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Unexpectedly prolonged wash-out period of exogenous testosterone after discontinuation of intramuscular testosterone undecanoate depot injection (Nebido® or Reandron®) in men with congenital hypogonadotrophic hypogonadism.

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Abstract

Context: Intramuscular Testosterone undecanoate (TU) depot injection has become a popular preparation for the treatment of hypogonadism. Progressive accumulation of the product occurs with successive injections and gradual increment in injection interval is required in most cases to prevent testosterone-induced erythrocytosis. However, the wash-out period of exogenous testosterone after discontinuation of intramuscular TU depot injection has not been previously studied. Knowledge of the wash-out period of TU is of particular interest in cases of newly diagnosed prostate cancer and for those who plan to start spermatogenesis-induction therapy with gonadotropins.

Patients and design: We performed a retrospective study to investigate the wash-out period of exogenous testosterone after discontinuation of TU depot injection in 4 men with congenital hypogonadotrophic hypogonadism (HH). TU injections were discontinued in this group of patients in order to allow them to enrol in a clinical trial of spermatogenesis-induction therapy. The time interval for serum testosterone concentration to drop below 6nmol/L was examined.

Results: The rate of decline in serum testosterone (both total and free) levels was surprisingly shallow, with these 4 men taking an average of 30 weeks for testosterone level to decline from within the eugonadal range (mean total testosterone: 14.7 nmol/L; range: 12.8 - 19.1) to under 6 nmol/L.

Conclusion: This study demonstrated a potential prolonged washout period among profoundly hypogonadal men who had been regularly receiving TU depot injection. Further studies with larger patient cohort are required to examine the biochemical and clinical details on the wash-out period among men receiving this product.

Correspondence

Intramuscular Testosterone undecanoate (TU) depot 1g (Nebido[®] or Reandron[®]) is an increasingly popular testosterone preparation in view of convenience and pharmacokinetic profile. The datasheet recommends that it be given at 10-14 week intervals, except for the first two injections given six week apart. With a fixed dose-interval, accumulation of the product can occur with successive injections, as shown by progressively increased area-under-curve for serum testosterone (T) from first to fifth to thirteenth injections¹⁻³. Our own practice is to proactively manage the injection-interval over the first 2-3 years of treatment, progressively extending it if necessary over successive injections, in order to avoid T-induced erythrocytosis.

Although the pharmacokinetic profile of TU from single dose to complete washout is well-established from phase I and II studies, there are no data on the washout period (time for serum T to return to the pre-treatment hypogonadal range) for patients in steady-state. *i.e.* who have been receiving TU for several years and whose injection-interval, optimised for the desired trough T and haematocrit, is reasonably consistent (± 1 week). However, a study of TU as a potential male hormonal contraceptive found that suppression of spermatogenesis could persist for up to 5 months following discontinuation of the hormonal therapy⁴. This led us to suspect that the steady-state washout (SSW) time might be similarly prolonged. Knowledge of SSW data might be of particular interest to clinicians under two specific circumstances. First, when newly-developed high-grade prostate cancer is suspected, or diagnosed. Second, for men with hypogonadotrophic hypogonadism (HH) planning to start spermatogenesis-induction therapy with gonadotropins, as they will need to convert to indirect androgen replacement through human chorionic gonadotropin (hCG)-stimulated endogenous T synthesis. Fortunately, we have yet to encounter the first scenario, but were faced with the second during the process of recruitment and randomisation to a phase III clinical trial⁵. This trial (NCT number: 01709331) investigated the efficacy and safety of MK-8962 (corifollitropin alfa) in combination with hCG in adult men with HH who remain azoospermic when treated with hCG alone.

We report a series of 4 men with congenital HH (baseline levels of gonadotrophins and testosterone below 1.5 IU/l and 3nmol/l, respectively), median age 34.5 years (range: 25 - 44) taking an average of 30 weeks (range: 20 - 52) for testosterone level to decline from eugonadal range (mean total testosterone 14.7 nmol/l; range: 12.8 - 19.1) to <6 nmol/l. All these men had been on steady-state treatment with TU for at least 3

years, with a median injection-interval optimised at 12 ± 1 weeks. Their clinical characteristics are shown in the Supplementary data. TU injections were discontinued in order to allow these men to enrol in a clinical trial of spermatogenesis-induction therapy with an investigational gonadotrophin molecule, for which serum T concentration below 6 nmol/l was a prerequisite for enrolment in the active phase of the study⁵. As per UK clinical trial regulations, these men received no payment for study participation; only reimbursement of their reasonable travel expenses.

Serum T was assayed centrally by Quest Diagnostics (Heston, Middlesex, UK) using a liquid chromatography-tandem mass spectrometry method and Thermofinigan analyser (c.v 4.26%). Sex hormone binding globulin (SHBG) and albumin were measured locally by two-site sandwich immunoassay, using electro-chemiluminescence technology, and by a dye-binding assay, respectively (both by Roche Modular System, Roche Diagnostics, Lewes, UK), enabling free T to be calculated using a mass action formula⁶. The rate of decline in serum T (both total and free) levels proved to be so shallow (Figure 1) that only two of the four men could ultimately be recruited to this study within the permissible time-frame.

