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Research

Effect of chronic administration of 7α-methyl-19-nortestosterone on serum testosterone, number of spermatozoa and fertility in adult male bonnet monkeys (*Macaca radiata*)

S. G. Ramachandra[1], V. Ramesh[1], H. N. Krishnamurthy[1], N. Kumar[2], K. Sundaram[2], M. P. Hardy[3] and A. Jagannadha Rao[3]*

[1]*Primate Research Laboratory, Indian Institute of Science, Bangalore, India;* [2]*Population Council, Center for Biomedical Research, NY 10021, USA; and* [3]*Department of Biochemistry and Department of MRDG, Indian Institute of Science, Bangalore 560 012, India*

Hormonal approaches to male contraception that are based on the suppression of LH secretion require androgen replacement treatment to maintain sexual behaviour and secondary sexual characteristics. Androgen supplementation not only involves large and frequent doses of testosterone esters but also results in undesirable effects on the prostate gland. In an attempt to avoid such problems, a synthetic androgen, 7α-methyl-19-nortestosterone (MENT), which is much more potent than testosterone, has been developed. In the present study, MENT was administered at different doses (25, 50, 100, 300 and 1000 μg day^{-1}) either alone or in combination with oestradiol via Silastic implants for a specified period to adult male bonnet monkeys (*Macaca radiata*). Blood and semen samples were collected at specific intervals and analysed for serum testosterone and seminal parameters, respectively. The results of the present study clearly indicate that administration of MENT at all doses tested results in suppression of the nocturnal surge of testosterone (by day 3), as well as a decrease in the number of spermatozoa (by day 45). Co-administration of oestradiol resulted in a reduction in the dose of MENT required to suppress the nocturnal surge. None of the male bonnet monkeys treated with MENT were able to impregnate females, clearly demonstrating the efficacy of MENT in blocking fertility in male bonnet monkeys.

Introduction

Sex steroids have been used to block the synthesis and secretion of pituitary gonadotrophins, thereby suppressing fertility in females. Although a similar approach using testosterone has shown some potential in males, a practical application that does not require frequent injections of androgen and incur the possible risk of over-stimulation of the prostate gland has yet to be developed. Long-acting testosterone derivatives, such as testosterone undecanoate, have been tested as potential male antifertility agents in an attempt to overcome this problem (Schurmeyer and Nieschlag, 1984; Weinbauer *et al.*, 1986). In this regard, the synthetic androgen 7α-methyl-19-nortestosterone (MENT) has been developed because of its high potency. The anabolic effects of MENT on skeletal muscle are ten times higher than those of testosterone (Sundaram *et al.*, 1993). In the same study, it was also demonstrated that the potency of MENT as an androgen is four times higher than that of testosterone. However, unlike testosterone, MENT is not 5α-reduced, so that the adverse stimulatory effects on the prostate gland are minimal (Agarwal and Monder, 1988; Kumar *et al.*, 1992). In addition, MENT is also 12 times more potent than testosterone in the suppression of serum gonadotrophin (Kumar *et al.*, 1992). In the primate model, MENT is ten times more potent than testosterone with regard to the clinically desirable end points of gonadotrophin suppression and anabolism (Cummings *et al.*, 1998). As oestradiol potently suppresses the hypothalamo–pituitary axis, augmentation of the antifertility potential of MENT was evaluated by testing the effects of chronic administration of MENT alone or in combination with oestradiol on the number of spermatozoa and fertility in adult male bonnet monkeys.

*Correspondence
Email: ajrao@biochem.iisc.ernet.in

Materials and Methods

Animals

Colony-born adult male bonnet monkeys (*Macaca radiata*) of proven fertility (demonstrated by having sired at least one offspring) and female monkeys of proven fertility (that have given birth to at least one offspring) were selected for the study. Adult males, weighing 6–8 kg, that showed a clear nocturnal surge of serum testosterone were included in this study. It was demonstrated previously that the serum testosterone concentration in samples collected at 22:00 h was at least threefold higher than that in samples collected at 10:00 h. The significance of the nocturnal surge of

1470-1626/2002

testosterone as an index of male reproductive function, and its dependence on LH and prolactin, has been reported by Rao *et al.* (1990). All the procedures carried out on the animals were approved by the Institutional Ethics Committee of the Indian Institute of Science (Protocol no. 21).

Treatment

Effect of MENT on the nocturnal surge of testosterone. MENT was obtained from the Center for Biomedical Research (New York). In the first set of experiments, MENT was delivered at a known rate for 28 days using an osmotic mini pump (model 2ML4; Alza Corporation, Palo Alto, CA) that was implanted s.c. and changed at intervals of 28 days. The doses of MENT administered were 100, 300 and 1000 μg day^{-1}. The efficacy of MENT in suppressing the hypothalamo–pituitary–gonadal axis was assessed by its ability to inhibit the nocturnal surge of testosterone.

