, semen samples produced and venepuncture performed. Subjects were required to continue their current method of contraception. Compliance was assessed by pill returns and direct questioning of subjects.

Sexual interest and activity were investigated pre-treatment and at 12 week intervals during treatment and recovery. A structured interview was used to quantify sexual activity over the preceding two weeks (Martin et al., 2000b).

Assays
Semen samples were submitted after 3–7 days abstinence. Each semen sample was assessed for sperm concentration, and azoospermia was confirmed by examination of the pellet following centrifugation of the ejaculate, samples with sperm seen only in the pellet being given a nominal concentration of 1×10⁹/ml. Both laboratories take part in external quality assurance schemes based at the University of Tygerberg.

Blood samples were separated by centrifugation for 15 min at 3000 g and serum stored at –20°C until hormone assay. LH and FSH were measured using reagents standardized against the WHO matched reagent program (2nd IRP 94/632 for FSH, 1st IRP 68/40 for LH). In Cape Town, FSH and testosterone was measured by the ACS 180 automated chemiluminescent assay (Bayer Corporation, Johannesburg, South Africa; sensitivity 0.1 IU/l for FSH, 0.35 nmol/l for testosterone), and LH by immunoradiometric assay (MAIAClone, Serono, Johannesburg; sensitivity 0.9 IU/l). Sagamu samples were assayed for testosterone by radioimmunoassay (RIA) (Corker & Davidson, 1978), and for LH and FSH by time-resolved immunofluorometric assay (DELFIA, Wallac, Turku, Finland) and by highly sensitive immunoradiometric assay (NETRIA, London, UK) respectively as previously described (Martin et al., 2000b), with assay sensitivity of 0.15 IU/l for LH and 0.1 IU/l for FSH. Interassay coefficients of variation were <9% in all cases. In both centres, general biochemical and haematological analyses were measured using routine methodologies at 12 weekly intervals.

Data analysis
Results are presented as mean ± SEM. Hormonal data were log transformed to correct non-equality of variance before analysis of variance (ANOVA) and sperm concentrations were cube root transformed prior to ANOVA. Analysis of co-variance (ANCOVA) was used to test for an effect of the dose of desogestrel after adjusting for baseline values. Paired t-tests were used to investigate time points at which a significant treatment effect was seen. Categorical data were analysed by Fisher's exact test and non-parametric data by the Kruskal-Wallis test.

Results

Baseline characteristics, adverse events and withdrawals
The treatment groups in Cape Town and Sagamu were similar in their baseline characteristics (Table I) although pretreatment sperm concentrations were higher in the Cape Town men than in Sagamu (P < 0.008). Eleven men in Cape Town withdrew before completing 24 weeks treatment. Reasons for withdrawal
included no longer wishing to continue the study (4), non-compliance (1), extruded testosterone pellet (1), fainted after pellet insertion (1), raised blood pressure (1), impotence (1), elevated plasma glucose (1) and moved from area (1). Two of these subjects withdrew at 20 weeks treatment, and are therefore included in the analyses. The subject who developed hypertension during the study had blood pressure readings of 130/85 and 130/90 mmHg pretreatment. This rose to 150/110 after 8 weeks treatment, at which point he was withdrawn from the study. His hypertension persisted and required treatment. One subject was noted to have an elevated fasting plasma glucose concentration after 12 weeks treatment (8.0 mmol/l). During a subsequent glucose tolerance test (75 mg glucose) plasma glucose was 9.4 mmol/l at 2 hr. Study medication was discontinued. He was shown to have a normal fasting plasma glucose concentration 10 weeks later and again one year later. Four men withdrew in Sagamu: three subjects declined repeated testosterone pellet insertion and one subject moved from the area. Data are therefore reported on 22 men in Cape Town and 17 men in Sagamu.

There was one episode of extrusion of the testosterone pellets in the Cape Town cohort and one in Sagamu. This occurred shortly before the end of the treatment phase in the Cape Town individual: his data are included. In the subject in Sagamu, the single pellet was extruded at 42 weeks i.e. 6 weeks following the third insertion procedure. A further pellet was immediately re-administered. This subject had already been azoospermic for 3 months, and his data are included in the analysis.

