Treatment of anorchia with oral testosterone undecanoate: pharmacodynamics and clinical effectiveness

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Abstract. The pharmacodynamics of plasma testosterone (T) and androstenedione (A) levels were studied in ten hypogonadal boys after oral administration of testosterone undecanoate (TU). Plasma T and A levels were measured by specific radioimmunoassays. Six hours after a single dose of 120 mg TU, there was a significant increase ($P < 0.005$) in plasma T and A with a median T peak level of 940 ng/100 ml. Furthermore, twelve agonadal boys treated with a mean dose of 60 mg TU/day were examined over a period of 18–24 months. During this therapy, plasma T and A levels were significantly higher than before ($P < 0.005$), whereas plasma levels of LH and FSH did not decrease significantly. With the exception of one anorchic boy, all patients showed signs of sexual maturation, such as growth of pubic and axillary hair, and steady development of bone age during oral TU treatment.

The replacement therapy of testosterone (T) in patients suffering from deficient endocrine function of the testes is characterized by the following disadvantages:

The oral administration of genuine T is rather ineffective due to the rapid metabolism of the hormone both in the liver and in the intestinal wall (Foss & Camb 1939; Harri et al. 1970). Recently, however, Johnsen et al. (1974) have shown that 200 mg of oral T can produce normal male serum T levels for 5–7 h in eunuchs and therefore might be a useful form of androgen therapy (Johnsen 1978).

Synthetic methyl-testosterone is orally active, but may lead to liver dysfunction, such as jaundice or cirrhosis (Werner et al. 1950; Glover & Wilkinson 1968).

The injection of long-acting testosterone esters is not only inconvenient but also painful, particularly for children, and invariably results in unphysiologically high and fluctuating levels of T (Aakvaag & Vogt 1969).

Recent studies both in rats (Coert et al. 1975) and in adult males (Nieschlag et al. 1975; Franchimont et al. 1978) have shown a definite increase in plasma T upon oral administration of testosterone undecanoate (TU). A part of this lipophilic compound is incorporated into chylomicrons within the intestinal wall and thus enters the lymphatic rather than the portal vein system (Coert et al. 1975). Pathological effects of TU on hepatic function have not been observed.

The present study was conducted to evaluate the pharmacodynamics of plasma testosterone levels after oral administration of TU in boys. Furthermore, the clinical effectiveness of TU for the treatment of boys with anorchia was investigated in a long-term study.

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1 Andriol®, Organon.
Material and Methods

Protocol

1) Pharmacodynamic study

A total of 10 boys, aged 10–16 years, were studied. Seven of these children suffered from biochemically and/or surgically ascertained anorchia, three from delayed puberty. Five of these children had undergone a previous TU treatment of 10 months duration on the average.

The study was performed under varied conditions: Six children received a single dose of 120 mg TU at 09.00 h. Blood samples were taken immediately before TU administration, at 10.00, 11.00, 12.00, 15.00, 18.00, 21.00, as well as at 09.00 and 15.00 h the following day.

Five children received TU in different doses and intervals: Two boys received 2 × 20 mg/day, one was given 2 × 40 mg/day, and the last two children were administered 3 × 20 mg/day. TU was given two times daily at 09.00 and 18.00 h, and a noon dose was added for the last two children. Blood samples were collected prior to TU administration, at 21.00, 24.00 h and at 09.00 h the following morning.

All blood samples were drawn into heparinized tubes and the plasma was stored at −20°C.

2) Long-term study

A total of 12 boys with anorchia received TU over a period of 18–24 months.

Six patients aged 10–13 years had never undergone an androgen treatment prior to this study. In these boys, administration of an initial dose of 20 mg TU/day was started after both LH and FSH had reached hypergonadotrophic levels.

Six patients between 13 and 15 years of age had previously received other preparations of testosterone, such as fluoxymesterone orally or injections of testosterone esters. In all 12 patients, the initial TU dose was raised — depending on the individual stage of sexual maturation — to a maximum dose of 120 mg/day which was administered in three cases.