LH suppression. Five adult male monkeys were castrated bilaterally and 7 days later were implanted with mini-osmotic pumps releasing 100 μg MENT day^{-1} for 14 days to ascertain the ability of MENT to inhibit LH secretion. Blood samples were collected on day 7 and day 14 after implantation.

Effect of MENT alone or in combination with oestradiol on fertility. As fertility trials require a long period of treatment, dose responses for MENT were defined using Silastic implants, which provided a sustained release of the steroid. The preparation of Silastic capsules that were capable of delivering fixed concentrations of MENT was carried out according to the procedure described by Ewing *et al.* (1983). Accordingly, an appropriate length of Silastic tubing containing a fixed concentration of MENT was implanted to the back of each male monkey. Different doses of MENT were administered by varying the length of the Silastic implants as well as the number of implants. Silastic capsules delivering 25, 50, 100, 300 and 1000 μg MENT day^{-1} ($n = 5$ for each dose) were surgically implanted s.c. in the upper back region of each monkey.

Surgery

Animals were anaesthetized with ketamine hydrochloride (10 mg kg^{-1} body weight). A small incision was made on the back of the monkey and Silastic implants containing MENT were placed in subcutaneous tissue and the wound was closed with silk sutures. The sutures were removed on day 7 after surgery.

Combination of MENT and oestradiol. A lower dose of MENT was tested in combination with oestradiol to explore the possibility of further enhancing the antigonadotrophic effect. A preliminary study revealed that a 1 cm Silastic capsule containing 11 mg oestradiol is capable of maintaining serum oestradiol concentrations at 50 pg ml^{-1} for 150 days; oestradiol concentrations in control monkeys range between 5 pg ml^{-1} and 20 pg ml^{-1}. On the basis of these results, Silastic capsules capable of delivering 25 μg MENT and a capsule of oestradiol capable of maintaining serum oestradiol concentrations at 25 pg ml^{-1} were implanted in male bonnet monkeys. In another group of bonnet monkeys, the doses of both steroids were doubled.

The duration of the study ranged from 90 to 245 days. During this period, blood samples were collected on specified days at 10:00 h and 22:00 h, and serum was separated by centrifugation at 800 ***g*** for 20 min and stored at –20°C until analysis. Semen samples were collected once every 15 days by penile stimulation (Ramesh *et al.*, 1998), and the total number of spermatozoa and sperm motility were determined under a light microscopy. Sperm motility was scored on a scale ranging from highly motile (+++++) to immotile (0).

Fertility trials. Fertility trials were conducted at specified time points between day 90 and day 180 with two groups of animals receiving hormone treatment via Silastic implants and the control group that received a placebo. The groups were as follows: (i) group 1: placebo (empty capsules) controls ($n = 5$); (ii) group 2: 100 μg MENT alone each day ($n = 5$); (iii) group 3: 50 μg MENT each day and a Silastic tube containing sufficient oestradiol to maintain serum oestradiol concentrations at 50 pg ml^{-1} throughout the experiment ($n = 5$). The fertility status of the animals was determined by keeping male bonnet monkeys in a cage with a female of proven fertility at days 9–14 of the menstrual cycle. The ovulatory status of the female was ascertained by determining serum oestradiol concentrations on days 7, 8, 9 and 10, and serum progesterone concentrations on days 18–24 of the menstrual cycle. In the primate colony at the Indian Institute of Science, the menstrual cycle is considered to be ovulatory when serum oestradiol concentrations are at least 200 pg ml^{-1} between day 7 and day 10 and serum progesterone values are at least 2 ng ml^{-1} between day 18 and day 24 of the menstrual cycle (Rao *et al.*, 1997). Each male was kept in a cage with three different females during the fertile period of the menstrual cycle. This procedure was performed on the basis of data showing that a maximum of three exposures to a male of proven fertility for three ovulatory cycles is sufficient for a female to become pregnant (Rao *et al.*, 1997). In addition, each female that did not become pregnant during the three exposures to a MENT-treated male was exposed again for three ovulatory cycles to a control male of proven fertility to ensure that the female monkey used in the study was fertile.

Radioimmunoassay of hormones

Serum LH concentrations were measured by radioimmunoassay using a macaque LH kit (generously provided by the NICHD, Bethesda, MD). The sensitivity of the radioimmunoassay was 0.1 ng ml^{-1}, and the intra- and interassay coefficients of variation were 7.5 and 9.0%,