Occasional minor adverse events were reported including discomfort at the testosterone implant site, decreased libido, increased libido and headaches. Compliance in Cape Town as assessed by direct questioning and pill returns was high, with only 5 of the men who completed the study reporting missing 5 or more doses. However pill returns suggested less complete compliance with, in particular, 3 men who showed incomplete suppression of spermatogenesis returning 20, 40 and 54 doses. Compliance in Sagamu was very high. As assessed by pill returns, 3.1% of desogestrel doses were missed. Two episodes of missed pills of 9 and 4 consecutive doses were identified, the former in the 3rd month of treatment in a subject who subsequently withdrew from the study, the latter in the 2nd month in a subject who became azoospermic at 16 weeks treatment.

There were significant increases in weight ($P < 0.001$) in both groups in both centres although no subjects withdrew because of this. In Cape Town, mean weight increase was $3.1 \pm 0.5$ kg (range 0–5) in the 150 µg group and $3.8 \pm 1.1$ kg (range –3 to +4.5) in the 300 µg group. In Sagamu, mean weight increase was $4.7 \pm 1.0$ kg (range 2–8) in the 150 µg group and $3.8 \pm 1.4$ kg (range –2 to +10.5) in the 300 µg group. There were no significant changes in weight during the recovery phase in any of the 4 groups.

**Sperm concentrations**

The primary analysis was assessment of suppression of spermatogenesis to the two cut-off points of $\leq 1 \times 10^6$/ml (severe oligozoospermia) and azoospermia. Suppression of spermatogenesis was profound in both Cape Town and Sagamu (Figure 1), with no differences in sperm concentration between the two treatment groups in either centre.

In Cape Town, azoospermia was achieved by 8/10 men in the 150 µg group and by 8/12 men in the 300 µg group who completed at least 20 weeks treatment. In addition, one individual in the 150 µg group who withdrew from the study at 8 weeks treatment was already azoospermic giving an overall prevalence of 74%. One individual in the 150 µg group and the 4 men in the 300 µg group who did not achieve such consistently profound suppression of spermatogenesis, had sperm concentrations $> 10 \times 10^6$/ml throughout the duration of treatment, whereas the other individual in the 150 µg group had a sperm concentration of $1 \times 10^6$/ml at 4 and 24 weeks treatment, with concentrations $> 20 \times 10^6$/ml at other time points during treatment. These apparent non-responders were from all ethnic groups. While it was impossible to accurately assess compliance in these individuals, the pattern of variable and modest suppression of both spermatogenesis and gonadotrophin concentrations suggest non-compliance or intermittent compliance with study medication. This was supported by pill returns, as discussed above. Sperm concentrations recovered to normal ($> 20 \times 10^6$/ml) in all except one man during the 16 week recovery phase. LH and FSH also remained suppressed to undetectable concentrations in this individual, and he subsequently admitted to having started taking anabolic steroids.

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### Table 1: Pretreatment characteristics of subjects in Cape Town and Sagamu (values are mean ± SEM)

