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A Ten-Year Safety Study of the Oral Androgen Testosterone Undecanoate

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ABSTRACT: Testosterone undecanoate (Andriol®) is an oral androgen that provides the hypogonadal patient with the unmodified testosterone molecule. It was introduced in the mid-1970s. This is a report on the safety of this oral androgen. Of 35 men originally included in the study, 33 could be followed up for a minimum of 10 years. In them no alteration in the biochemical parameters of liver function could be detected. Upon annual measurements (7–9 hours after ingestion of testosterone undecanoate), serum levels of testosterone ranged between 5.4 ± 1.9 and 6.5 ± 1.9 nmol/L (normal range 8–24) and of 5α-dihydrotestosterone between 3.2 ± 1.8 and 3.5 ± 1.7 nmol/L (normal range 0.8–2.5). These levels remained constant during the study period, indicating that there is no increased hepatic enzymatic breakdown of the androgen over time. Eight men were older than 50 years at the start of the study. Over the 10-year period in two of them a mild reduction in urine flow was measured, whereas in the other six this could not be demonstrated. Digital examination of the prostate did not reveal signs of prostate tumors. Testosterone undecanoate appears to be a safe oral androgen. A yearly checkup of the patient on therapy with this androgen seems adequate.

Key words: Drug safety, liver functions, gynecomastia, benign prostate hyperplasia.

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This is the report of a safety study of the oral androgen testosterone undecanoate (TU; Andriol®) in 33 hypogonadal men over a total period of 10 years. In 1986 a report on the safety of TU over the first 5 years was published (Gooren, 1986). Androgen replacement therapy in hypogonadal men aims to parallel the physiological pattern of testosterone production of eugonadal men. Ideally the mode of treatment should provide the hypogonadal patient with a product identical to the natural hormone in such quantities that physiological androgen levels are attained. Whereas the daily testosterone production of the eugonadal male is 7 mg, doses up to 400 mg free testosterone are needed to achieve physiologically active levels when this drug administered by mouth (Johnsen et al, 1976); this is due to inactivation by the liver after absorption from the digestive tract. Subsequently, modifications of the testosterone molecule (such as alkylation of the 17α-position) have been devised to evade immediate hepatic enzymatic breakdown. Unfortunately the severe hepatotoxic effects of 17α-alkylated androgens render them obsolete at present, particularly because alternatives are now available (Wilson and Griffin, 1980).

The oral androgen TU (Andriol®) is absorbed from the digestive tract via the lymph system and reaches the peripheral circulation before inactivation takes place in the liver. TU provides the patients, after its deesterification, with the unmodified testosterone molecule (Coert et al, 1975). Two studies (Skakkebaek et al, 1981; Gooren, 1987) have demonstrated its short-term clinical efficacy with regard to sexual functioning in men, but long-term studies have not been carried out. The clinically effective dose is 80–240 mg/day (2–6 capsules of 40 mg). Two studies (Schürmeyer et al, 1983; Cantrill et al, 1984) indicate that maximum serum testosterone levels are reached 2–6 hours after ingestion of TU. Subsequent serum testosterone levels fluctuate widely, and the serum testosterone peaks are relatively short-lived. In this respect TU compares unfavorably with parenteral testosterone esters, transdermal testosterone preparations, and testosterone pellets (Cantrill et al, 1984; for review see Behre et al, 1990). The major advantage of TU is its oral administration, appreciated by many patients. It has further been found that sexual functioning may continue or can be restored with levels of testosterone at 50–60% of the physiological range (Gooren, 1987; Buena et al, 1993). The latter may explain the clinical efficacy of TU not constantly producing physiological testosterone levels or even subnormal levels.

A dose of 80–240 mg TU/day constitutes a greater than normal load to the liver: 50–150 mg testosterone as compared to the estimated daily physiological production of 5–9 mg. Therefore long-term safety studies on potential hepatoxic effects are appropriate. Administration of TU generates relatively high levels of 5α-dihydrotestosterone (DHT) and of 17β-estradiol (E2) derived from peripheral

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conversion of testosterone. Though the pathophysiology of benign prostate hyperplasia is still unclear, both DHT and E2 have been implicated in its etiology (Wilson, 1980). Therefore this aspect must be addressed in the evaluation of the safety of an androgen compound.

Sex steroids can induce hepatic drug metabolizing enzymes and subsequently higher steroid doses may be required over time to achieve pharmacologically active levels of the steroid. Therefore plasma levels of testosterone and DHT were monitored.