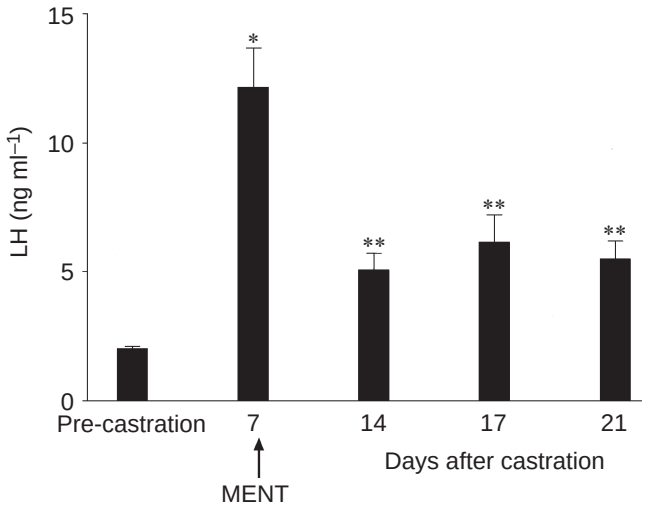

Fig. 1. Effect of administration of 7α-methyl-19-nortestosterone (MENT) (100 μg day^{-1}) on serum LH concentrations (mean ± SEM, $n = 5$) in male bonnet monkeys (*Macaca radiata*). Serum LH was estimated by radioimmunoassay using a macaque LH kit. *Significantly different from pre-castration value ($P < 0.05$), **Significantly different from day 7 value ($P < 0.05$).

respectively. Iodination of LH was carried out by the Iodogen method (Salacinski *et al.*, 1981). The specific activity of the ^{125}I-labelled LH was 10–15 μci ng^{-1}. Serum testosterone concentrations were measured using a procedure described by Mukku *et al.* (1981). The assay had a sensitivity of 10 pg per tube, and the intra- and interassay coefficients of variation were 8.3 and 9.8%, respectively.

Statistical analyses

All data are expressed as mean ± SEM. The hormonal concentrations and seminal parameters were analysed by ANOVA followed by Student–Newman–Keuls' comparisons to test for differences among means. Differences were regarded as significant at $P < 0.05$.

Results

Effect of administration of MENT on serum LH concentrations in castrated monkeys

As expected, after castration, there was an increase in serum LH concentrations of male bonnet monkeys. However, an increase in serum LH concentration was not observed in castrated animals that were treated with 100 μg MENT day^{-1} (Fig. 1) and this effect was observed even at day 14 after MENT treatment, indicating that administration of MENT results in inhibition of the hypothalamo–pituitary–gonadal axis.

Inhibition of the nocturnal surge of serum testosterone by MENT in intact monkeys

Preliminary studies carried out using MENT delivered by the osmotic pumps showed that at all doses, suppression of the nocturnal surge of testosterone was observed by day 3, and lower doses (25 and 50 μg) were as effective as higher doses ($P < 0.005$) (Table 1). The profile of serum testosterone concentrations in the 100 μg dose group is presented (Fig. 2); data from the other groups demonstrate the same outcome and are not shown. After removal of the MENT implants, the nocturnal testosterone surge reappeared within 10 days. Similar results were obtained when MENT was administered via Silastic capsules at doses of 25, 50, 100, 300 and 1000 μg per day.

Suppression of spermatogenesis by MENT or MENT in combination with oestradiol

Before the start of the experiment, the number of spermatozoa of the monkeys selected for the study ranged from 181×10^6 to 458×10^6 per ejaculate (Table 2). By day 45, in addition to the abolition of the nocturnal surge of serum testosterone, a sharp decrease in the number of spermatozoa was observed, ranging from 9×10^6 to 87×10^6 per ejaculate (Table 2). A representative profile of the number of spermatozoa in monkeys that received 100 μg MENT is presented (Fig. 3). At doses of 25–100 μg MENT, there was a trend towards steeper and more consistent decreases ($P < 0.005$) in the number of spermatozoa compared with the higher doses such as 300 and 1000 μg.

The data on serum testosterone concentrations are summarized (Figs 4 and 5) and indicate that, although both the MENT and oestradiol combination regimens were equally effective in suppressing the nocturnal serum testosterone surge, the suppression of the number of spermatozoa by treatment with 50 μg MENT in combination with 50 pg oestradiol was greater and more prolonged (Fig. 6) than the suppression after the 25 μg MENT and 25 pg oestradiol regimen (Fig. 7). It should also be noted that although the number of spermatozoa remained suppressed in monkeys treated with 50 μg MENT in combination with 50 pg oestradiol, they tended to increase gradually in monkeys treated with 25 μg MENT in combination with 25 pg oestradiol ($P < 0.005$). Sperm motility was significantly reduced by day 45 after MENT administration (data not presented) and during the subsequent period there were too few spermatozoa to permit a reliable assessment of motility.

Effect on fertility

Of the several treatment regimens studied, only two groups of animals, that is, those receiving 100 μg MENT or 50 μg MENT + 50 pg oestradiol, were subjected to fertility testing because they showed the most consistent suppression of the number of spermatozoa.