<table>
<thead>
<tr>
<th>Centre</th>
<th>Cape Town</th>
<th>Sagamu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desogestrel dose (µg)</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.0 ± 1.4</td>
<td>27.5 ± 1.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.7 ± 2.4</td>
<td>64.1 ± 2.3</td>
</tr>
<tr>
<td>Sperm concentration ($\times 10^6$/ml)</td>
<td>79 ± 9</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>3.6 ± 0.7</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>24.5 ± 1.5</td>
<td>26.2 ± 2.1</td>
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There were no significant differences in any of the above variables between groups in either centre. Sperm concentration was significantly higher in Cape Town than in Sagamu ($P = 0.008$).
Testosterone concentrations fell initially during treatment in both groups in Cape Town (Figure 2a, \( P < 0.001 \) in both groups) while remaining within the normal range, with a small rise following re-administration of testosterone at 12 weeks (12 versus 16 weeks, \( P < 0.05 \)). Testosterone concentrations during the recovery phase were similar to pretreatment values. Testosterone concentrations also fell during treatment in both treatment groups in Sagamu (pretreatment versus 4 weeks treatment \( P < 0.05 \) in both groups, Figure 2b). Thereafter testosterone concentrations showed minor fluctuations in keeping with the pattern of repeated administration of the testosterone pellets. The fluctuations were more clearly apparent in the 300 µg desogestrel group, with testosterone concentrations 4 weeks following the 3rd and 4th administration being significantly higher than pre-administration concentrations 4 weeks previously (\( P = 0.02 \) and \( P = 0.007 \) respectively). The corresponding fluctuations in the 150 µg group were not statistically significant. Analysis of the effect of increasing the dose of testosterone to 400 mg demonstrated that this had a small, but statistically non-significant effect, on circulating testosterone concentrations over the 12 weeks following administration (Figure 2c). However at 52 weeks of treatment i.e. at the time of discontinuation of desogestrel treatment, testosterone concentrations were lower in those men who had received 200 mg testosterone at each insertion (8.3 ± 1.1 nmol/l) compared with those who had received 400 mg testosterone at week 36 (13.8 ± 1.1 nmol/l, \( P = 0.006 \)). Testosterone concentrations showed a rise 4 weeks after discontinuing testosterone treatment (\( P = 0.004 \)) to concentrations similar to pretreatment.

LH and FSH were suppressed in both treatment groups in both centres. Both LH and FSH were consistently suppressed during testosterone/desogestrel treatment in the Cape Town group (both \( P < 0.001 \), Figure 3). Gonadotrophins were suppressed to the limit of detection for the duration of desogestrel treatment in most men and were not significantly different between dosage groups, with subsequent restoration to pretreatment concentrations during the recovery phase. Mean treatment concentrations of both LH and FSH were less suppressed in those 6 men who showed significant

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**Figure 1.** Sperm concentrations at pre-treatment baseline, during desogestrel and testosterone administration (indicated by bar), and following withdrawal of desogestrel treatment in Cape Town (a) and Sagamu (b). The arrows indicate the time points at which testosterone was administered. Open circles, 150 µg desogestrel group; filled circles, 300 µg group. Values are mean ± SEM.

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at the end of the treatment phase. He had become azoospermic prior to starting taking the non-study steroids.

In Sagamu all 17 men in the two groups achieved azoospermia during desogestrel/testosterone treatment. Suppression was however relatively slow, with severe oligozoospermia achieved by 5/9 men in the 150 µg group and 7/8 men in the 300 µg group within 24 weeks of treatment. Azoospermia was achieved by 2 and 6 men respectively by that time point. This may reflect the fact that all men had received only the lower dose of testosterone, 200mg/12 weeks, up to that time point. Median time to azoospermia was 30 weeks in the 150 µg desogestrel group and 18 weeks in the 300 µg group; these were not statistically significantly different. Most men already showed severe oligozoospermia or azoospermia by the time the increased dose of testosterone was administered. However, one man in each group maintained sperm concentrations >10 ×10⁹/ml during the first 24 weeks treatment, and was then administered the 400 mg testosterone dose from that time i.e. at 24 and 36 weeks. In both subjects the next semen sample (i.e. 4 weeks later, at 28 weeks) and all subsequent semen samples during desogestrel/testosterone treatment showed severe oligozoospermia or azoospermia.

Following discontinuation of desogestrel, all men were followed up until sperm concentration had returned to the normal range with the exception of one man who defaulted from follow-up during the recovery phase. Recovery appeared slower in the 300 µg desogestrel group, although this did not reach statistical significance. No men were azoospermic beyond 8 weeks recovery in either group, and mean sperm concentrations at 16 weeks recovery were 33 ×10⁹/ml in the 150 µg group and 22 ×10⁹/ml in the 300 µg group.