Subjects and Methods

This study began in April 1977 and in the following 16 months 35 hypogonadal men, aged 15–62 years at the start of the treatment, could be included. In 12, TU was the first type of androgen treatment, whereas the remaining 23 had been on parenteral androgen administration previously. During the first 36 months of TU administration the patients were examined every 3 months and thereafter every 6 months. No side effects had occurred by 72 months of TU administration and then a yearly checkup was deemed appropriate. Of the 35 men, 33 patients could be followed up for a minimum of 120 months. One patient died at age 56 (after 92 months of TU therapy) of a bronchus malignancy and one 32-year-old man went to live abroad (after 80 months of TU therapy). The dose of TU was 80–200 mg/day (2–5 capsules), depending on the severity of the patient's androgen deficiency.

At each visit to the clinic, the blood pressure was measured and the prostate was digitally examined. The following laboratory screening was carried out: bilirubin, alkaline phosphatase, γ-glutamyltransferase, serum glutamic oxaloacetic transaminase (SGOT; = SASAT), serum glutamic pyruvic transaminase (SGPT; = SALAT), lactic dehydrogenase (LDH; = LD), α-fetoprotein, thrombotest and kaolin–cephalin time, and acid phosphatase. These parameters were all measured with methods of the routine hospital laboratory. In a follow-up period of between 74 and 90 months, the routine laboratory methods for determinations of liver function were changed with subsequently higher values of the reference range. To allow comparison and detection of upward or downward trends in values of parameters, the results with the new methods have been reconverted to values of the earlier laboratory methods with the help of the conversion factors provided by the laboratory at the time of the change of methods.

Plasma testosterone and DHT values were also measured annually to detect whether TU therapy induced an increase of hepatic drug metabolizing enzymes with resulting lower serum testosterone and DHT values over time. Testosterone, E2, and DHT were measured using routine methods (RIA) of the endocrine laboratory.

Determination of DHT

Blood sampling occurred between 1400 and 1600 hours, while the last ingestion of TU had taken place with the subjects' breakfast (generally between 0700 and 0900 hours). All eight patients who were older than 50 years at the start of the TU therapy could be followed up. Their urine flow was measured annually to detect manifestations of benign prostate hyperplasia in an early phase and to monitor its progression; the normal hospital equipment was used to measure the average flow in ml/second (total volume voided/time). Over the last 2 years of the study blood levels of prostate-specific antigen (PSA) were measured in all subjects.

Patients gave their consent to participate in this study, which was approved by the hospital committee on investigations in humans.

Statistical Analysis

Analysis of variance was used to determine whether the liver function tests, levels of testosterone and DHT, and the urine flow demonstrated a trend towards higher or lower values over the period of the study.

Results

TU appeared to be tolerated well by the patients. Twenty-three of the total of 33 subjects had been treated with parenteral testosterone esters previously, and they also felt that TU restored sexual functioning satisfactorily.

Routine laboratory measurements of liver function tests are presented in Table 1 as mean values ± SD, unless they were recorded as below a certain limit. No impairment of liver functions was observed, nor was there a tendency in any of the parameters towards higher/lower values. The same applied to levels of prostatic acid phosphatase. The levels of PSA, measured only over the last 2 years of the study, were within the reference limits of the laboratory (<4 μg/L). Levels of testosterone/DHT and 17β-estradiol also remained stable, without a tendency to lower/higher values over time (Table 1). It is of note that the levels of testosterone were subnormal (between 5.4 ± 1.9 and 6.5 ± 1.9 nmol/L). The blood samples of our patients were drawn 7–9 hours after ingestion of their last dosage and approximately 3–4 hours before their next one. The normal range of our laboratory is 8–24 nmol/L in eugonadal men. This reference value was established in 120 healthy male hospital workers aged 20–60 years in samples drawn at midday. Levels of DHT (between 3.2 ± 1.8 and 3.5 ± 1.7 nmol/L) were, however, slightly above the normal range in men (0.8–2.5). So were the E2 levels. Urine flow did not undergo a significant reduction during the follow-up period in the group of eight men in whom this had been monitored (Table 1). In two patients a moderate reduction over 10 years was measured, but no specific measures were needed. On digital examination none of the patients had signs of a prostate tumor.

Table 1. *Liver function tests and testosterone levels in 33 men taking 80–200 mg oral testosterone undecanoate (TU)/day*