The ovulatory nature of the menstrual cycle of the female monkeys exposed to the treated males is shown (Table 3). Only those cycles in which the values for serum oestradiol concentration on any day between day 7 and day 10 of the

Table 1. Inhibition of the nocturnal surge of testosterone in intact bonnet monkeys (*Macaca radiata*) treated with 7α-methyl-19-nortestosterone (MENT)

	Serum testosterone (ng ml^{-1})			
	Day 0		Day 3	
Group	10:00 h	22:00 h	10:00 h	22:00 h
Control	2.63 ± 0.73	19.40 ± 3.82	3.98 ± 0.70	23.20 ± 4.55
MENT (μg)				
25	5.08 ± 0.46	15.83 ± 2.89	2.20 ± 0.40	1.58 ± 0.21
50	4.70 ± 0.76	20.80 ± 5.40	2.33 ± 0.19	1.33 ± 0.29
100	3.40 ± 1.40	13.10 ± 2.20	2.52 ± 0.25	2.24 ± 0.44
300	4.42 ± 1.82	12.80 ± 3.16	2.99 ± 0.45	3.20 ± 0.40
1000	4.25 ± 1.10	15.10 ± 3.30	4.50 ± 0.75	3.93 ± 0.51

Values are mean ± SE (n = 5 animals).

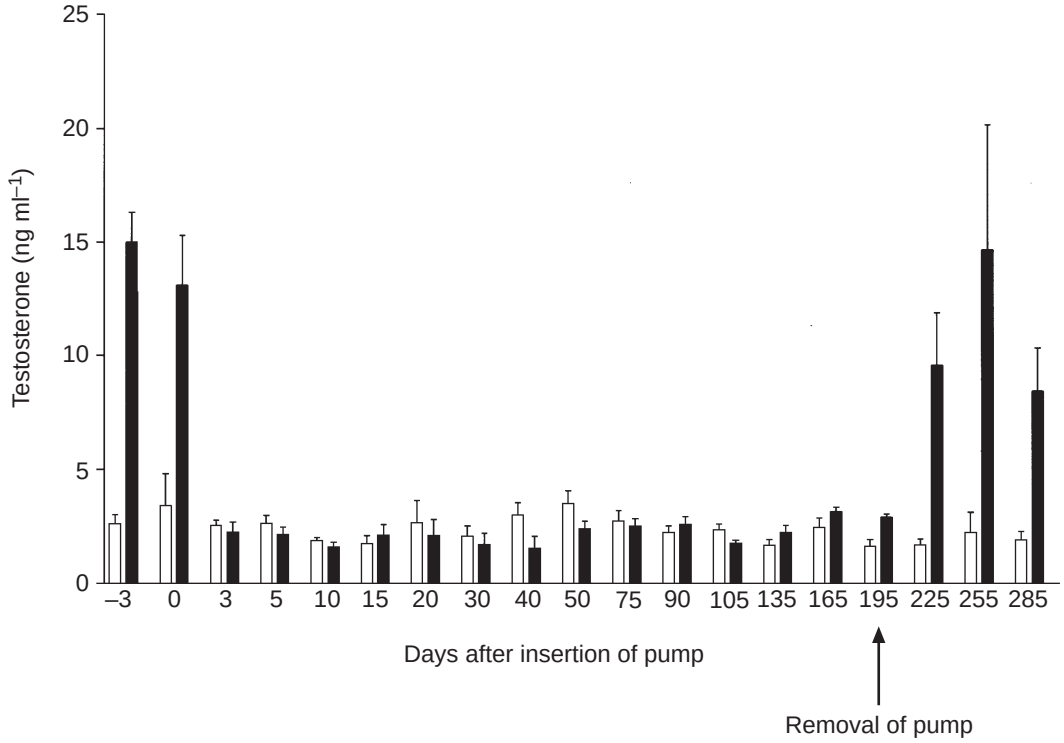

Fig. 2. Effect of administration of 7α-methyl-19-nortestosterone (MENT) (100 μg day^{-1}) via Silastic tubing on serum testosterone concentrations in serum samples collected at 10:00 h (□) and at 22:00 h (■) from male bonnet monkeys (*Macaca radiata*). Serum testosterone was estimated by radioimmunoassay and values presented are mean ± SE of five animals.

menstrual cycle were 200 pg ml^{-1} or above and serum progesterone concentration on any day between 18 and 24 was above 2 ng ml^{-1} were considered ovulatory and only such cycles were included in calculating the results.

The results from the present study reveal that although all the female monkeys exposed to untreated control males became pregnant, none of the females exposed to MENT or MENT + oestradiol-treated males became pregnant (Table 4). A total of ten females was exposed during three ovulatory cycles each (total of 30 cycles) to males in the 100 μg MENT-treated group. The males that received 50 μg MENT in combination with 50 pg oestradiol were exposed to five females during three ovulatory cycles for a total of 15 cycles. Interestingly, the females that were not impregnated by the MENT-treated males became pregnant within three exposures to control male monkeys, thus demonstrating that the females used were of normal fertility, and that the absence of pregnancy after exposure to MENT-treated males was not due to non-ovulatory cycles occurring at the time of the experiment. These results indicate that in

Table 2. Inhibition of the nocturnal surge of testosterone and sperm count in bonnet monkeys (*Macaca radiata*) treated with 7α-methyl-19-nortestosterone (MENT)

