International journal of andrology, 23, Suppl. 2: 13–15 (2000)

PN-ACN-913

7α-Methyl-19-nortestosterone (MENT): the optimal androgen for male contraception and replacement therapy

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Keywords: androgen, male contraceptive implants, prostate, 7α-Methyl-19-nortestosterone

Introduction

Androgen supplementation currently involves large, frequent doses of testosterone (T) esters that are associated with wide fluctuations of plasma T levels (Behre *et al.*, 1990). More recently, depot preparations and pellets that require less frequent administration have been developed (Partsch *et al.*, 1995; Handelsman, 1990). There is a need for an androgen preparation that provides appropriate, continuous replacement doses over long periods. To achieve this goal, 7α-methyl-19-nortestosterone (MENT), a synthetic androgen that is considerably more potent than T, is suitable. As a consequence, it is feasible to administer this androgen once a year by subdermal implants. Another important feature of MENT is that it does not undergo 5α-reduction in the prostate, as does T. 5α-reduction of T in the prostate leads to an amplification of its activity and increased prostate growth. Hence, a dose of MENT sufficient to maintain normal muscle mass and gonadotropin secretion will not hyperstimulate the prostate. This review summarizes the biological activity of MENT that form the basis of recommending MENT as a replacement androgen.

Tissue-selective effects of MENT

The biological potency of T and MENT was compared by studying the dose responses of ventral prostate (VP), levator ani (muscle) and gonadotropin secretion in castrated rats for 14 days. Based on the weights of VP, MENT was estimated to be four to five times more potent than T. By contrast, MENT was 10 times more potent than T on muscle and pituitary. Based on these considerations, it was hypothesized that a dose of MENT, which will maintain muscle mass and normal gonadotropin secretion, will be less supportive of prostate. In vitro studies have shown that MENT is resistant to enzymatic 5α-reduction (Agarwal & Monder, 1988). It is well established that in the prostate, T is enzymatically reduced to 5α-dihydrotestosterone (DHT), a more potent androgen, leading to an amplification of its action (Bruchovsky & Wilson, 1968). This observation suggested a possible mechanism for the differential action of MENT on this organ; i.e. the action of MENT cannot be amplified in the prostate. To investigate this, a 5α-reductase inhibitor was used to study the in vivo action of MENT (Kumar *et al.*, 1992). The effect of a 5α-reductase inhibitor (Finasteride) on the in vivo action of T and MENT was studied. Castrated rats were treated with the androgens with or without finasteride for 1 week. Finasteride inhibited the action of T on VP but not on muscle. In contrast, it did not alter the action of MENT on VP or muscle. These results suggest that MENT does not undergo 5α-reduction in vivo.

The differential effects of MENT and T seen in rats was investigated in cynomolgus monkeys. Castrated monkeys were given different doses of MENT or T via osmotic pumps. Serum LH levels were measured by bioassay and prostate volumes were measured by MRI. Complete suppression of LH was achieved with a minimum of 0.3 mg/day MENT, compared with 3.0 mg/day T. MENT supported body weight 10 times more potently than did T. Baseline prostate volumes were maintained with 0.1–0.2 mg/day MENT vs. 0.3 mg/day T. Thus, in monkeys, MENT was 10 times more potent than T with regard to the clinically desirable end points of gonadotropin suppression and anabolism, but only twice as potent at stimulating prostate growth (Cummings *et al.*, 1998).

The use of MENT as an androgen supplement was investigated in rhesus monkeys. Monkeys were treated with a GnRH agonist continuously via osmotic pumps. This led to a complete suppression of pituitary testicular axis. T levels were decreased and ejaculatory response was lost. Administration of MENT via subdermal implants restored ejaculatory function. The ejaculates were devoid of

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spermatozoa, indicating the potential of this approach in male contraception (Sundaram *et al.*, 1987).

Bioavailability and pharmacokinetics of MENT

Since we anticipate using MENT acetate (MENT Ac) rather than MENT in the implant form of this androgen in humans, the bioavailability of MENT following the administration of MENT and MENT Ac was investigated in cynomolgus monkeys (Kumar *et al.*, 1997). Equimolar concentrations of MENT or MENT Ac were administered as a continuous subcutaneous infusion via Alzet osmotic pumps. Serum MENT levels were measured by radioimmunoassay (RIA) in blood samples collected daily for 4 days during steady state. The serum MENT levels were not significantly different in the two groups (11.3 ± 1.6 vs. 13.1 ± 1.2 nmol/L). This suggested that MENT Ac was rapidly converted to MENT in circulation: The hydrolysis of MENT Ac to MENT was confirmed by the *in vitro* incubation of MENT Ac with blood or plasma and the demonstration of MENT in products following separation by HPLC.

Following the demonstration of the safety of MENT Ac in toxicity studies in rats, rabbits and monkeys, a pharmacokinetic study was performed in men. In normal men, a single intravenous bolus of 500 μg of MENT led to peak serum MENT levels by 3 min. The average terminal half-life and the metabolic clearance rate (MCR) were calculated to be 40 min and 2360 L/day, respectively. The results of the pharmacokinetic studies show that in both men and monkeys, the MCR of MENT is much faster than that reported for T. The faster MCR can be attributed, in part, to the finding that, in contrast to T, MENT showed no binding to sex hormone binding globulin (SHBG).

MENT Ac implant studies in men

MENT Ac implants are made of ethylene vinyl acetate cylindrical rods that measure 4.4 cm long and are 2.6 mm in diameter. The rods release approximately 400 μg MENT Ac per day.

In a study in normal men 1, 2 or 4 implants were inserted subdermally. Serum hormone levels were measured at weekly intervals. The implants were removed after 4 we The treatment led to a dose-dependent decrease in serum and gonadotropin levels. Two and four implants induced maximum suppression for the duration of treatment. All parameters returned to normal following removal of the implants (Noe *et al.*, 1999).

In hypogonadal men the ability of two MENT Ac implants to support sexual behavior was compared with that of intramuscular injections of T enanthate (200 mg at 3 week intervals). The study used a cross-over design and each phase of treatment lasted for 6 weeks. Responses to treatment were measured by a combination of daily diaries, questionnaires and interviews. The results showed that the response to two MENT Ac implants was similar to that of standard treatment with T enanthate. The implants were well tolerated and preferred over the frequent injection of T enanthate (Anderson *et al.*, 1999).

Conclusions

MENT is a synthetic androgen that is 10 times more potent than T. It can be administered via subdermal implants for long-term replacement therapy. In contrast to that of T, its action on the prostate is not amplified and it therefore has health benefits when used clinically.

Ackowledgements

This study, undertaken by the International Committee for Contraception Research of the Population Council, is part of the Contraceptive Development Program at the Population Council's Center for Biomedical Research, New York. We wish to acknowledge the generous support received from the US Agency for International Development (cooperative agreements DPE-3050-A-00-8059-00, CCP-A-00-94-00013-04 and HRN-A-00-99-00010-00), the National Institutes of Health (Center grant U54 HD29990), the United Nations Population Fund (UNFPA), The Bingham Trust, The Educational Foundation of America, The Lita Annenberg Hazen Foundation, The George Hecht Family Trust, The William and Flora Hewlett Foundation, The Andrew W. Mellon Foundation and The Rockefeller Foundation.

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