Parameters	Reference range	Months after start of TU									
		12	24	36	48	60	72	84	96	108	120
Bilirubin (μmol/L)	<9	<9	<9	<9	<9	<9	<9	<9	<9	<9	<9
Alkaline phosphatase (U/L)	<100	74 ± 12	75 ± 13	74 ± 13	78 ± 14	71 ± 11	74 ± 14	75 ± 13	76 ± 15	75 ± 12	74 ± 13
α-Glutamyttransferase (U/L)	<30	15 ± 4	18 ± 4	13 ± 7	15 ± 6	13 ± 7	16 ± 6	17 ± 5	15 ± 6	16 ± 5	17 ± 6
SGOT (= SASAT) (U/L)	5–15	8 ± 2	8 ± 3	9 ± 3	10 ± 3	9 ± 2	8 ± 3	10 ± 4	9 ± 3	9 ± 3	8 ± 4
SGPT (= SALAT) (U/L)	5–15	9 ± 2	10 ± 2	10 ± 2	9 ± 3	9 ± 3	10 ± 2	9 ± 3	10 ± 4	9 ± 3	10 ± 4
LDH (U/L)	<175	118 ± 20	112 ± 21	115 ± 27	128 ± 21	125 ± 22	110 ± 23	124 ± 26	119 ± 24	127 ± 31	116 ± 30
α-Fetoprotein (pg/L)	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Thrombotest (seconds)	44–55	47 ± 1.2	46 ± 1.5	46 ± 1.6	46 ± 1.6	46 ± 1.7	47 ± 1.9	46 ± 1.9	47 ± 1.2	46 ± 1.4	47 ± 1.5
Kaolin–cephalin (seconds)	46–50	48 ± 1.2	46 ± 1.4	46 ± 1.4	46 ± 1.5	46 ± 1.4	47 ± 1.4	48 ± 1.2	48 ± 1.4	48 ± 1.7	48 ± 1.4
Acid phosphatase (U/L)	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Testosterone (T) (nmol/L)	8–24	5.4 ± 1.9		6.0 ± 2.0		6.1 ± 1.8	5.9 ± 1.7	6.5 ± 1.9		6.7 ± 1.8	6.5 ± 1.4
Dihydrotestosterone (DHT) (nmol/L)	0.8–2.5	3.5 ± 1.2		3.4 ± 1.3		3.2 ± 1.8	3.3 ± 1.7	3.5 ± 1.7		3.2 ± 1.6	3.1 ± 1.4
17β-estradiol (E2) (pmol/L)	40–120	122 ± 37		135 ± 40		121 ± 42	136 ± 48	137 ± 32		126 ± 29	141 ± 35
Ratio T/DHT	8–12	1.6 ± 0.7		1.8 ± 0.8		1.9 ± 0.7	1.7 ± 0.8	1.9 ± 0.8		2.0 ± 0.8	2.0 ± 0.7
Urine flow (ml/second)	15–25	18 ± 4	20 ± 5	19 ± 5	18 ± 4	19 ± 5	20 ± 4	20 ± 4	20 ± 5	21 ± 4	19 ± 6

Of the eight men over 50 years of age at the start of the treatment, urine flow was also measured. Values are mean ± SD.

Discussion

Androgen replacement in hypogonadal men may imply several decades of drug administration. Generally these men are in good health and it will likely contribute to their well-being when they are reminded as little as possible of their medical condition. Consequently an oral androgen may be more acceptable to the patient than injectable androgens. Of the 23 patients in this study previously treated with parenteral androgens administered once per 2–3 weeks, 18 experienced their independence of injections as favorable. Another concern of oral androgen use is the long-term safety. Thirty-three of the initial cohort of 35 patients could be followed up for 10 years. In none of them could an impairment of liver function be detected. Data analysis did not reveal a tendency to alterations of parameters of liver functions to higher/lower values. This is pertinent because values may remain within reference ranges but yet show an upward/downward trend that might go undetected in clinical routine checks. Levels of testosterone and DHT remained stable over a 10-year period; this indicates that this oral androgen did not induce hepatic drug metabolizing enzymes, which would necessitate higher doses of the androgen to attain identical blood hormone levels.

In two middle-aged men a mild reduction in urine flow was measured. In the other six of the same subgroup this did not become manifest. Statistical analysis of the measurements with regard to this parameter did not demonstrate this to be a trend in this subgroup of elder men in the study. We were interested in this aspect because TU generates high levels of DHT and E2, and both many play a role in the etiology of benign prostate hyperplasia (Wilson, 1980). That signs of BPH were relatively rare in this subgroup may be ascribed to the fact that plasma testosterone levels with TU therapy are in the low range of normal values of eugonadal men; it is conceivable that the total sex steroid load to the prostate with TU was even lower than average in men.

As reported earlier (Gooren, 1986) gynecomastia was not observed in any of the nine patients specifically monitored for this symptom in the first 6 months of TU administration. In them TU had been the first type of androgen therapy they ever received. Gynecomastia is not uncommon when androgen administration is initiated. Studies from France suggest that treatment with DHT percutaneously, resulting in higher DHT blood levels, reduced pubertal gynecomastia (Kuhn et al, 1983). It could very well be that the high DHT blood levels generated by TU administration countered the effects of E2 on breast tissue.

In conclusion, TU appears to be an oral androgen that served 33 hypogonadal over a period of 10 years satis-

factorily in spite of low normal to subnormal testosterone levels. There is evidence, however, that restoration of sexual function in men does not require physiological levels of testosterone. There was no evidence of liver function disturbances, nor were there signs of acceleration of the development of BPH in these men. None of the patients had signs of a prostate tumor upon digital examination.

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