	Sperm count (10^6 per ejaculate)		Serum testosterone (ng ml^{-1})			
			Day 0		Day 45	
Group	Day 0	Day 45	10:00 h	22:00 h	10:00 h	22:00 h
Control	285 ± 34	258 ± 17	2.63 ± 0.73	19.40 ± 3.82	4.25 ± 0.48	17.40 ± 2.29
MENT (μg)						
25	181 ± 6	9 ± 8	5.08 ± 0.46	15.83 ± 2.89	1.85 ± 0.44	0.78 ± 0.56
50	246 ± 63	21 ± 9	4.70 ± 0.76	20.80 ± 5.40	2.10 ± 0.76	0.78 ± 0.26
100	224 ± 20	43 ± 9	3.40 ± 1.40	13.10 ± 2.20	3.01 ± 0.53	1.54 ± 0.54
300	458 ± 32	85 ± 26	4.42 ± 1.82	12.80 ± 3.16	3.05 ± 0.16	2.53 ± 0.33
1000	300 ± 43	87 ± 20	4.25 ± 1.10	15.10 ± 3.30	2.18 ± 0.97	1.27 ± 0.67

Values are mean ± SE (n = 5 animals).

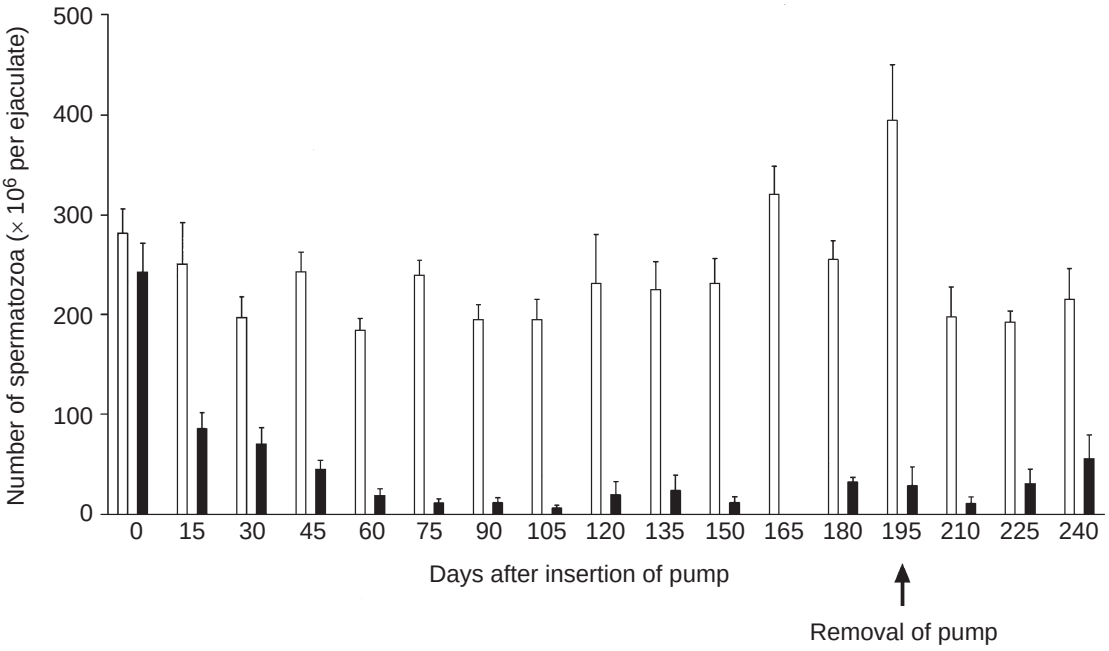

Fig. 3. Effect of administration of 100 μg 7α-methyl-19-nortestosterone (MENT) on the number of spermatozoa in adult male bonnet monkeys (*Macaca radiata*). Each value represents mean ± SE of five monkeys. □: Control; ■: 100 μg MENT.

these monkeys, suppression of the hypothalamo–pituitary–gonadal axis with an optimal dose of MENT alone or in combination with oestradiol at appropriate doses leads to infertility.

Discussion

The results of the present study clearly establish that administration of MENT causes a pronounced decline in the nocturnal surge of serum testosterone as early as day 3 after treatment and a significant decrease in the total number of spermatozoa at all doses of MENT tested. Although the concept of using feedback inhibition of hypothalamo–pituitary–gonadal axis by testosterone in males was tested by Reddy and Rao (1972), there has been comparatively little progress in practical application of this idea since the feasibility study published by a consortium backed by the World Health Organization (Anonymous, 1990). The lack of further study has been mainly attributable to the large dose of testosterone required to enforce azoospermia or, in the case of a GnRH antagonist, the necessity of androgen supplementation to maintain libido. Over the years, several long-acting derivatives of testosterone, such as enanthate and busiclate, have been used to supplement and suppress spermatogenesis in the limited clinical trials.

As several of the hormonal approaches to male contraception involved androgen supplementation, there have been attempts to synthesize potent androgen derivatives.

