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·*Review*·

More than eight years' hands-on experience with the novel long-acting parenteral testosterone undecanoate

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Abstract

Testosterone (T) as a compound for treatment of T deficiency has been available for almost 70 years, but the pharmaceutical formulations have been less than ideal. Traditionally, injectable T esters have been used for treatment, but they generate supranormal T levels shortly after the 2-3 weekly injection interval. T levels then decline very rapidly, becoming subnormal during the days preceding the next injection. The rapid fluctuations in plasma T are subjectively experienced as disagreeable. T undecanoate (TU) is a new injectable T preparation with a considerably better pharmacokinetic profile. After two initial injections separated by a 6-week interval, the following intervals between two injections are generally 12 weeks, eventually amounting to a total of four injections per year. Plasma T levels with this preparation are nearly always in the range of normal men, as are its metabolic products estradiol and dihydrotestosterone (DHT). It reverses the effects of hypogonadism on bone and muscle and metabolic parameters, and on sex functions. It is suitable for male contraception. Its safety profile is excellent because of the continuous normalcy of plasma T levels. No polycythemia has been observed and no adverse effects on lipid profiles. Prostate safety parameters are well within reference limits. TU is a valuable treatment option of androgen deficiency. *(Asian J Androl 2007 May; 9: 291–297)*

Keywords: testosterone treatment; testosterone undecanoate; pharmacokinetic profile; clinical efficacy; side effects; sexual dysfunction; male contraception

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1 Introduction

There are a number of new treatment modalities for androgen deficiency, such as transdermal testosterone

(T) gels, a buccal T tablet, and injectable long-acting T undecanoate (TU) in castor oil, which appears to be a real depot preparation requiring only four injections per year [1, 2]. In this review the pharmacokinetics, the first clinical experiences and the use of TU for the treatment of sexual dysfunction and male contraception are summarized.

2 Pharmacokinetic studies

Injectable TU was first used in China for the treatment of hypogonadism [3], and later also for contraception [4, 5]. The long half-life of the Chinese preparation was confirmed in monkeys [6] and in hypogonadal men in Europe. In a study by Behre *et al*. [7] it was found that TU dissolved in castor oil had better pharmacokinetic properties than TU dissolved in tea-seed oil. TU appeared to generate plasma T levels with longer half-lives, and which did not exceed the upper limit of normal. In an initial multiple-dose kinetics study, 13 hypogonadal men received four intramuscular injections of TU (Nebido, Bayer-Schering Pharma, Berlin, Germany) at 6-week intervals [8]. Serum T levels were never found to lie below the lower limit of normal and, only briefly after the 3rd and 4th injection, serum T levels were above the upper limit of normal, while peak and trough levels increased over the 24-week observation period with this regimen of an injection every 6 weeks. Serum estradiol and dihydrostestosterone (DHT) followed this pattern, not exceeding the normal limits [8]. The same research group performed a study to establish suitable injection intervals for TU. In seven hypogonadal men, injections were given at gradually increasing intervals between the 5th and 10th injection (starting with 6-week injection intervals) and from then on every 12 weeks. Steady state kinetics were assessed after the 13th injection. C_{max} was 32.0 ± 11.7 nmol/L and half-life was 70.2 ± 21.1 days. The mean C_{max} of 32 nmol/L seen during steady-state with TU administration was lower than that achieved by transdermal T gel (Testogel, Besins-Iscovesco, Paris, France) 100 mg/day (37.5 nmol/L). However, it was higher than with transdermal T gel 50 mg/day (28.8 nmol/L) and testosterone skin patch (Androderm, Watson Pharmaceuticals, Corona, CA, USA) 5mg/day (26.5 nmol/L). Before the next injection, the serum levels for T and its metabolites DHT and estradiol were mostly within the normal (eugonadal) range and showed a tendency to decrease with increasing length of injection intervals. The study concluded that after initial loading doses at 0 and 6 weeks, injection intervals of 12 weeks establish eugonadal values of serum T in almost all men [9].