**Reproductive hormones**

Testosterone concentrations fell initially during treatment in both groups in Cape Town (Figure 2a, \( P < 0.001 \) in both groups) while remaining within the normal range, with a small rise following re-administration of testosterone at 12 weeks (12 versus 16 weeks, \( P < 0.05 \)). Testosterone concentrations during the recovery phase were similar to pretreatment values. Testosterone concentrations also fell during treatment in both treatment groups in Sagamu (pretreatment versus 4 weeks treatment \( P < 0.05 \) in both groups, Figure 2b). Thereafter testosterone concentrations showed minor fluctuations in keeping with the pattern of repeated administration of the testosterone pellets. The fluctuations were more clearly apparent in the 300 µg desogestrel group, with testosterone concentrations 4 weeks following the 3rd and 4th administration being significantly higher than pre-administration concentrations 4 weeks previously (\( P = 0.02 \) and \( P = 0.007 \) respectively). The corresponding fluctuations in the 150 µg group were not statistically significant. Analysis of the effect of increasing the dose of testosterone to 400 mg demonstrated that this had a small, but statistically non-significant effect, on circulating testosterone concentrations over the 12 weeks following administration (Figure 2c). However at 52 weeks of treatment i.e. at the time of discontinuation of desogestrel treatment, testosterone concentrations were lower in those men who had received 200 mg testosterone at each insertion (8.3 ± 1.1 nmol/l) compared with those who had received 400 mg testosterone at week 36 (13.8 ± 1.1 nmol/l, \( P = 0.006 \)). Testosterone concentrations showed a rise 4 weeks after discontinuing testosterone treatment (\( P = 0.004 \)) to concentrations similar to pretreatment.

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Desogestrel with testosterone as a contraceptive in African men

Figure 2. Testosterone concentrations in (a) Cape Town and (b) Sagamu cohorts at pre-treatment baseline, during desogestrel and testosterone administration (indicated by bar), and following withdrawal of desogestrel treatment. Open circles, 150 µg desogestrel group; filled circles, 300 µg group. The arrows indicate the time points at which testosterone was administered. Panel (c) shows testosterone concentrations over weeks 36–52 of treatment in the Sagamu cohort, with subjects divided according to the dose of testosterone administered at 36 weeks: 200 mg (open symbols, n = 7) versus 400 mg (filled symbols, n = 10). Values are mean ± SEM.

There were no significant differences between treatment groups at any time point in either centre, thus the two groups were analysed together. In the Cape Town cohort, there were small but not statistically significant falls in total cholesterol (pretreatment 4.0 ± 0.2, 3.9 ± 0.2 mmol/l after 24 weeks) and HDL-C (pretreatment 1.23 ± 0.07; 1.20 ± 0.10 mmol/l after 24 weeks) but no change in LDL-C (pretreatment 2.40 ± 0.12; 2.40 ± 0.20 mmol/l after 24 weeks). There was no significant change in haemoglobin concentration during treatment (pretreatment 150 ± 24; 149 ± 29 g/l after 24 weeks). Similarly there were no significant changes in biochemical variables, including bilirubin, liver transaminases and alkaline phosphatase in either centre.

Sexual activity
There were no differences between treatment groups in either centre, thus both groups were analysed together. In Cape Town, there was no change in the frequency of sexual intercourse.
during treatment, which was reported a median of 3 occasions per two weeks (range 0–10) pretreatment and 4 occasions (range 0–8) after 24 weeks treatment. Three men complained of temporary impotence during the study, which resolved spontaneously without discontinuing study medication. There was no evidence of a decrease in sexual activity in subjects in the Sagamu cohort, despite the low dose of testosterone initially administered. In fact there was a significant increase in the reported frequency of sexual intercourse, from a median of 2 occasions per 2 weeks pretreatment (range 0–4) to 4 times at 12, 24 and 48 weeks treatment (range 2–5, 0–7 and 2–5 times respectively; \( P = 0.02 \)). This was maintained at 5 times (range 1–6) per 2 weeks at the end of the recovery period.