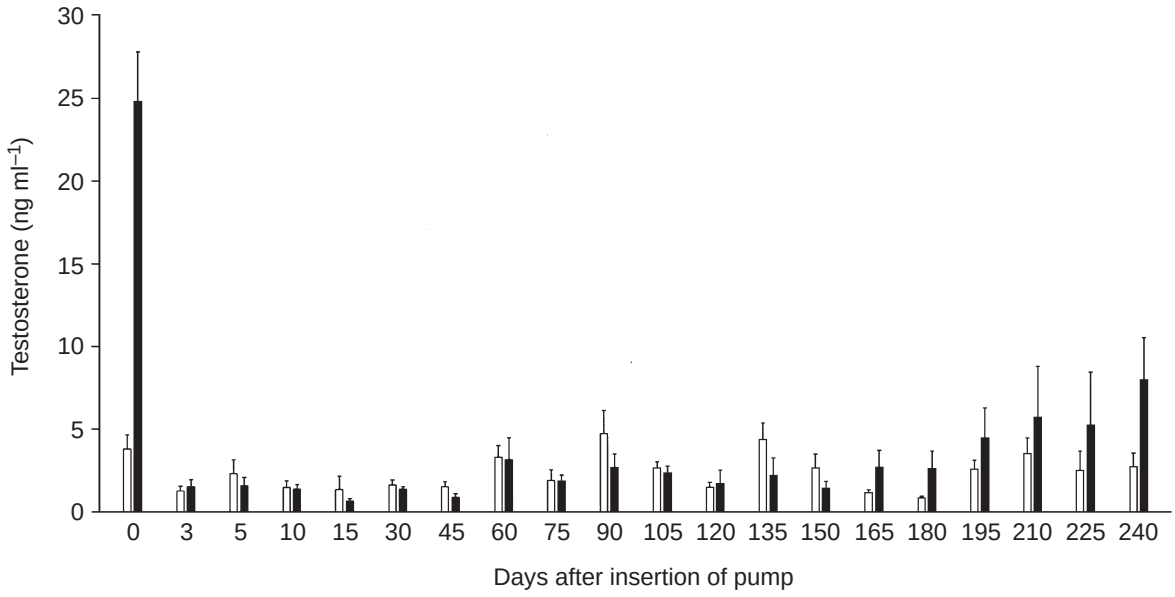

Fig. 4. Effect of administration of 50 μg 7α-methyl-19-nortestosterone MENT and 50 pg oestradiol on serum testosterone concentrations in adult male bonnet monkeys (*Macaca radiata*). Each value represents mean ± SE of five monkeys. Samples were collected at 10:00 h (□) and at 22:00 h (■).

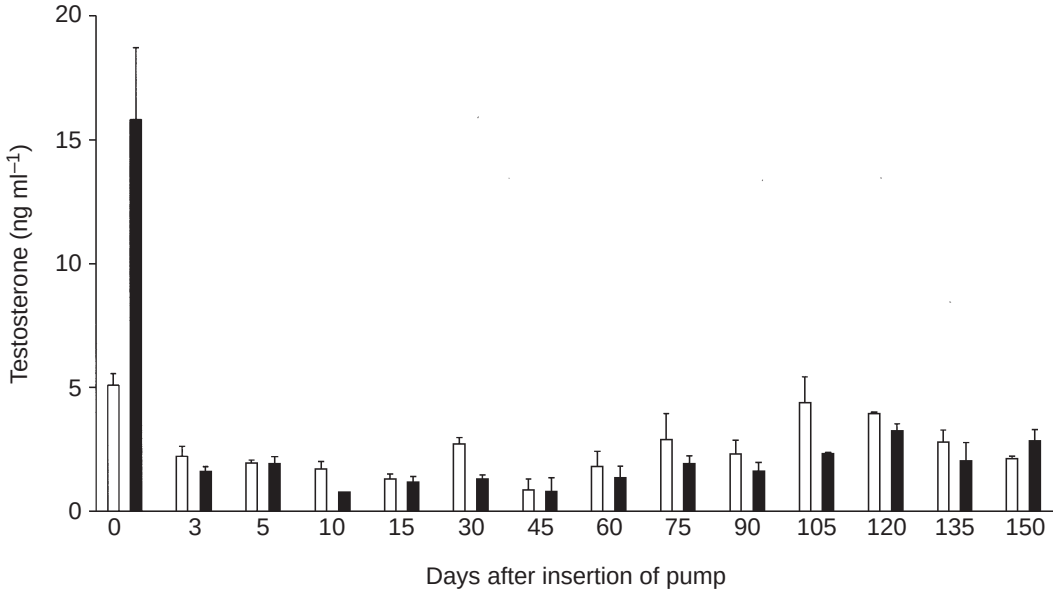

Fig. 5. Effect of administration of 25 μg 7α-methyl-19-nortestosterone (MENT) and 25 pg oestradiol on serum testosterone concentrations in adult male bonnet monkeys (*Macaca radiata*). Each value represents mean ± SE of five monkeys. Samples were collected at 10:00 h (□) and at 22:00 h (■).