Clinical long-term experience up to 120 weeks was also published in 2004 by another group (Bueber V *et al*. Treatment of hypogonadal men with long-acting testosterone undecanoate (TU): Clinical and pharmacokinetic results after intramuscular application of 1 000 mg TU every three months up to 120 weeks. The Endocrine Society's 86th Annual Meeting, June 16–19, 2004, p. 445 [PS-556]). Twenty-six hypogonadal patients received TU (1 000 mg/4mL) in a first-stage of the study in weeks 0, 6, 16, 26 and 36, followed by an additional stage of up to 120 weeks with injections every 12 weeks. Supranormal peak concentrations of total and free T occurred 2 weeks after the first injection, then a decrease to within the physiological range was observed. At the end of the study, during the wash-out period, serum T levels declined to the low pre-treatment levels 14 weeks after the final injection. A parallel increase of 17β-estradiol levels was seen, but the decrease to pre-treatment levels was sooner than that of T and occurred by 4 weeks after the last injection. Serum LH and FSH were suppressed during the treatment period, while sex hormone binding globulin (SHBG) remained stable. Serum prostate-specific antigen (PSA) rose from 0.660 to 0.976 ng/mL ($P < 0.01$) after 120 weeks, but did not exceed the normal range. Prostate volume increased from 19.6 to 26 mL ($P < 0.05$). Osteocalcin rose from 0.734 to 1.049 nmol/L ($P < 0.01$). Bone mineral density (BMD) did not change. Standard laboratory tests and uroflow did not change. Sexual interest (assessed by use of the Aging Male Symptoms score [AMS] questionnaire) increased.

There is now long-term experience of more than 8 years with TU in 22 hypogonadal men [10].

Individual dosing intervals ranged from 10 to 14 weeks. Serum trough levels of T were generally above the lower limit of normal, indicating sufficient substitution over the previous injection interval. In contrast to short-acting T esters, perceptions of fluctuations in androgen serum concentrations were rare. If this was the case, it occurred during the last 2 weeks before the next injection, indicating that levels of T had fallen below normal. Interestingly, patients recognize psychosomatic symptoms when plasma T levels fall below an individual threshold value [11]. Summarizing the two key studies by Zitzmann and Nieschlag [12] and Schubert *et al*. [13], the following regimen of administration is recommended for TU therapy in hypogonadal men: the second injection

of 1 000 mg TU should be administered 6 weeks after the first injection of 1 000 mg TU (loading dose), followed by injections every 12 weeks. An individualisation of the TU therapy should be recommended. If the T serum concentration before the 4th injection lies between 10–15 nmol/L, then the injection interval should be maintained every 12 weeks. If the T serum concentration at this time is lower than 10 nmol/L, then the injection interval should be shortened to 10 weeks. If the T level is, however, greater than 15 nmol/L, then the injection interval can be extended to 14 weeks. Additionally, clinical symptoms carry weight for the individualisation of injection intervals with TU therapy [11]. The loading dose of TU achieved by the first two injections with an interval of 6 weeks is also recommended for patients who are being transferred from short-acting T injections (e.g. T enanthate [TE] 250 mg) to treatment with TU.

3 Therapy of hypogonadism with TU

The efficacy of TU has been compared to the previous standard therapy of 250 mg TE i.m. administered every three weeks in a 30-week controlled, prospective, randomized, parallel-group study [13]. During the first 30 weeks of the comparative phase, 40 hypogonadal men with T levels below 5 nmol/L were randomly assigned to either 250 mg TE i.m. every 3 weeks (n = 20) or TU three times at 6-week intervals followed by a 9-week interval. Following the first 30 weeks of the comparative part of the study, all patients received TU every 12 weeks in the one-arm follow-up study over an additional 30 months. During the first 30 weeks there were no differences in sexual parameters (spontaneous morning erections, total erections, ejaculations) between the two groups. After 30 weeks, serum PSA levels in both treatment groups had risen slightly, but remained stable during long-term TU administration and stayed within the normal range over the entire observation period. Prostate volumes increased during the first 30 weeks to a similar degree with both T preparations but then remained stable until the end of the follow-up study [13]. Comparing the mean baseline levels with the mean levels after follow-up, there was an increase of serum T (from 3.9 to 16.2 nmol/L), of PSA serum levels (from 0.27 to 0.75 ng/mL) and of prostate volume (from 14.5 to 20.2 mL), whereas a decline of serum total cholesterol (from 235.3 to 202.4 mg/dL), low-density lipoprotein (LDL) cholesterol (from 158.8 to 134.9 mg/dL), high-density lipoprotein (HDL) cholesterol (from 46.1 to 42.8 mg/dL) and triglycerides (from 199.9 to 161.2 mg/dL) was observed. Using a standardized self-evaluation questionnaire for assessing psychosexual effects of TU treatment, it was found that scores for sexual thoughts/fantasies and sexual interest/desire doubled. The score for satisfaction of sex life also increased. Improvements were seen for waking erections, total number of erections, and number of ejaculations. The psychological parameters for depression, fatigue and anxiety decreased within the first 3-6 weeks and remained stable thereafter. There were no statistically significant differences between TE and TU. No significant change was observed in the score for aggressiveness in either group, indicating that this parameter was not affected by the treatment provided. These results obtained in hypogonadal men are paralleled in some respects by the study of O'Connor *et al*. [14] showing that a single injection of 1 000 mg TU to 28 eugonadal young men, elevating mean T levels above normal, was associated with significant increases in anger-hostility from baseline to week 2 after the injection. It was accompanied by an overall reduction in fatigueinertia, and did not increase aggressive behaviour or induce any changes in non-aggressive or sexual behaviour.