Clinical and biochemical examinations of all children were performed at least every 6 months. At each checkup the following data were gathered: developmental stages of pubic and axillary hair according to Tanner (1961), and sexual maturity as expressed in beard growth, erections, masturbation etc. Patients were also questioned as to any undesirable effects of the drug. Blood samples were taken for the measurement of plasma T, androstenedione (A), LH and FSH levels. A precise time schedule between drug administration and blood sampling could not be followed in every instance, since all these boys were out-patients.

At random intervals, in serum samples collected simultaneously, GOT, GPT, γ GT and bilirubin levels were measured. Bone age was determined every 12 months according to Greulich & Pyle (1959).

Testosterone and androstenedione plasma levels (individual values, medians and ranges) in hypogonadal boys after a single oral dose of 120 mg testosterone undecanoate (TU). The range of testosterone plasma levels in normal adult males is indicated by the hatched bar.

![Fig. 1.](image-url)
Individual plasma levels of testosterone (top) and androstenedione (bottom) in 5 hypogoandal boys after different TU doses. The range of testosterone and androstenedione plasma levels in normal adult males found in our laboratory is indicated by the hatched bar.

**Preparations**
Soft gelatin capsules containing 20 or 40 mg of TU (17β-hydroxy-4-androstene-3-one 17β-undecanoate), dissolved in oleic acid were used.

**Steroid determination**
Plasma concentrations of T and A were determined by radioimmunological methods after Sephadex LH-20 chromatography as previously described (Weil et al. 1979). The only major cross-reacting steroids were dihydrotestosterone (64%) and A (4%) which were separated from T by Sephadex LH-20 chromatography before the radioimmunoassay. T-17β-undecanoate did not cross-react with the antiserum used for T determination. Plasma LH and FSH concentrations were measured by a standard double antibody radioimmunoassay technique previously evaluated in our laboratory (Bidlingmaier et al. 1977).

**Statistical analysis**
For statistical evaluation of the data, Mann-Whitney’s U-test (Mann & Whitney 1947) was used. Differences between means were considered as statistically significant when $P < 0.01$. 
Results

1) Pharmacodynamic study

After a single oral dose of 120 mg TU, there was a highly significant increase ($P < 0.005$) of plasma T levels in all patients, extending from 2 to 12 h after TU administration (Fig. 1). Between 2 and 9 h median T concentrations reached the normal range of healthy adult males (Knorr et al. 1974). No difference in plasma T levels could be seen between the previously TU treated and the untreated patients. Plasma A levels also increased significantly ($P < 0.005$) and concomitantly to T, yet, the peak of median A levels occurred 3 h earlier than the T peak (Fig. 1).

Under different doses of TU administered, plasma T levels increased markedly (Fig. 2, top). Although there was wide individual variation, all boys reached at least the lower limit of the normal adult male T range. After 24 h, control levels were observed in all patients. Plasma A levels increased in a similar pattern (Fig. 2, bottom).

Table 1.
Mean levels ($\pm$ sp) of plasma LH and FSH (ng/ml) in healthy boys throughout childhood and puberty. Plasma LH and FSH concentrations were measured by a double antibody radioimmunoassay using commercial kits. One milligram of FSH corresponded to 169 $\pm$ 19 mg of the human pituitary standard LER 977, 1 mg LH to 66 $\pm$ 6 mg LER 907, respectively.

<table>
<thead>
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<th>Age (years)</th>
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<td>0.9 $\pm$ 0.6</td>
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<td>FSH</td>
<td>0.3 $\pm$ 0.2</td>
<td>0.7 $\pm$ 0.3</td>
<td>0.9 $\pm$ 0.5</td>
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2) Long-term study

Plasma levels of LH and FSH in agonalad boys before and during TU treatment of 18–24 months duration are plotted in Fig. 3. Both LH and FSH did not decrease during a mean dosage of 60 mg TU/day. There were no significant differences between the gonadotrophin levels before and during treatment. The normal ranges of LH and FSH levels in healthy boys studied in our laboratory are listed in Table 1.