There was no evidence of HH reversal among these men; all being azoospermic at baseline, with consistently undetectable gonadotrophins persisting even when serum total and calculated free T concentration had fallen unequivocally below the normal adult male reference range. Testicular volumes also remained <3ml throughout this period. Two subjects exhibited slight “rebound” in serum T levels at one point. This phenomenon was not unknown to us from 10 years’ experience with TU and is consistent with T release from intramuscular TU depots not invariably occurring in a completely predictable, linear manner over time. Moreover, serum T at any time-point is unlikely to be exclusively derived from the intramuscular depot related to the most recent TU injection. It is likely that some of the circulating serum T is also derived from “older” depots. However, as per study protocol, both patients and their primary care physicians were carefully questioned regarding the possibility that they might have briefly used a T shot-acting T product. Although we found no evidence whatsoever for this and are confident that it did not occur, the possibility cannot be entirely excluded.

The observation of prolonged wash-out period following discontinuation of TU injections in hypogonadal men is of pharmacokinetic interest and has potential clinical implications. First, the prolonged SSW time for

TU injection might impact on the optimisation of spermatogenesis-induction therapy; therapeutic adjustment of hCG dose could prove more difficult without knowing the proportion of serum T derived from endogenous hCG-driven secretion. HH men who wish to achieve fertility, but having substantial amounts of exogenously-derived T still being released from previous IM depot injections, would thus need to be treated pragmatically with the highest dose of hCG, short of causing T-driven erythrocytosis. Such a regime might be less likely to achieve the high intratesticular T levels that are required for optimal Sertoli cell function.

Second, prolonged male-range T concentrations following discontinuation of TU injections might have implications for hypogonadal men diagnosed with high-grade, androgen-sensitive prostate cancer. Although T replacement therapy can be cautiously considered in hypogonadal men previously treated with curative intent for low-risk prostate cancer, and without evidence of active disease ⁷, the administration of T to men with active prostate cancer has been associated with adverse outcomes. Hence, most specialists treating a man with prostate cancer would aim to achieve complete clearance of T from the circulation as rapidly as possible. Were this to be unachievable due to prolonged T depot-effect, then anti-androgen therapy would likely need to be considered.

The reason for the prolonged circulating total and free T concentrations in these men HH is not readily apparent. Although the individual variance in body composition and adiposity could potentially result in delayed testosterone clearance ⁸, SHBG levels remained relatively steady and only began to rise when serum total T fell well-within the hypogonadal range. There was also no evidence of renal or liver dysfunction to suggest reduced hepatic or extrahepatic clearance. On the other hand, genetic polymorphism might contribute to inter-individual variability in T clearance and metabolism and a common polymorphism in the UGT2B17 gene has been shown to have a modest effect on serum testosterone level following TU therapy ⁹ although these men were not tested for this variant.

In summary, there has hitherto been a general lack of detailed data relating to the wash-out period among men receiving steady-state TU. We have demonstrated for the first time the potential for SSW period among men receiving TU injections, with up to 13 months being potentially required for exogenous testosterone to be fully-cleared. Better understanding of the determinants (both genetic and non-genetic) of TU clearance might improve the selection of TU dosage and injection intervals.

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Figure 1 legend.

Trend of total T (nmol/L) and calculated free T (pmol/L) concentrations for patients A-D.

X-axis shows the time since discontinuation of TU with 0 indicating the day they received their last TU injections. Left Y-axis shows total T concentration and right Y-axis the calculated free T concentration.

Serum T was assayed centrally by Quest Diagnostics (Heston, Middlesex, UK) using a liquid chromatography-tandem mass spectrometry method and Thermofinigan analyser (C.V: 4.26%).

The data are limited by irregular measurement of serum T concentration; hence the trajectories of the decline are less accurate than would have been the case with fixed intervals for blood sampling. Gonadotrophins for all 4 men were <0.5IU/L at each time point of T measurement.

Figure 1. The trend of total testosterone (nmol/L) and calculated free testosterone concentration (pmol/L) for patient A-D since the last dose of testosterone undecanoate injection.

Supplement A

Patient Characteristics

Patient	Diagnosis	Genetic variants	Age of diagnosis (years)	Age when T commenced (years)	Pubertal induction required?	Age at last TU injection (years)
A	KS	KAL1 (W237X) hemizygous	22	- Low-dose monthly Sustanon® 50mg, age 17-19 years, when he was (inappropriately) presumed to have simple pubertal delay. - Physiological testosterone replacement commenced from age 22 with a variety of preparations, most recently TU.	Yes, absent puberty at diagnosis	43
B	normosmic CHH	none identified	19	- TU from age 19 years.	Yes, absent puberty at diagnosis	24
C	KS	PROK2 (R73C) heterozygous	34	- Mixture of Sustanon® 250mg and hCG 1,500 IU, age 34-36 years; switched to TU from age 37.	Yes, absent puberty at diagnosis	40
D	KS	CHD7 (M340V) heterozygous	17	- Sustanon® 250mg, age 17-18 years, then switched to TU.	Yes, absent puberty at diagnosis	27