It is now clear that TU is at least as effective and safe as the standard injectable formulation and requires only four injections per year in long-term treatment while maintaining serum T levels within the physiological range. There are data to confirm the safety and efficacy of long-term TU therapy of hypogonadal patients treated over a period of more than 8 years [15]. The study included 22 patients who received TU up to 8.5 years at injection intervals of approximately 12 weeks. Patients reported restoration of sexual functions and positive changes in mood patterns. In contrast to short-acting TE preparations, patients rarely reported perceptions of fluctuations in androgen concentrations. Over the whole treatment period, PSA concentrations did not exceed the normal range and prostate size remained below 30 mL in all patients. Haemoglobin and hematocrit increased initially during treatment but remained within the normal range over the entire treatment period. Computer tomography of the lumbar spine showed that bone density improved in all patients during the first 2 years and remained stable thereafter. Body mass index (BMI) decreased during the first 2 years of treatment. Serum total cholesterol levels did not change over the treatment period and se-

rum LDL levels decreased slightly, parallel to the decrease of BMI, and serum HDL levels increased slightly over time. There were no relevant changes in blood pressure or heart rate. Overall, treatment with intramuscular TU appeared to have beneficial effects on body composition and lipid profile (Zitzmann M, von Eckardstein S, Saad F, Nieschlag E. Long-term experience with injections of testosterone undecanoate for substitution therapy in hypogonadal men. In: 87th Annual Meeting of the Endocrine Society; 2005 June 4–7; San Diego, CA; p. 306).

The above studies were confirmed recently by a study in elderly men (Jacobeit JW, Schulte HM. Long-acting intramuscular testosterone undecanoate [TU, Nebido®] in treatment of aging males with hypogonadism. 8th European Congress of Endocrinology, Glasgow, 1–5 April 2006, Poster No. P184).

Thirty-three hypogonadal men with primary, secondary or late-onset hypogonadism, between the ages of 45–79 years, were treated with TU. Serum T levels increased from 9.0 ± 3.8 nmol/L at baseline to 13.5 ± 4.6 nmol/L after 6 weeks and to 16.4 ± 6.4 nmol/L after 30 weeks of treatment. DHT levels increased from 0.98 ± 0.48 nmol/L to 3.1 ± 1.0 nmol/L. Serum PSA levels fluctuated minimally in the normal range. In two patients, the length between two injections could be prolonged from 12 to 14 weeks. All patients reported improved mood, sexual function and quality of life.

4 Treatment of erectile dysfunction (ED) with TU

There is a renewed interest in the treatment of erectile dysfunction (ED) with T. Apart from its well-known effects on libido, T appears to have significant direct effects on anatomical and physiological properties of erectile tissue [16, 17], and there are some interesting new observations. In support of a direct effect of T on penile tissues, treatment with TU appeared to improve veno-occlusive dysfunction evidenced by cavernosographic changes in hypogonadal patients with severe ED, diabetes mellitus, obesity and/or metabolic syndrome who had earlier not responded to PDE5 inhibitors and alprostadil injections [18, 19]. One patient having venous leakage prior to T administration received treatment with TU at 12–14 week intervals following a loading dose of 6 weeks. The patient showed improved sexual function after 9 weeks of treatment and repeated cavernosography after 12 weeks revealed that the venous leakage had receded [18]. The results from this case study suggest that TU has a positive impact on the veno-occlusive properties of penile trabecular tissues in hypogonadal ED patients. This finding has been replicated in five out of 12 hypogonadal patients [19]. These results confirm data obtained from animal studies showing that androgen insufficiency leads to veno-occlusive dysfunction, which cannot be restored with PDE-5 inhibitor treatment alone [20].

In a study assessing the impact of T therapy alone on ED, 22 hypogonadal men with ED received injections with TU, and sexual function was assessed using the International Index of Erectile Function (IIEF). While in all patients T therapy alone significantly improved the sexual desire domain of the IIEF (from 4.5 to 8.4 on a scale of 10), in 12 out of 22 patients (54%) the erectile function domain score increased from 12 at baseline (moderate ED) to 25 (indicating normal erectile function) at week 24. It is of note that the effect of T on erectile function may appear as late as 12-24 weeks of administration of T [21]. These observations have been extended to larger groups of patients confirming the results of the above study, which have been submitted for publication.