**Discussion**

These data demonstrate the high efficacy of the combination of oral desogestrel with a depot formulation of testosterone in suppressing spermatogenesis in African men, and confirm and extend our previous findings in Caucasian and Chinese men (Kinniburgh *et al.*, 2002). To our knowledge this is the first report of the investigation of a potential hormonal male contraceptive in sub-Saharan Africa. This study therefore demonstrates proof of concept for this regime as a hormonal male contraceptive in all ethnic groups studied. We have previously reported the acceptability of the concept of hormonal male contraception in Cape Town across ethnic groups (Martin *et al.*, 2000a): the present study confirms the willingness of men to take part and contribute to the more equitable sharing of responsibility for contraception (Glasier *et al.*, 2000).

Spermatogenesis was rapidly and profoundly suppressed by this regimen, with both doses of desogestrel. There were no differences in either the rate of degree of suppression of spermatogenesis between the two desogestrel doses, although in Sagamu there was a clear trend towards a higher prevalence of azoospermia within 24 weeks of treatment in the 300 \( \mu \)g group. Combining the present data with our previous investigation of this regimen in Edinburgh, Scotland and Shanghai, China shows that azoospermia was achieved in a total of 83/98 men (85%; 95% confidence interval 76–91%) overall, and 44/48 (92%; 95% CI 80–98%) in the 300\( \mu \)g group. Azoospermia was achieved in all men in the 300 \( \mu \)g group in Edinburgh, Shanghai and Sagamu, whereas in Cape Town both treatment groups contributed to those not becoming azoospermic. Careful assessment of compliance identified that at least 4 of the 6 non-azoospermic men in Cape Town appeared not to have taken a significant proportion of the desogestrel tablets although it was impossible to quantify this.
have allowed the demonstration of The relative biochemical hypogonadism induced may however be
recognized largely because of the short-acting testosterone
preparation (Martin et al., 2000a) such complexity might compromise the acceptability of a novel preparation. Furthermore, in that study, men in Cape Town showed the most positive response to injectable male contraception (Martin et al., 2000a). Administration of a depot progestogen, by injection (Handelsman et al., 1996) or implant (Anderson et al., 2002) would also avoid difficulties with compliance and should be investigated in these populations.

The dose of testosterone studied here (400 mg re-administered 12-weekly) was designed to provide replacement within the physiological range, if at a slightly lower level than normal in some men. This dose of testosterone has been previously demonstrated to have no significant suppressive effect on spermatogenesis when administered alone (Handelsman et al., 2000). The doses of desogestrel administered here, have been demonstrated to have a suppressive effect on gonadotrophins in normal men (Wu et al., 1999) but, while inducing a fall in testosterone that would not be tolerated for prolonged periods, gonadotrophin suppression was not of sufficient degree to result in suppression of spermatogenesis to the extent required for male contraception. Testosterone-only and desogestrel-only groups were not therefore included in the study design, although we acknowledge that this does not allow the relative contributions of the testosterone and desogestrel components to be separately assessed in these specific populations.

As expected and as previously reported using similar testosterone regimens (Martin et al., 2000b; Kinniburgh et al., 2002), there were falls in testosterone concentrations during treatment in both centres, particularly in Sagamu where the dose of testosterone administered was lower than intended. The relative biochemical hypogonadism induced may however have allowed the demonstration of findings not previously recognized largely because of the short-acting testosterone preparations frequently used in similar studies result in high, often supraphysiological, testosterone concentrations over the days following injection. Firstly, the high efficacy of this low dose of testosterone may reflect the relative stability of testosterone concentrations with this formulation, emphasizing the importance of a depot formulation and contrasts with the low efficacy of transdermal administration testosterone, which results in variable and frequently subphysiological testosterone concentrations (Hair et al., 2001). In two subjects in Sagamu who had maintained near normal sperm concentrations when given 200mg testosterone, increasing the dose to 400mg at 24 weeks was followed by prompt and complete suppression of spermatogenesis, illustrating the important role of testosterone in achieving azoospermia in this combination. While the testosterone pellets used in this study have well-recognized disadvantages including the need for a minor surgical insertion procedure and occasional expulsion (Handelsman, 1998), they remain a valuable prototype with the pharmacodynamics of a near zero-order release preparation. Secondly, all men showed complete suppression of spermatogenesis to azoospermia despite readily-detectable circulating gonadotrophin concentrations, especially FSH, in the 150 µg desogestrel group. This indicates that mechanisms other than complete suppression of gonadotrophin secretion may be involved in the induction of azoospermia, at least with this regimen. These may include a direct testicular effect, as has been suggested to contribute to the high prevalence of azoospermia in regimens based on the anti-androgenic progestogen cyproterone acetate (Meriggiola et al., 1996, 1998). This does not contradict the central understanding that suppression of gonadotrophins is the primary basis for the suppression of spermatogenesis with hormonal regimens. The less marked fluctuations in serum testosterone concentrations during desogestrel/testosterone treatment in the 150 µg than 300 µg group may reflect less complete suppression of endogenous testosterone, as also suggested by the higher LH concentrations in that group.