One such compound, MENT, has been evaluated extensively for its androgenic potency (Sundaram *et al.*, 1996). It has been demonstrated that MENT can be administered as a substitute for testosterone for 1 year by sub-dermal implants. MENT does not undergo 5α-reduction and is ten times more potent than testosterone in suppressing the increase in the gonadotrophin concentrations after castration. In *Macaca fascicularis*, administration of 100 μg MENT per day maintained prostate volume (Cummings *et al.*, 1998). This finding indicates that doses of this steroid that result in gonadotrophic suppression neither hyperstimulate the prostate gland nor detract from its normal secretory function.

After establishing a minimum dose of MENT for effective suppression of the nocturnal surge of testosterone, we considered whether further inhibition of the reproductive

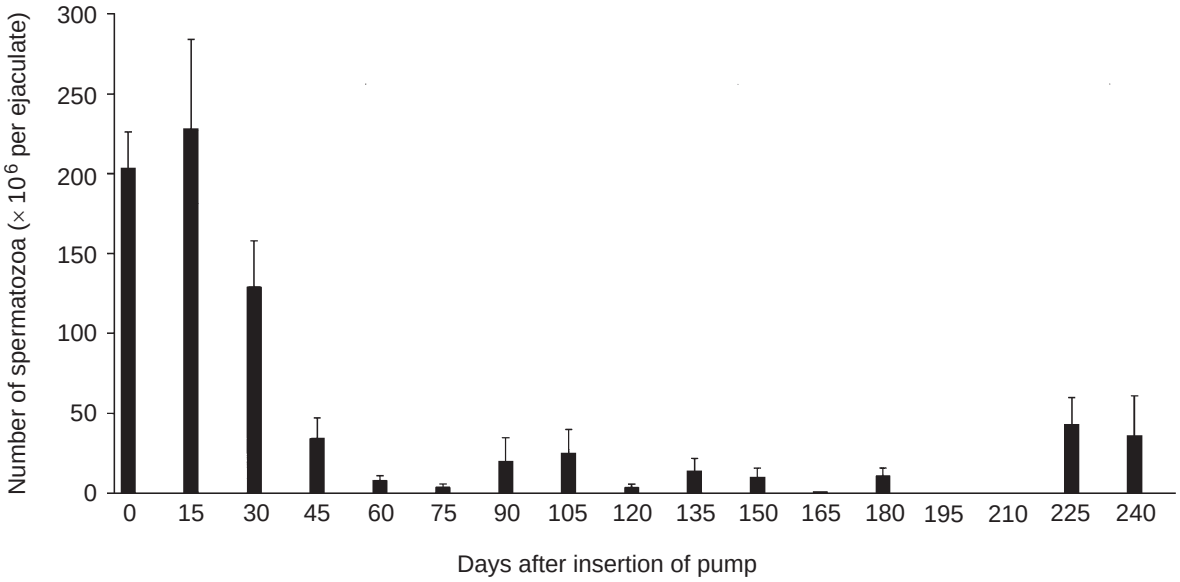

Fig. 6. Effect of administration of 50 μg 7α-methyl-19-nortestosterone (MENT) plus 50 pg oestradiol on the number of spermatozoa in adult male bonnet monkeys (*Macaca radiata*). Each value represents mean ± SE of five monkeys.

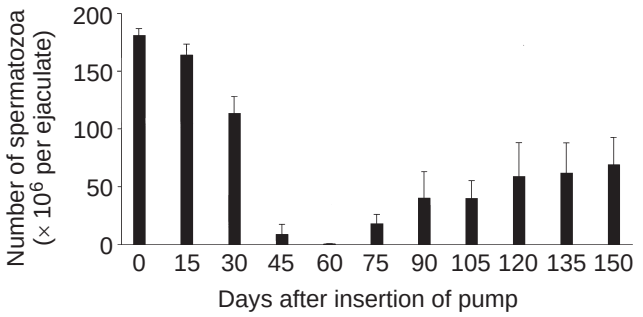

Fig. 7. Effect of administration of 25 μg 7α-methyl-19-nortestosterone (MENT) plus 25 pg oestradiol on the number of spermatozoa in adult male bonnet monkeys (*Macaca radiata*). Each value represents mean ± SE of five monkeys.

axis could be achieved by adding a low dose of oestrogen, because oestradiol is the most potent suppressor of LH secretion among the sex steroids (Ewing *et al.*, 1983). Moreover, a recent study in humans showed that administration of oestradiol in combination with testosterone by sub-dermal depot release augmented the gonadotrophic suppression compared with testosterone alone (Handelsman *et al.*, 2000). Although the study on humans did not record a change in the final percentage of men that achieved azoospermia with oestrogen supplementation, this issue remains open for exploration using a greater range of dosage combinations and with MENT as the androgen. Thus, it is hypothesized that because the aromatized metabolite of MENT is more oestrogenic than oestradiol, the aromatized metabolite of testosterone, a MENT + oestradiol combination would effectively suppress male fertility.