As shown in Fig. 4, the plasma levels of T and A were significantly higher during TU replacement than before therapy ($P < 0.005$). However, during treatment there was a wide individual fluctuation of T levels, ranging from 15 up to 860 ng/100 ml. The concentrations of testosterone after 6, 12, 18 and 24 months of therapy did not differ significantly from each other.

All patients not previously treated with androgens (pubertal stage 1) exhibited a steady development of pubic and axillary hair during TU treatment, with the exception of one boy (Fig. 5). The other boys who previously had been given other preparations of androgens showed further sexual development during TU administration.

![Fig. 4.](image_url)

Individual plasma levels of testosterone and androstenedione ($x \equiv$ median) in agonalad boys ($n = 12$) before and during TU therapy (average dose: 60 mg/day).

![Fig. 5.](image_url)

Development of pubic and axillary hair in agonalad boys ($n = 6$, not treated with androgens previously) during treatment with an average daily dose of 60 mg TU.
Bone maturation advanced gradually in all patients during the observation period (Fig. 6). All boys, except the one who developed neither pubic nor axillary hair, reported signs associated with progressive sexual maturation, such as growth of beard, erections, masturbations etc.

None of the patients noticed any untoward effects of the drug. The results of serum bilirubin levels and hepatic enzyme activities indicated normal liver function.

Discussion

Nieschlag et al. (1975) studied the pharmacodynamics of plasma testosterone (T) and androstenedione (A) levels in normal adult males after a single oral dose of 100 mg TU. They found a significant increase of both androgens with a mean peak level of T 5 h after TU had been administered. After another 5 h, all T and A levels had returned to control values. In the present study, we found a similar increase of both plasma T and A levels in hypogonadal boys with T peaks between 3 and 6 h after a single dose of 120 mg TU (Fig. 1).

The parallel rise of plasma testosterone and androstenedione levels found by Nieschlag et al. (1975) and confirmed in the present study is obviously due to the rapid conversion of testosterone to androstenedione (Horton & Tait 1966; Baird et al. 1969).

Mies & Kreml (1977) and Franchimont et al. (1978) reported marked and progressive increases of plasma T in adult hypogonadal males after 3, 6 and 9 weeks of TU administration. The doses used ranged between 120 and 240 mg TU/day.

According to our data, plasma T levels in agonal boys rose significantly during long-term TU therapy (Fig. 4). But the present results did not indicate a further T increase after 6, 12, 18, and 24 months of therapy with a mean dose of 60 mg TU/day.

In our patients, a great variation in individual plasma T levels was seen during continuous TU replacement therapy (Fig. 4). These relatively large fluctuations are partly a consequence of the lack of a precise daily time schedule between drug administration and blood sampling. Furthermore, there were considerable differences in the individual
plasma T increases after administration of the same TU dose (Fig. 1 and 2). Therefore, the measurement of a single plasma T level a day is of only limited value for the biochemical assessment of androgen replacement therapy.

A mean dose of 60 mg TU/day administered over a period of 18–24 months did not significantly decrease the hypergonadotrophic LH and FSH levels found in gonadal boys (Fig. 3). This finding is in contrast to the study of Franchimont et al. (1978) in which a pronounced and progressive decrease of plasma gonadotrophins was reported in hypergonadotrophic hypogonadal males during TU administration for 9 weeks. However, the doses applied, ranging between 120 and 240 mg/day, were considerably higher than those used in our study.

Except one boy, all our patients treated with TU over 18–24 months clinically showed a marked progress in pubertal development (Figs. 5 and 6). According to these clinical parameters, it is evident that TU is an effective androgen compound able to induce sexual maturation in hypogonadal boys. However, none of our patients reached full sexual maturity before the end of this study. Therefore, we cannot conclude at present that oral replacement therapy with TU alone is sufficient to bring about a full and lasting sexual maturation.

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