5 TU for male contraception

Exogenous administration of T functions as a contraceptive in the male by suppressing the secretion of LH and FSH from the pituitary. This approach to contraceptive development appears safe and fully reversible; however, sperm concentrations are not suppressed to zero in all men. Therefore, researchers have combined T with progestins to further suppress pituitary gonadotropins and optimize contraceptive efficacy [22–24]. Surprisingly, studies in East Asian men show that intramuscular TU alone affords better suppression of spermatogenesis and protection against pregnancy than does male condom use, and thus use of TU alone could suffice for contraceptive use in East Asian men [25].

In contrast to East Asians, only approximately 60% of Caucasian volunteers exhibited azoospermia following treatment with TU alone administered every 6 weeks [26]. However, these results with TU, which are comparable to those obtained following weekly injections of TE, offer the advantage of longer injection intervals, and therefore TU is the most promising androgen preparation for further development as a male contraceptive if com-

bined with potent progestins [22–24]. To increase long-term acceptability of the regimen, TU injection intervals might even be prolonged to 8 or 12 weeks. Meriggiola *et al*. [27] showed that injections of TU every 8 weeks combined with 200 mg of the long-acting parenteral norethisterone enanthate (NETE) very effectively suppressed spermatogenesis in normal men.

For many years, the lack of suitable T formulations in terms of pharmacokinetics and of convenience of administration has hampered the development of male hormonal contraceptives. Recent studies using TU represent a turning point in the development of male hormonal contraceptives [22–24]. Despite the requirement for regular injections, the acceptability of this regimen (TU combined with NETE) is high [23, 27].

6 Safety and tolerability

TU is generally well tolerated. Local irritation at the site of injection is moderate, does not last longer than three days and can be minimised by administering TU slowly over a period of at least 1 min. Very few patients reported irritation or pain at the injection site despite the large volume of injection of 4 mL. No patient discontinued treatment as a result of problems of local discomfort. TU should be injected deeply into the gluteal muscle. The patient should be in a prone position. During the first year of TU treatment, for safety reasons, erythropoiesis parameters and prostate size and serum PSA should be monitored in men above the age of 45 years at quarterly intervals and then yearly thereafter [28].

Several treatment options exist for hypogonadal patients; the most commonly used are injectable T esters such as TE with injection intervals of 2–3 weeks. Their administration is associated with supra-physiological peak values shortly after the injection and to sub-physiological levels in the days before the new injection. This often leads to mood swings or emotional instability. Another important consequence of the supra-physiological T levels under treatment with TE is the induction of elevations of the hematocrit [29]. Of 70 older men with low serum T receiving 200 mg of TE every other week, 30% developed a hematocrit greater than 52% [30, 31]. In another study of 32 hypogonadal men receiving 200 mg TE every other week, 14 patients (43.8%) had at least one occurrence of an elevated hematocrit value [32]. Elevated hematocrit values may lead to thrombo-embolic events.

No major adverse effects were encountered in the clinical trials of TU. This is not surprising as the pharmaceutically active component is T itself. Common side effects of T administration, such as gynecomastia, breast tenderness and acne were reported in only a minority of patients. This absence of side effects is probably to be ascribed to the largely normal physiological levels of T, and its derivatives DHT and estradiol, achieved with TU. Adverse effects were observed in the initial studies when the dosing schedule was not yet well established and the higher frequency of administration of TU led to higher-than-normal levels of T. Significant increase in PSA and prostate size were noted in some of these trials; however, this is a result of the fact that hypogonadal men have subnormal PSA values and small prostate sizes at baseline and the increase is observed with every treatment modality of T administration upon normalization of plasma T levels. In a systematic review, the average PSA increase after initiation of T therapy was 0.3 ng/mL in young hypogonadal men and 0.44 ng/mL in older men [33].

In the further course of treatment with TU, PSA levels and prostate size remained stable and within the normal range. Similarly, increases of parameters of erythropoiesis to eugonadal values were observed, but there was no occurrence of polycythemia as observed in studies with the more traditional T esters [29, 31, 32]. Only one study showed a transient decline in serum HDL cholesterol; however, its value remained within the normal range. For a review see Harle *et al*. [2]. It is clear now that TU is at least as effective and safe as the standard injectable formulation and eventually requires only four injections per year, while maintaining serum T levels within the physiological range. There are data to confirm the safety and efficacy of long-term TU therapy in hypogonadal patients treated over a period of more than 8 years. TU appears to be a safe modality of T treatment, because with the presently established dosage regimen, plasma T levels remain in the physiological range.

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