In the present study, the effects of administering MENT alone or in combination with oestradiol were evaluated in adult male bonnet monkeys. This species of monkey has been used extensively for a variety of studies and all the reproductive hormone profiles have been published (Rao *et al.*, 1997). The bonnet monkey breeds well in captivity and under controlled breeding (that is, using animals that show ovulatory cycles, with a fertility index of 80–85%; Rao *et al.*, 1997). The results of the present study clearly establish that administration of MENT results in suppression of the nocturnal surge of testosterone as well as a decrease in the number of spermatozoa. In addition, the combined dose regimens of MENT + oestradiol were more effective than MENT alone in suppressing the nocturnal surge of serum testosterone and decreasing the number of spermatozoa. Of the two combination doses tested, 50 μg MENT with 50 pg oestradiol was more effective than 25 μg MENT + 25 pg oestradiol at suppressing both parameters.

Administration of MENT was associated with a decrease in testosterone concentrations observed as early as day 3 of treatment, but the decrease in the number of spermatozoa was observed only after day 45. It was evident that these effects were specific to MENT as both testosterone concentrations and the number of spermatozoa returned to normal within a short period after removal of the implants. The ability of MENT to interfere with hypothalamo–pituitary–gonadal axis was also evident from the decrease in the after castration increase in serum LH concentrations.

The ability of lower doses of MENT to suppress serum testosterone concentrations and the number of spermatozoa more effectively than the higher doses of MENT (300 and 1000 μg) could be due to the inherent androgenic effects at the higher doses. This is also evident from the fact that none

Table 3. Serum concentration of oestradiol and progesterone in female bonnet monkeys (*Macaca radiata*) used for breeding studies with male monkeys that were treated with 7α-methyl-19-nortestosterone (MENT)

Group	Total number of animals	Total number of ovulatory cycles exposed	Peak serum oestradiol[a] (pg ml^{-1}) (days 7–10)	Peak serum progesterone[a] (ng ml^{-1}) (days 16–24)
Control	5	20	429.13 ± 20.25	4.18 ± 0.16
100 µg MENT (n = 10)	10	30	535.80 ± 40.36	2.82 ± 0.13
50 µg MENT + 50 pg oestradiol (n = 5)	5	15	680.00 ± 38.35	2.93 ± 0.12

[a]Maximum concentration of serum oestradiol on any day between day 7 and day 10 and maximum concentration of serum progesterone on any day between day 16 and day 24 was considered for calculation.
Values are mean ± SE.

Table 4. Fertility study on 7α-methyl-19-nortestosterone (MENT)-treated and control bonnet monkeys (*Macaca radiata*)

Group	Number of animals	Number of ovulatory cycles exposed	Number of pregnancies
Control	5	20	15
100 µg MENT	10	30	0
50 µg MENT + 50 pg oestradiol	5	15	0

of the animals treated with MENT showed muscle wasting, loss of body weight or testicular volume, which are commonly seen when testosterone concentrations are decreased. In fact, all of the animals gained weight during the course of the treatment period, which provides additional evidence of the anabolic effect of MENT. It has been reported previously that a combination of testosterone and oestradiol is more effective in inhibiting LH release, testicular testosterone production and thus spermatogenesis compared with testosterone alone (Ewing *et al.*, 1983). It was therefore of interest to examine whether the inclusion of oestradiol in combination with MENT was more effective than MENT alone. The results from the present study indicate that inclusion of 50 pg oestradiol in combination with 50 µg MENT was more effective than 100 µg MENT alone. This dose of oestradiol did not cause detectable gynaecomastia as judged by physical examination of the animals. These results indicate that MENT in combination with oestradiol may be potentially exploited for male contraception and at the same time avoids the unwanted side effects of increased oestrogen action. Further refinement of this potential may be realized with the advent of selective oestrogen response modulators (Thiebaud and Secrest, 2001). It may be possible, for example, to develop a MENT + oestradiol regimen using a selective oestrogen response modulator in place of oestradiol, thereby potentiating the antigonadotrophic effects of the synthetic androgen without changing, or even decreasing, the circulating concentrations of oestradiol.

Fertility studies have clearly established the efficacy of MENT in interfering with fertility in the treated monkeys. None of the 15 monkeys treated with MENT was able to impregnate females of proven fertility, and these females did become pregnant when exposed to control males, thus establishing that the females used for breeding studies were of normal fertility. It is pertinent to note that in a clinical study (Noe *et al.*, 1999), it has been demonstrated that administration of MENT by implants resulted in a dose-dependent decrease in gonadotrophin and serum androgen concentrations, without adverse reactions or changes in clinical chemistry and haematology.

Taken together, the results of the present study indicate that a low dose of MENT is effective in suppressing gonadotrophins with consequent antifertility effects, without resulting in adverse effects on libido or weight loss. The effective dose of MENT may be lowered further by combined administration of low-dose oestradiol.

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