In neither Cape Town nor Sagamu were there significant changes in lipoproteins during desogestrel/testosterone treatment. Such changes, most notably a fall in HDL-C, are commonly found during testosterone treatment of normal men, either alone (Bagatell et al., 1994; Anderson et al., 1995; Wu et al., 1996) or in combination with a progestogen (Wallace and Wu, 1990; Anawalt et al., 1999; Kamischke et al., 2001) and have been previously reported during oral desogestrel/testosterone treatment (Wu et al., 1999; Anawalt et al., 2000). In our previous study with the present regimen, we found a small but significant fall in HDL-C concentrations in a Caucasian but not Chinese cohort (Kinniburgh et al., 2002). Chinese men similarly showed no suppression in HDL-C during high-dose testosterone treatment (Wu et al., 1996). The present results may indicate a similar resistance to this androgenic effect among black African men. There were also no changes in haemoglobin concentration in either centre, despite the low replacement dose of testosterone in Sagamu. This contrasts with the dose-dependent fall in haemoglobin seen with cyproterone acetate even in combination with testosterone enanthate (Meriggiola et al., 1996), and the increase in haemoglobin reported with higher doses of injectable preparations with progestogen (Kamischke et al., 2001). While it is not possible to interpret the clinical significance of small changes in a study population, it is likely to be advantageous to minimize the non-reproductive effects of contraceptive steroid administration for widespread use.

Ethnic variations in the degree of suppression of spermatogenesis during trials of prototype hormonal male contraceptive regimens have been reported, with Chinese and Asian populations typically showing a higher prevalence of azoospermia than Caucasian populations (World Health Organization, 1995). While the data using testosterone-only administration appears to show this clearly, comparative studies using testosterone/progestogen combinations have not been widely performed. Differences in androgen metabolism and feedback sensitivity (Lookingbill et al., 1991; Wang et al., 1998), germ cell apoptosis (Sinha Hikim et al., 1998) and diet (Santner et al., 1998) may contribute to this although direct evidence is lacking. Our previous data in Caucasian and Chinese men accurately. Lesser degrees of non-compliance were identified in some men who became azoospermic, thus while it appears that this dose of desogestrel may have a safety margin, much further work will be required to clarify this issue. While an oral preparation of a male contraceptive was generally perceived more favourably by potential users than an injectable preparation (Martin et al., 2000a) such complexity might compromise the acceptability of a novel preparation. Further-
(Kinniburgh et al., 2002) and the present results do not suggest that ethnicity is a major factor in the response to this regimen. It would be of interest to know whether other regimens that do show apparent ethnic differences in response would show such differences in black populations. Patterns of contraceptive usage differ between developed and developing regions of the world, with greater use of clinic-based regimens in the developing world [United Nations Population Fund (UNFPA), 1998]. It is therefore important for both biomedical and operational reasons to investigate novel contraceptive methods in a range of social and ethnic settings.

In conclusion, the combination of depot testosterone with oral desogestrel resulted in azoospermia in 16/22 men in the Cape Town cohort and all 17 men in the Sagamu cohort, confirming the high efficacy of this combination. This study also demonstrates the feasibility of studying and developing hormonal male contraception in African populations.

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References


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